08/33466

CSA047349

SUPERINTENDENCIA DE INVEN

Industria y Comercio

Organizacion y Digitalizacion CSA Ltda

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISION DE NUEVAS CREACIONES

08-33466

SOLICITUD

PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE INDOL 1,3-DISUSTITUIDO PARA USO COMO MODULADORES DE PPAR

SOLICITANTE: PLEXXIKON, INC.

DIRECCIÓN: 91 Bolivar Drive, Suite A, Berkeley, CA 94710. Estados Unidos de América

A61K 31/405

APODERADO: CARLOS R. OLARTE

BOGOTÁ 03 de Abril de 2008

P2008/000044

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-033466- -00000-0000
Fecha: 2008-04-03 16:00:53 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIY!! Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 508

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

P2008/000044

(1) **SOLICITUD DE:**

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: PLEXXIKON, INC.
Dirección: 91 Bolivar Drive, Suite A, Berkeley, CA 94710. Estados Unidos de América
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos de América
Teléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) **REPRESENTANTE O APODERADO**

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

(4) **INVENTOR (ES) (72)**

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2006/034747 Fecha Septiembre 6, 2006

Publicación Internacional No. WO 2007/030559 Fecha Marzo 15, 2007

(6) **Título (54)** **DERIVADOS DE INDOL 1,3-DISUSTITUIDO PARA USO COMO MODULADORES DE PPAR**

(7) **Clasificación Internacional (51)** C07D 409/14, C07D 413/14, A61K 31/405, A61P 3/10

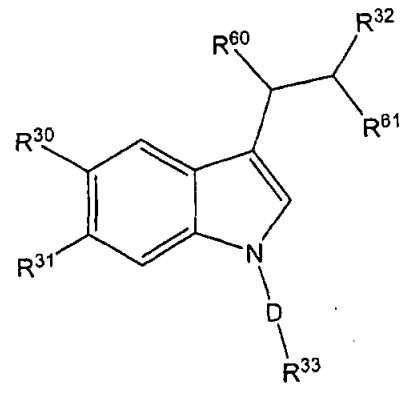
(8) **Prioridad**

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Septiembre 7, 2005	60/715,327

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
X	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso. Adjunto copia simple. Ver Expediente No. 06-003.175
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
X	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
	Traducción del examen preliminar internacional efectuado por la IPEA.
	De ser el caso, copia del contrato de acceso.
	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
	De ser el caso, certificado de depósito del material biológico.
	Arte final 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
	De ser el caso, modificaciones efectuadas a la solicitud internacional.
X	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

LISTA DE INVENTORES **PCT/US2006/034747**

1. **JACK LIN,**
   181 Falcon Way,
   Hercules, CA 94547
   Estados Unidos de América
   Nacionalidad: Estadounidense

2. **PATRICK WOMACK,**
   910 Steiner Street, San Francisco,
   CA 94117
   Estados Unidos de América
   Nacionalidad: Estadounidense

3. **BYUNGHUM LEE,**
   3222 Martin Circle,
   Marina, CA 93933
   Estados Unidos de América
   Nacionalidad: Estadounidense

4. **SHI SHENGHUA,**
   3979 Vía Cangrejo,
   San Diego, CA 92130
   Estados Unidos de América
   Nacionalidad: Estadounidense

5. **CHAO ZHANG,**
   397 Springfield Plaza,
   Moraga, CA 94556
   Estados Unidos de América
   Nacionalidad: China

6. **REBECCA ZUCKERMAN,**
1620 Clinton Avenue,
Alameda, CA 94501
Estados Unidos de América
Nacionalidad: Estadounidense

7. **DEAN R. ARTIS,**
50 Arlmont Drive,
Kensington, CA 94707
Estados Unidos de América
Nacionalidad: Estadounidense

8. **PRABHA N. IBRAHIM,**
3380 Lubich Drive,
Mountain View, CA 94040
Estados Unidos de América
Nacionalidad: Estadounidense

9. **WEIRU WANG,**
14 Del Rey Court,
Lafayette, CA 94549
Estados Unidos de América
Nacionalidad: China

445

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-033466- -00000-0000
Fecha: 2008-04-03 16:00:53 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 508

RECIBO OFICIAL DE CAJA : 08 - 24,726
FECHA : MARZO 26 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	107000	26/03/2008	4,811,000.00

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

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

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS
Traductor: Jorge Enrique Sierra Reyes.

Nota del Traductor:

El poder otorgado por Plexxikon Inc. a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro, tiene los siguientes textos, firmas y sellos en inglés:

Manuscrito: "Ver reconocimiento adjunto"

Gregory J. Smith
Condado de San Diego
Asesor/Registrador/Registrador del Condado

Oficina del Asesor
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 2363771 - Fax: (619) 557-4056

www.sdarcc.com

Oficina del Registrador del Condado
1600 Pacific Highway, Room 260, PO Box: 121750 - San Diego, CA 92112-1750
Tel. (619) 237-0502 - Fax: (619) 557-4155

Yo, Gregory J. Smith, Asesor/Registrador/Registrador del Condado de San Diego, Estado de California, con un sello de Ley, certifico por medio del presente documento que DIANE S. GARCIA, cuyo nombre está suscrito al Juramento o certificado de prueba o reconocimiento del instrumento anexo y por consiguiente escrito, era al momento de tomar dicho juramento, o prueba de reconocimiento, un Notario Público en y para dicho condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes de dicho estado para tomarlos y administrar juramentos y tomar los reconocimientos y pruebas de hechos y otros instrumentos por escrito para ser registrados en este estado. Estoy familiarizado

Traductor Oficial
JORGE E. SIERRA REYES

con la escritura de dicho Notario Público y creo que la firma en dicho juramento o certificado de prueba o reconocimiento es genuina. Además certifico que según las leyes del Estado de California, dicho juramento o certificado de prueba o reconocimiento requiere estar sellado, pero la impresión de dicho sello no es exigido por las leyes del Estado de California para ser archivado en mi oficina o en ningún otro lugar.

Fecha: 1º de Junio de 2006.

Firmado en constancia,

(Firmado) Gregory J. Smith, Asesor y Registrador del Condado.

Sello: "Asesor y Registrador del Condado – Condado de San Diego, California".

Oficinas disponibles para servirle:

Chula Vista	El Cajon	Kearny Mesa	San Marcos

Nota: El Modelo de Certificación Notarial lleva la siguiente firma y sello:

Notario Público (Firma): Diane S. Garcia. Notario Publico del Estado de California – Condado de San Diego – Comisión No. 1408800 – Expira el 1º de Abril de 2007. Sello.

Apostilla adjunta:

Traductor Oficial
JORGE E. SIERRA REYES

ESTADO DE CALIFORNIA
Secretario de Estado

APOSTILLA

(Convention du La Haye du 5 octobre 1961)

1. País:	ESTADOS UNIDOS DE AMÉRICA
	El presente documento público
2. Ha sido firmado por:	Gregory J. Smith
3. Actuando en calidad de:	Asesor y Registrador del Condado
4. Lleva el sello/estampilla de:	Condado de San Diego
	Certificado
5. En:	San Diego, California
6. El:	Día primero de Junio de 2006
7. Por:	Sub Secretario de Estado, Estado de California
8. Bajo el No.	137876
9. Sello / estampilla:	Gran Sello de Estado de California
10. Firma:	BRUCE McPHERSON, Secretario de Estado. Por: Carolyn J. Johnson
Sello pequeño:	"Oficina del Secretario de Estado"

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Poder" Fecha: 5 de Junio de 2006. Traductor: Jorge Enrique Sierra Reyes. Licencia No. 376 de 1993, del Ministerio de Justicia. Dirección: Carrera 15 No. 99-13 Oficina 411. Teléfono: (57-1) 2182308, (57-1) 6232925. Bogotá, Colombia. E-mail: treseser1@yahoo.com. 7431

Traductor Oficial
JORGE E. SIERRA REYES

State of California

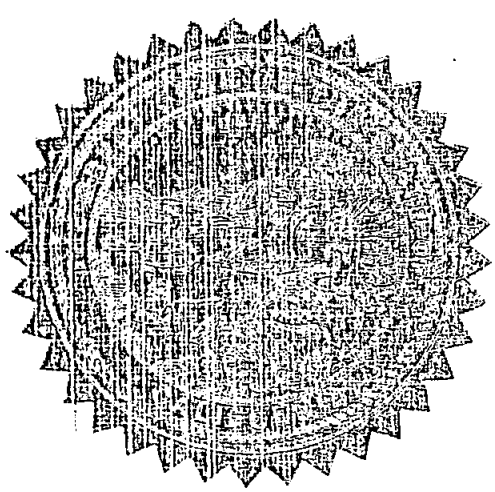
SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by GREGORY J. SMITH*
3. *acting in the capacity of ASSESSOR/RECORDER/COUNTY CLERK*
4. *bears the seal/stamp of the county of SAN DIEGO*
   State of California

CERTIFIED

5. *At SAN DIEGO, California*
6. *The 1ST day of JUNE, 2006*
7. *by Deputy Secretary of State, State of California*
8. *No. 137876*
9. *Stamp/Seal*
10. *Signature*





Secretary of State

BY _____

(REV. 4-05)

OSP 05 90772

Gregory J. Smith

COUNTY OF SAN DIEGO

ASSESSOR / RECORDER / COUNTY CLERK

ASSESSOR'S OFFICE
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 236-3771 • Fax (619) 557-4056

www.sdarcc.com

RECORDER/COUNTY CLERK'S OFFICE
1600 Pacific Highway, Room 260
P.O. Box 121750 • San Diego, CA 92112-1750
Tel. (619) 237-0502 • Fax (619) 557-4155

I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

DIANE S GARCIA whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: June 1, 2006 Witness by hand

G. J. Smith

GREGORY J SMITH, County Assessor/Recorder/Clerk

Branch Offices Available To Serve You

CHULA VISTA
590 Third Avenue
Chula Vista, CA 91910-5617
(619) 498-2200

EL CAJON
200 S. Magnolia Avenue
El Cajon, CA 92020-4524
(619) 401-5700

KEARNY MESA
9225 Clairemont Mesa Blvd.
San Diego, CA 92123-1211
(858) 505-6262

SAN MARCOS
334 Via Vera Cruz, Suite 150
San Marcos, CA 92078-2638
(760) 940-6868

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Zaava Ravid
Jacqueline Chaparro
Jose Luis Londoño
Camilo Alvarez
Felipe Mendoza
Camilo Rodríguez
Santiago Pardo

Of Counsel
Guillermo Chahín
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

PLEXXIKON, INC.

domiciled in

domiciliado en

91 Bolivar Drive, Suite A, Berkeley, CA 94710 USA

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: 1/16/06

City,Country/Ciudad,País: Berkeley, CA USA

See attached acknowledgment

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	Certificación Notarial
On this date, January 16, 2006 The undersigned Notary Public certifies:	En esta fecha; el Notario Público suscrito certifica:
1. That Dean R. Artis of legal age and domiciled in 91 Bolivar Drive, Berkeley, California 94710 USA signed the foregoing document.	1. Que mayor de edad y domiciliado suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as Vice President of Plexxikon, Inc.	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That Plexxikon, Inc., having its principal place of business located in Berkeley, CA United States is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.	4. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s): Certificate of the President and Secretary of Plexxikon, Inc.	5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature): Diane S. Garcia
Diane S. Garcia
Notary Public-State of California
San Diego County
Commission No. 1408800
Expires April 1, 2007

DIANE S. GARCIA
Commission # 1408800
Notary Public - California
San Diego County
My Comm. Expires Apr 1, 2007

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS
Traductor: Jorge Enrique Sierra Reyes.

Nota del Traductor:

El Certificado de Presidente y Secretaria de Plexxikon Inc. lleva los siguientes textos, firmas y sellos en inglés:

Gregory J. Smith
Condado de San Diego
Asesor/Registrador/Registrador del Condado

Oficina del Asesor
1600 Pacific Highway, Room 103
San Diego, CA 92101-2480
Tel. (619) 2363771 – Fax: (619) 557-4056

www.sdarcc.com

Oficina del Registrador del Condado
1600 Pacific Highway, Room 260. PO Box: 121750 - San Diego, CA 92112-1750
Tel. (619) 237-0502 – Fax: (619) 557-4155

Yo, Gregory J. Smith, Asesor/Registrador/Registrador del Condado de San Diego, Estado de California, con un sello de Ley, certifico por medio del presente documento que DIANE S. GARCIA, cuyo nombre está suscrito al Juramento o certificado de prueba o reconocimiento del instrumento anexo y por consiguiente escrito, era al momento de tomar dicho juramento, o prueba de reconocimiento, un Notario Público en y para dicho condado, debidamente nombrado y juramentado y debidamente autorizado por las leyes de dicho estado para tomarlos y administrar juramentos y tomar los reconocimientos y pruebas de hechos y otros instrumentos por escrito para ser registrados en este estado. Estoy familiarizado con la escritura de dicho Notario Público y creo que la firma en dicho juramento o certificado de prueba o reconocimiento es genuina. Además certifico que según las leyes del Estado de California, dicho juramento o certificado de prueba o reconocimiento requiere estar sellado, pero la impresión de dicho sello no es

Traductor Oficial
JORGE ENRIQUE SIERRA REYES

exigido por las leyes del Estado de California para ser archivado en mi oficina o en ningún otro lugar.

Fecha: 8 de Mayo de 2006.

Firmado en constancia,

(Firmado) Gregory J. Smith, Asesor y Registrador del Condado.

Sello: "Asesor y Registrador del Condado - Condado de San Diego, California".

Oficinas disponibles para servirle:

Chula Vista El Cajon Kearny Mesa San Marcos

CERTIFICADO DEL PRESIDENTE Y SECRETARIA DE PLEXXIKON INC.
91 Bolivar Drive
Berkeley, CA 94710

La suscrita, Kathleen Sereda Glaub, certifica lo siguiente:

1. Ella es la Presidente y Secretaria debidamente elegida, calificada y vigente de Plexxikon Inc., una empresa de California (la "Empresa") y está familiarizada con los hechos que se certifican aquí, estando debidamente autorizada para certificarlos y para hacer las declaraciones conforme están certificadas por ella en este documento.
2. Plexxikon Inc. está debidamente constituida, está vigente y el otorgamiento del Poder está dentro del alcance de sus propósitos corporativos y ha sido debidamente autorizado para todas las acciones necesarias por parte de la Empresa.
3. Cada persona mencionada más adelante tiene especificado su puesto al frente, la firma al frente del nombre de dicho funcionario es la firma genuina y tal persona

Traductor Oficial
JORGE E. SIERRA REYES

está autorizada para ejecutar documentos en nombre de la Empresa; cualquier documento ejecutado por dicha persona entrará en vigencia contra la Empresa.

Nombre	Cargo	Firma
Dean Richard Artis	Vicepresidente, *Lead Generation*	(Firmado)

El suscrito ha ejecutado este certificado como funcionario de la Empresa, este día 2 de mayo de 2006.
(Firmado) Kathleen Sereda Glaub, Presidente y Secretaria.

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS DE CALIFORNIA

Estado de California, Condado de San Diego
El día 5-2-2006, ante mí, Diane Garcia, Notario, se presentaron personalmente DEAN RICHARD ARTIS/KATHLEEN SEREDA GLAUB, a quienes conozco personalmente como las personas cuyos nombres están suscritos al instrumento adjunto y reconocieron ante mí que ellos lo ejecutaron en sus condiciones autorizadas y que por sus firmas en el instrumento, las personas o la entidad a nombre de la cual ellos actuaron, ejecutaron el instrumento.

En constancia, firmo y sello. (Firmado) Diane S. Garcia - Notario Público.
Sello: Diane S. Garcia - Notario Público de California, Condado de San Diego. Mi comisión #1408800 vence el 1º de Abril de 2007.

Descripción del documento adjunto.
Título o tipo de documento: Certificado
Fecha del documento: 5-2-2006.
No. de páginas: 1
El firmante está representando a PLEXXIKON INC.

Traducción Oficial
JORGE E. [illegible] REYES

Apostilla adjunta:

ESTADO DE CALIFORNIA
Secretario de Estado
APOSTILLA
(Convention du La Haye du 5 octobre 1961)

1. País:	ESTADOS UNIDOS DE AMÉRICA
	El presente documento público
2. Ha sido firmado por:	Gregory J. Smith
3. Actuando en calidad de:	Asesor y Registrador del Condado
4. Lleva el sello/estampilla de:	Condado de San Diego
	Certificado
5. En:	San Diego, California
6. El:	Día 8 de Mayo de 2006
7. Por:	Sub Secretario de Estado, Estado de California
8. Bajo el No.	137384
9. Sello / estampilla:	Gran Sello de Estado de California
10. Firma:	BRUCE McPHERSON, Secretario de Estado.
	Por: (ilegible)
Sello pequeño:	"Oficina del Secretario de Estado"

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Certificado" Fecha: 5 de Junio de 2006. Traductor: Jorge Enrique Sierra Reyes. Licencia No. 376 de 1993, del Ministerio de Justicia. Dirección: Carrera 15 No. 99-13 Oficina 411. Teléfono: (57-1) 2182308, (57-1) 6232925. Bogotá, Colombia. E-mail: treseser1@yahoo.com. 7432

Traductor Oficial
JORGE E. SIERRA REYES

State of California

SECRETARY OF STATE
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document

2. *has been signed by GREGORY J. SMITH*

3. *acting in the capacity of COUNTY ASSESSOR/RECORDER/CLERK*

4. *bears the seal/stamp of the county of SAN DIEGO*
   State of California

CERTIFIED

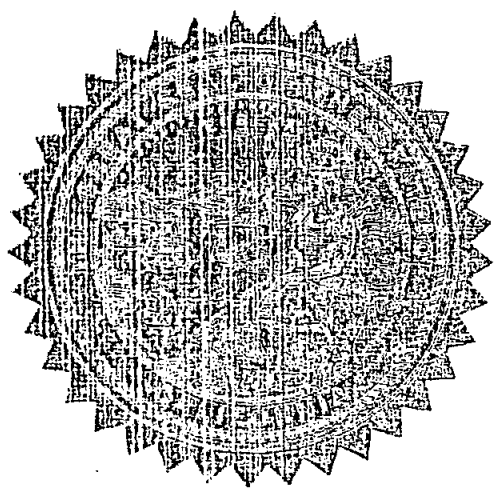
5. *At SAN DIEGO, California* 6. *The 8TH day of MAY, 2006*

7. *by Deputy Secretary of State, State of California*

8. *No. 137384*

9. *Stamp/Seal*

10. *Signature*



Bruce McPherson
Secretary of State
BY Sherry Miller



Gregory J. Smith

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I, GREGORY J SMITH, Assessor/Recorder/County Clerk of the County of San Diego, State of California, having by law a Seal, DO HEREBY CERTIFY that:

DIANE S GARCIA whose name is subscribed to the oath or Certificate of Proof or Acknowledgement of the annexed instrument and thereon written, was at the time of taking such oath, or Proof or Acknowledgement, a Notary Public, in and for said County, duly commissioned and sworn and duly authorized by the laws of said State to take the same and administer oaths and to take the Acknowledgements and Proofs of Deeds and other instruments in writing to be recorded in this State. I am acquainted with the handwriting of such Notary Public and believe that the signature to said oath or Certificate of Proof Acknowledgement is genuine. I further certify that under the laws of the State of California the said oath or Certificate of Proof or Acknowledgement is required to be under seal, but the impression of said seal is not required by the laws of the State of California to be filed in my office or in any other place.

DATED: May 8, 2006 Witness by hand

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CERTIFICATE OF THE PRESIDENT AND SECRETARY

OF

PLEXXIKON INC.
91 Bolivar Drive
Berkeley, CA 94710

The undersigned, Kathleen Sereda Glaub, hereby certifies as follows:

1. She is the duly elected, qualified and acting President and Secretary of Plexxikon Inc. a California corporation (the "***Company***"), and is familiar with the facts herein certified and is duly authorized to certify the same, and to make the statements as certified by her herein.

2. Plexxikon Inc. is duly incorporated, validly existing and the grant of the Power of Attorney is within the scope of its corporate purposes and has been duly authorized by all necessary actions on the part of the Company.

3. Each person named below holds the office set forth opposite such officer's name, the signature opposite such officer's name is such officer's genuine signature and such person is authorized to execute document on behalf of the Company, and any documents executed by such person shall be effective against the Company.

Name	**Title**	**Signature**
Dean Richard Artis	Vice President, Lead Generation	

The undersigned has executed this certificate as an officer of the Company this 2nd day of May, 2006.

Kathleen Sereda Glaub, President and Secretary

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of SAN DIEGO } ss.

On 5-2-2006 (Date) before me, DIANE GARCIA NOTARY (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared DEAN RICHARD ARMS KATHLEEN SEREDA GLAZIB (Name(s) of Signer(s))

☑ personally known to me
☐ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

DIANE S. GARCIA
Commission # 1408800
Notary Public - California
San Diego County
My Comm. Expires Apr 1, 2007

WITNESS my hand and official seal.

Diane S. Garcia
Signature of Notary Public

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 039363-2903	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2006/034747	International filing date *(day/month/year)* 06 September 2006 (06.09.2006)	Priority date *(day/month/year)* 07 September 2005 (07.09.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PLEXXIKON, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 11 March 2008 (11.03.2008)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
Facsimile No. +41 22 338 82 70	e-mail: pt04.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/034747	06.09.2006	07.09.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D409/14 C07D413/14 A61K31/405 A61P3/10

Applicant
PLEXXIKON, 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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

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

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

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

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

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Johnson, Claire Telephone No. +49 89 2399-8287

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/034747

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☒ furnished subsequently to this Authority for the purposes of search.

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/US2006/034747

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. 22-26,33-37

because:

☒ the said international application, or the said claims Nos. 22-26,33-37 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/034747

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

1. Statement

Novelty (N)	Yes:	Claims	12-14, 21
	No:	Claims	1-11, 15-20, 22-37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-21,27-32
	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

III. Non-establishment of opinion

Claims 22-26 and 33-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

The claims include isomers of the compounds of the general formulae. The term isomers includes constitutional isomers, positional isomers, etc. There is however no support or disclosure (Articles 5 and 6 PCT) in the application for compounds which do not have the structure given in the formulae of the claims, i.e. an indole core substituted at the 3-position by a carboxylic acid group. No search or examination will be performed for isomers of the present formulae.

The term prodrug is not considered to define the matter for which protection is sought in a clear manner as required by Article 6 PCT. There are many possible functional groups present in the compound of formula I. There is no information in the application or the prior art as to which functional groups in which positions may be derivatised to give compounds having the attributes of prodrugs (i.e. compounds which are inactive per se, and which are broken down in the body to give active compounds). The skilled man would only be able to ascertain whether particular compounds were within the scope of claim 1 by performing in vivo tests, which is considered to go beyond the routine experimentation to be reasonably expected of him.

V. Reasoned statement

Reference is made to the following document:
D1: WO2005/009958

Novelty

D1 discloses compounds of formula (I) useful as PPAR modulators. Formula (I) encompasses the subject matter of all the present claims. It must be noted that the disclosure of this document is not confined to the examples but embraces the general formulae as well, and that novelty cannot therefore be established by merely

excluding the specific examples given in this document. As D1 does not appear to specifically disclose the possibility that the R^2 optionally substituted aralkyl group is ortho-substituted by a group equivalent to present T-B, claims 12-14 may be considered a novel selection from D1, as may the specific compounds of present claim 21.
Claims 1-11, 15-20 and 22-37 do not fulfil the requirements of Article 33(2) PCT.

Inventive step
In view of their lack of novelty, claims 1-11, 15-20 and 22-37 cannot be inventive.
Re. claims 12 and 21:
The technical problem underlying these claims appears to be the provision of PPAR modulators. D1 describes compounds of a general formula encompassing the subject matter of claims 12 and 12 for use as PPAR modulators. It would be obvious for the skilled person to solve this problem by selecting compounds already generically known from D1 to have the desired activity.
Claims 1-37 do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability
Claims 1-21 and 27-32 fulfil the requirements of Article 33(4) PCT.
No unified criteria exist in the PCT Contracting States for assessing whether present claims 22-26 and 33-37 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII. Certain observations

Claim 11 contains two moieties defined as E. Claims 34 and 35 contain definitions of moieties that are not present in the formulae.

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

(19) World Intellectual Property Organization
International Bureau

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15 March 2007 (15.03.2007)

PCT

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(74) Agents: **WARBURG, Richard J.** et al.; Foley & Lardner LLP, P.O. Box 80278, San Diego, CA 92138-0278 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: 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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

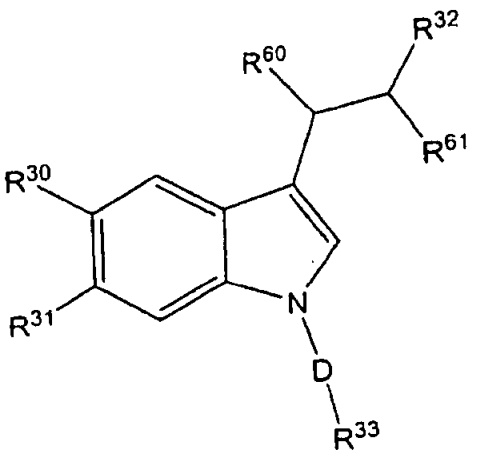
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Published:
— *with international search report*

(88) Date of publication of the international search report:
13 September 2007

[Continued on next page]

(54) Title: 1, 3-DISUBSTITUTED INDOLE DERIVATIVES FOR USE AS PPAR MODULATORS



(57) Abstract: Compounds are described that are active on PPARs, including pan-active compounds and compounds selective for any one or any two of PPARα, PPARγ and PPARδ. Also describe are methods of use of the compounds in treating various diseases.

WO 2007/030559 A3

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PPAR ACTIVE COMPOUNDS

RELATED PATENT APPLICATIONS

[0001] This application claims the benefit of U.S. Prov. App. No. 60/715,327, filed September 7, 2005, which is incorporated herein by reference in its entirety and for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to the field of modulators for members of the family of nuclear receptors identified as peroxisome proliferator-activated receptors.

BACKGROUND OF THE INVENTION

[0003] The following description is provided solely to assist the understanding of the reader. None of the references cited or information provided is admitted to be prior art to the present invention. Each of the references cited herein is incorporated by reference in its entirety, to the same extent as if each reference were individually indicated to be incorporated by reference herein in its entirety.

[0004] The peroxisome proliferator-activated receptors (PPARs) form a subfamily in the nuclear receptor superfamily. Three isoforms, encoded by separate genes, have been identified thus far: PPARγ, PPARα, and PPARδ.

[0005] There are two PPARγ isoforms expressed at the protein level in mouse and human, γ1 and γ2. They differ only in that the latter has 30 additional amino acids at its N terminus due to differential promoter usage within the same gene, and subsequent alternative RNA processing. PPARγ2 is expressed primarily in adipose tissue, while PPARγ1 is expressed in a broad range of tissues.

[0006] Murine PPARα was the first member of this nuclear receptor subclass to be cloned; it has since been cloned from humans. PPARα is expressed in numerous metabolically active tissues, including liver, kidney, heart, skeletal muscle, and brown fat. It is also present in monocytes, vascular endothelium, and vascular smooth muscle cells. Activation of PPARα induces hepatic peroxisome proliferation, hepatomegaly, and

hepatocarcinogenesis in rodents. These toxic effects are not observed in humans, although the same compounds activate PPARα across species.

[0007] Human PPARδ was cloned in the early 1990s and subsequently cloned from rodents. PPARδ is expressed in a wide range of tissues and cells with the highest levels of expression found in the digestive tract, heart, kidney, liver, adipose, and brain.

[0008] The PPARs are ligand-dependent transcription factors that regulate target gene expression by binding to specific peroxisome proliferator response elements (PPREs) in enhancer sites of regulated genes. PPARs possess a modular structure composed of functional domains that include a DNA binding domain (DBD) and a ligand binding domain (LBD). The DBD specifically binds PPREs in the regulatory region of PPAR-responsive genes. The DBD, located in the C-terminal half of the receptor contains the ligand-dependent activation domain, AF-2. Each receptor binds to its PPRE as a heterodimer with a retinoid X receptor (RXR). Upon binding an agonist, the conformation of a PPAR is altered and stabilized such that a binding cleft, made up in part of the AF-2 domain, is created and recruitment of transcriptional coactivators occurs. Coactivators augment the ability of nuclear receptors to initiate the transcription process. The result of the agonist-induced PPAR-coactivator interaction at the PPRE is an increase in gene transcription. Downregulation of gene expression by PPARs appears to occur through indirect mechanisms. (Bergen & Wagner, 2002, *Diabetes Tech. & Ther.*, 4:163-174).

[0009] The first cloning of a PPAR (PPARα) occurred in the course of the search for the molecular target of rodent hepatic peroxisome proliferating agents. Since then, numerous fatty acids and their derivatives, including a variety of eicosanoids and prostaglandins, have been shown to serve as ligands of the PPARs. Thus, these receptors may play a central role in the sensing of nutrient levels and in the modulation of their metabolism. In addition, PPARs are the primary targets of selected classes of synthetic compounds that have been used in the successful treatment of diabetes and dyslipidemia. As such, an understanding of the molecular and physiological characteristics of these receptors has become extremely important to the development and utilization of drugs used to treat metabolic disorders.

[0010] Kota et al., 2005, *Pharmacological Research* 51: 85-94, provides a review of biological mechanisms involving PPARs that includes a discussion of the possibility of

using PPAR modulators for treating a variety of conditions, including chronic inflammatory disorders such as atherosclerosis, arthritis and inflammatory bowel syndrome, retinal disorders associated with angiogenesis, increased fertility, and neurodegenerative diseases.

[0011] Yousef et al., 2004, *Journal of Biomedicine and Biotechnology* 2004(3):156-166, discusses the anti-inflammatory effects of PPARα, PPARγ and PPARδ agonists, suggesting that PPAR agonists may have a role in treating neuronal diseases such as Alzheimer's disease, and autoimmune diseases such as inflammatory bowel disease and multiple sclerosis. A potential role for PPAR agonists in the treatment of Alzheimer's disease has been described in Combs et al., 2000, *Journal of Neuroscience* 20(2): 558, and such a role for PPAR agonists in Parkinson's disease is discussed in Breidert et al. 2002, *Journal of Neurochemistry*, 82: 615. A potential related function of PPAR agonists in treatment of Alzheimer's disease, that of regulation of the APP-processing enzyme BACE, has been discussed in Sastre et al. 2003, *Journal of Neuroscience* 23(30):9796. These studies collectively indicate PPAR agonists may provide advantages in treating a variety of neurodegenerative diseases by acting through complementary mechanisms.

[0012] Discussion of the anti-inflammatory effects of PPAR agonists is also available in Feinstein, 2004, *Drug Discovery Today: Therapeutic Strategies* 1(1):29-34 in relation to multiple sclerosis and Alzheimer's disease; Patel et al., 2003, *The Journal of Immunology*, 170:2663-2669 in relation to chronic obstructive pulmonary disease (COPD) and asthma; Lovett-Racke et al., 2004, *The Journal of Immunology*, 172:5790-5798 in relation to autoimmune disease; Malhotra et al., 2005, *Expert Opinions in Pharmacotherapy*, 6(9):1455-1461 in relation to psoriasis; and Storer et al., 2005, *Journal of Neuroimmunology*, 161:113-122 in relation to multiple sclerosis.

[0013] This wide range of roles for the PPARs that have been discovered suggest that PPARα, PPARγ and PPARδ may play a role in a wide range of events involving the vasculature, including atherosclerotic plaque formation and stability, thrombosis, vascular tone, angiogenesis, cancer, pregnancy, pulmonary disease, autoimmune disease, and neurological disorders.

[0014] Among the synthetic ligands identified for PPARs are thiazolidinediones (TZDs). These compounds were originally developed on the basis of their insulin-sensitizing

effects in animal pharmacology studies. Subsequently, it was found that TZDs induced adipocyte differentiation and increased expression of adipocyte genes, including the adipocyte fatty acid-binding protein aP2. Independently, it was discovered that PPARγ interacted with a regulatory element of the aP2 gene that controlled its adipocyte-specific expression. On the basis of these seminal observations, experiments were performed that determined that TZDs were PPARγ ligands and agonists and demonstrated a definite correlation between their *in vitro* PPARγ activities and their *in vivo* insulin-sensitizing actions. (Bergen & Wagner, *supra*).

[0015] Several TZDs, including troglitazone, rosiglitazone, and pioglitazone, have insulin-sensitizing and anti-diabetic activity in humans with type 2 diabetes and impaired glucose tolerance. Farglitazar is a very potent non-TZD PPARγ-selective agonist that was recently shown to have antidiabetic as well as lipid-altering efficacy in humans. In addition to these potent PPARγ ligands, a subset of the non-steroidal antiinflammatory drugs (NSAIDs), including indomethacin, fenoprofen, and ibuprofen, have displayed weak PPARγ and PPARα activities. (Bergen & Wagner, *supra*).

[0016] The fibrates, amphipathic carboxylic acids that have been proven useful in the treatment of hypertriglyceridemia, are PPARα ligands. The prototypical member of this compound class, clofibrate, was developed prior to the identification of PPARs, using *in vivo* assays in rodents to assess lipid-lowering efficacy. (Bergen & Wagner, *supra*).

[0017] Fu et al., *Nature*, 2003, 425:9093, demonstrated that the PPARα binding compound, oleylethanolamide, produces satiety and reduces body weight gain in mice.

[0018] Clofibrate and fenofibrate have been shown to activate PPARα with a 10-fold selectivity over PPARγ. Bezafibrate acts as a pan-agonist that shows similar potency on all three PPAR isoforms. Wy-14643, the 2-arylthioacetic acid analogue of clofibrate, is a potent murine PPARα agonist as well as a weak PPARγ agonist. In humans, all of the fibrates must be used at high doses (200-1,200 mg/day) to achieve efficacious lipid-lowering activity.

[0019] TZDs and non-TZDs have also been identified that are dual PPARγ/α agonists. By virtue of the additional PPARα agonist activity, this class of compounds has potent lipid-altering efficacy in addition to antihyperglycemic activity in animal models of diabetes and lipid disorders. KRP-297 is an example of a TZD dual PPARγ/α agonist

(Fajas, 1997, *J. Biol. Chem.*, 272:18779-18789); furthermore DRF-2725 and AZ-242 are non-TZD dual PPARγ/α agonists. (Lohray, et al., 2001, *J. Med. Chem.*, 44:2675-2678; Cronet, et al., 2001, Structure (Camb.) 9:699-706).

[0020] In order to define the physiological role of PPARδ, efforts have been made to develop novel compounds that activate this receptor in a selective manner. Amongst the α-substituted carboxylic acids previously described, the potent PPARδ ligand L-165041 demonstrated approximately 30-fold agonist selectivity for this receptor over PPARγ, and it was inactive on murine PPARα (Liebowitz, et al., 2000, *FEBS Lett.*, 473:333-336). This compound was found to increase high-density lipoprotein levels in rodents. It was also reported that GW501516 was a potent, highly-selective PPARδ agonist that produced beneficial changes in serum lipid parameters in obese, insulin-resistant rhesus monkeys. (Oliver et al., 2001, *Proc. Natl. Acad. Sci.*, 98:5306-5311).

[0021] In addition to the compounds discussed above, certain thiazole derivatives active on PPARs have been described. (Cadilla et al., Internat. Appl. PCT/US01/149320, Internat. Publ. WO 02/062774, incorporated herein by reference in its entirety.)

[0022] Some tricyclic-α-alkyloxyphenylpropionic acids have been described as dual PPARα/γ agonists in Sauerberg et al., 2002, *J. Med. Chem.* 45:789-804.

[0023] A group of compounds that are stated to have equal activity on PPARα/γ/δ is described in Morgensen et al., 2002, *Bioorg. & Med. Chem. Lett.* 13:257-260.

[0024] Oliver et al., describes a selective PPARδ agonist that promotes reverse cholesterol transport. (Oliver et al., *supra*).

[0025] Yamamoto et al., U.S. Patent No. 3,489,767 describes "1-(phenylsulfonyl)-indolyl aliphatic acid derivatives" that are stated to have "antiphlogistic, analgesic and antipyretic actions." (Col. 1, lines 16-19.)

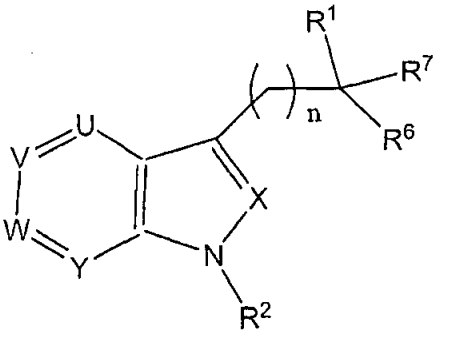
[0026] Kato et al., European Patent Application 94101551.3, Publication No. 0 610 793 A1, describes the use of 3-(5-methoxy-1-p-toluenesulfonylindol-3-yl)propionic acid (page 6) and 1-(2,3,6-triisopropylphenylsulfonyl)-indole-3-propionic acid (page 9) as intermediates in the synthesis of particular tetracyclic morpholine derivatives useful as analgesics.

[0027] This application is related to the following published patent applications: WO 2005009958, US 20050038246, and US 20050288354, each of which are hereby incorporated by reference herein in their entireties including all specifications, figures, and tables, and for all purposes.

SUMMARY OF THE INVENTION

[0028] The present invention relates to compounds active on PPARs, which are useful for a variety of applications, e.g., therapeutic and/or prophylactic methods involving modulation of at least one of PPARα, PPARδ, and PPARγ. Included are compounds that have significant pan-activity across the PPAR family (PPARα, PPARδ, and PPARγ), as well as compounds that have significant specificity (at least 5-, 10-, 20-, 50-, or 100-fold greater activity) on a single PPAR, or on two of the three PPARs.

[0029] In one embodiment, the invention involves the use of compounds of Formula I as modulators of one or more of the PPARs, PPARα, PPARδ, and PPARγ, where Formula I is:



Formula I

all salts, prodrugs, tautomers and isomers thereof,

wherein:

U, V, W, X, and Y are independently N or CR^8, wherein at most two of U, V, W, and Y are N;

R^1 is selected from the group consisting of $C(O)OR^{16}$ and a carboxylic acid isostere;

R^2 is selected from the group consisting of hydrogen, optionally substituted lower alkyl, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ and $-S(O)_2R^{21}$;

R^6 and R^7 are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

R^6 and R^7 combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl;

R^8 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^9$, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{21}$;

R^9 is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{10} and R^{11} together with the nitrogen to which they are attached form a 5-7 membered monocyclic heterocycloalkyl or a 5 or 7 membered monocyclic nitrogen containing heteroaryl;

R^{16} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyoalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{20} is selected from the group consisting of $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{21} is selected from the group consisting of $-OR^{17}$, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{12}, R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally

substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

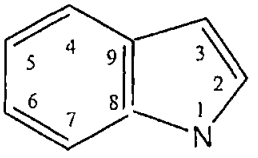
R^{17} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and $-C(O)R^{18}$;

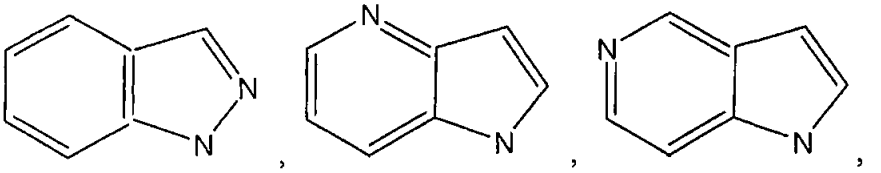
R^{18} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyoalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

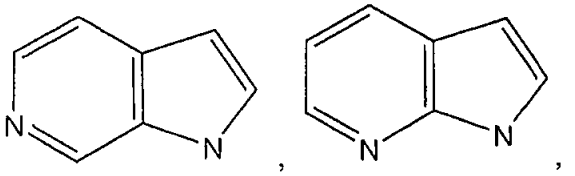
Z is O or S; and

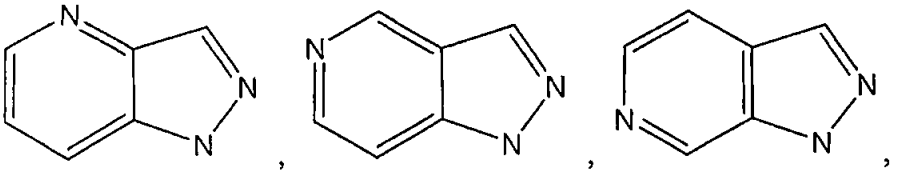
n = 0, 1, or 2.

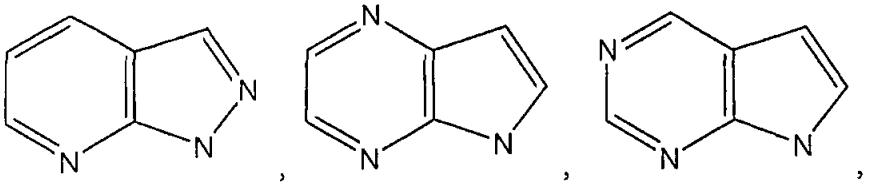
[0030] In some embodiments involving compounds of Formula I, the bicyclic core shown for Formula I has one of the following structures:

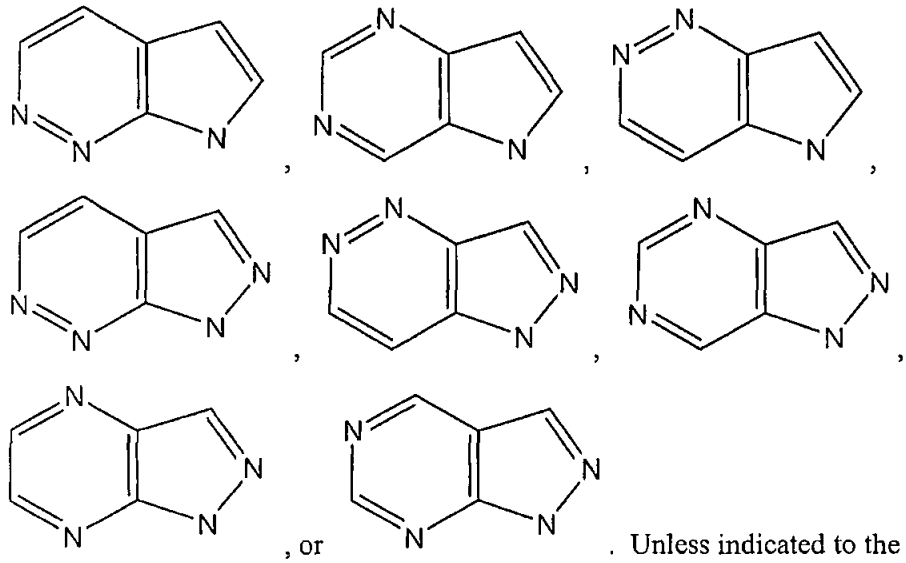








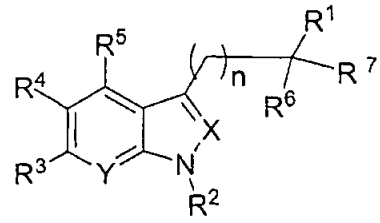




. Unless indicated to the contrary, reference to positional numbering of bicyclic structures provided herein is based on the numbering of indole as shown above.

[0031] In some embodiments involving compounds of Formula I including a bicyclic core as shown above, such compounds can include substituents as described for Formula I, with the understanding that ring nitrogens other than the nitrogen corresponding to position 1 of the indole structure are unsubstituted. In some embodiments, the compounds have one of the bicyclic cores shown above and substitution selections as shown herein for compounds having an indolyl core; the compounds have one of the bicyclic cores above, and the substituents shown at the 5-position are instead attached at the 6-position.

[0032] In some embodiments involving compounds of Formula I, the compounds have a structure of Formula Ia, namely



Formula Ia

all salts, prodrugs, tautomers and isomers thereof,

wherein:

U is CR^8, wherein R^8 is R^5;

V is CR^8, wherein R^8 is R^4;

W is CR^8, wherein R^8 is R^3;

R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^9$, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{21}$; and

n, X, Y, R^1, R^2, R^6, R^7, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{20} and R^{21} are as defined in Formula I above.

[0033] In some embodiments, such compounds are compounds of Formula I with Y=N; with Y=CR^8; with Y=CH; with all R substituents other than R^1, R^2, and R^4 as H (for each of X as N, X as CH, and X as CR^8); and with R^6 and R^7 as H (for each of X as N, X as CH, and X as CR^8).

[0034] In some embodiments, n=1; n=1 and X and/or Y is CH; n=1, X and/or Y is CH, and R^6 and R^7 are H; n=1 and X and/or Y=CR^8.

[0035] In some embodiments, n=1, R^2 is $-S(O)_2R^{21}$, with R^{21} being optionally substituted aryl or optionally substituted heteroaryl. In some embodiments, in which n=1, and R^2 is $-S(O)_2R^{21}$, with R^{21} being optionally substituted aryl or optionally substituted heteroaryl, the aryl group is a 5- or 6-membered ring; the aryl group is a 6-membered ring; in further embodiments in which the aryl group is a 6-membered ring, the ring is substituted with one or two groups independently selected from the group consisting of halogen, aryl substituted lower alkyl, heteroaryl substituted lower alkyl, lower alkoxy, aryl substituted lower alkoxy, heteroaryl substituted lower alkoxy, cycloalkyl, aryl, aryloxy, heteroaryl, and heteroaryloxy; in further embodiments in which a 6-membered ring is substituted with halogen or lower alkoxy, the ring is substituted at the 3-position (meta), 4-position (para), or 3- and 4-positions (meta and para); in further embodiments in which a 6-membered ring is substituted at the 4-position, or 3- and 4-positions, or the 4-position substitutent is lower alkyl, or the 4-position substituent is not lower alkyl, or the 4-position substituent is halogen (e.g., fluoro or chloro), or the 3- and 4-position substituents are fluoro, or the 3- and 4-position substitutents are chloro, or one of the 3- and 4-position substituents is fluoro and the other is chloro, or the 3-position is halogen (e.g., fluoro or chloro) and the 4-position is lower alkoxy (e.g., methoxy or ethoxy), or the 3-position is lower alkoxy (e.g., methoxy or ethoxy) and the 4-position is halogen (e.g., fluoro or

chloro), or the 3-position is chloro and the 4-position is lower alkoxy, or the 3-position is lower alkoxy and the 4-position is chloro; or the 6-membered ring is fused with a second 5- or 6-membered aromatic or non-aromatic carbocyclic or heterocyclic ring. In further embodiments in which the aryl group is a 5-membered ring, the ring is substituted with one or two groups located at ring positions not adjacent to the ring atom linked to the $-S(O)_2-$ group; or the 5-membered ring is substituted with one or two ring substituents selected from the group consisting of halogen, aryl substituted lower alkyl, heteroaryl substituted lower alkyl, lower alkoxy, aryl substituted lower alkoxy, heteroaryl substituted lower alkoxy, cycloalkyl, aryl, aryloxy, heteroaryl, and heteroaryloxy; the ring is substituted with chloro; the ring is substituted with lower alkoxy; or the ring is substituted with lower alkyl; or the ring is substituted with optionally substituted aryl or optionally substituted heteroaryl; or the ring is substituted with optionally substituted aryloxy or optionally substituted heteroaryloxy; or the 5-membered ring is fused with a second 5- or 6-membered aromatic or non-aromatic carbocyclic or heterocyclic ring.

[0036] In some embodiments in which n=1, and R^2 is $-S(O)_2R^{21}$, with R^{21} being optionally substituted aryl or optionally substituted heteroaryl, R^4 is not H or lower alkoxy, or R^4 is not H or OR^9.

[0037] In some embodiments, n=2; or n=2 and X and/or Y is CH; or n=2, X and/or Y is CH, and R^6 and R^7 are H; or n=2 and X and/or Y is CR^8; or n=2 and X and/or Y are N.

[0038] In some embodiments in which n=2, R^4 is not H, halogen, lower alkyl, lower alkoxy, or lower alkylthio; or R^4 is not H, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} alkylthio; R^4 is not C_{1-3} alkoxy; or R^4 is not methoxy.

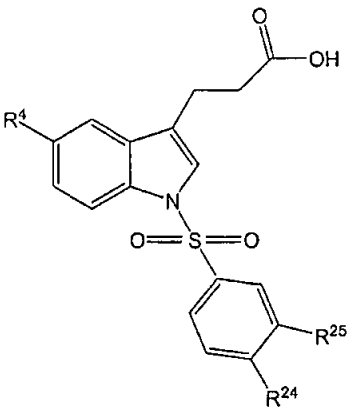
[0039] In some embodiments, n=2, R^2 is $-S(O)_2R^{21}$, with R^{21} being optionally substituted aryl or optionally substituted heteroaryl. In some embodiments, in which n=2, and R^2 is $-S(O)_2R^{21}$, with R^{21} being optionally substituted aryl or optionally substituted heteroaryl, the aryl group is a 5- or 6-membered ring; or the aryl group is a 6-membered ring; in further embodiments in which the aryl group is a 6-membered ring, the ring is substituted with one or two groups independently selected from the group consisting of halogen, lower alkyl, aryl substituted lower alkyl, heteroaryl substituted lower alkyl, aryl substituted lower alkoxy, heteroaryl substituted lower alkoxy, cycloalkyl, aryl, aryloxy, heteroaryl, and heteroaryloxy; in further embodiments in which a 6-membered ring is

substituted with halogen or lower alkoxy, the ring is substituted at the 3-position (meta), 4-position (para), or 3- and 4-positions (meta and para); in further embodiments in which a 6-membered ring is substituted at the 4-position, or 3- and 4-positions, the 4-position substitutent is lower lower alkyl, or the 4-position substituent is not lower alkyl, or the 4-position substituent is halogen (e.g., fluoro or chloro), or the 3- and 4-position substituents are fluoro, or the 3- and 4-position substitutents are chloro, or one of the 3- and 4-position substituents is fluoro and the other is chloro, or the 3-position is halogen (e.g., fluoro or chloro) and the 4-position is lower alkoxy (e.g., methoxy or ethoxy), or the 3-position is lower alkoxy (e.g., methoxy or ethoxy) and the 4-position is halogen (e.g., fluoro or chloro), or the 3-position is chloro and the 4-position is lower alkoxy, or the 3-position is lower alkoxy and the 4-position is chloro; or the 6-membered ring is fused with a second 5- or 6-membered aromatic or non-aromatic carbocyclic or heterocyclic ring. In further embodiments in which the aryl group is a 5-membered ring, the ring is substituted with one or two groups located at ring positions not adjacent to the ring atom linked to the $-S(O)_2-$ group; or the 5-membered ring is substituted with one or two ring substituents selected from the group consisting of halogen, aryl substituted lower alkyl, heteroaryl substituted lower alkyl, lower alkoxy, aryl substituted lower alkoxy, heteroaryl substituted lower alkoxy, cycloalkyl, aryl, aryloxy, heteroaryl, and heteroaryloxy; or the ring is substituted with chloro; or the ring is substituted with lower alkoxy; or the ring is substituted with lower alkyl; or the ring is substituted with optionally substituted aryl or optionally substituted heteroaryl; or the ring is substituted with optionally substituted aryloxy or optionally substituted heteroaryloxy; or the 5-membered ring is fused with a second 5- or 6-membered aromatic or non-aromatic carbocyclic or heterocyclic ring.

[0040] In some embodiments, in which n=2, and R^2 is $-S(O)_2R^{21}$, with R^{21} being a substituted 6-membered aryl group, the substitution on the aryl group is not methoxy, or the substitution on the aryl group is not lower alkoxy; or R^4 and the substitution on the aryl group are not both lower alkoxy; or R^4 and the substitution on the aryl group are not both methoxy; or R^4 is not lower alkoxy; or R^4 is not methoxy.

[0041] Certain further embodiments include compounds described for corresponding embodiments as described above for both n=1 and n=2.

[0042] In some embodiments, compounds of Formula I have a structure of Formula Ib as shown below:



Formula Ib

all salts, prodrugs, tautomers and isomers thereof,

wherein:

U is CR^8, wherein R^8 is H;

V is CR^8, wherein R^8 is R^4;

W is CR^8, wherein R^8 is H;

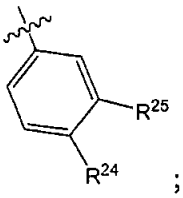
X is CR^8, wherein R^8 is H;

Y is CR^8, wherein R^8 is H;

n is 1;

R^1 is –COOH;

R^6 and R^7 are hydrogen;

R^2 is $-S(O)_2R^{21}$, wherein R^{21} is  ;

R^4 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^9$, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{21}$;

R^{24} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, $-OR^{19}$, and $-O(CH_2)_pO$-aryl;

p is 1, 2, 3, or 4;

R^{25} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, and $-OR^{19}$; or

R^{24} and R^{25} combine to form cycloalkyl, heterocycloalkyl, aryl or heteroaryl fused with the phenyl ring;

R^{19} is selected from the group consisting of optionally substituted lower alkyl and optionally substituted aryl; and

R^9, R^{10}, R^{11}, R^{20} and R^{21} are as defined in Formula I above.

[0043] In some embodiments, R^4 is optionally substituted lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy), optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted lower alkyl (e.g., methyl or ethyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or halogen.

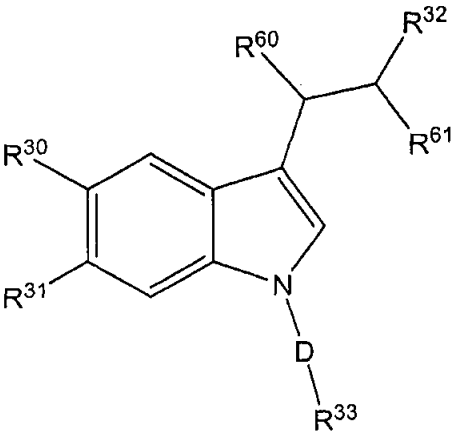
[0044] In some embodiments, R^4 is optionally substituted lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy), optionally substituted lower alkyl (e.g., methyl or ethyl), optionally substituted aryl, optionally substituted heteroaryl, or halogen.

[0045] In some embodiments, compounds of Formula I can be as specified for Formula Ib, but with the phenyl ring to which R^{24} and R^{25} are attached as a heteroaryl ring, wherein when the heteroaryl ring is a 5-membered ring, R^{24} and R^{25} are not attached to the 5-membered ring atoms that are adjacent to the 5-membered ring atom attached to the sulfonyl group shown in Formula Ib.

[0046] In some embodiments of compounds of Formula Ib, R^4 is lower alkoxy and R^{24} and R^{25} are chloro; or R^4 is lower alkoxy and R^{24} and R^{25} are fluoro; or R^4 is lower alkoxy and R^{24} is lower alkoxy; or R^4 is lower alkoxy and R^{24} is lower alkyl; or R^4 is methoxy or ethoxy and R^{24} and R^{25} are chloro; or R^4 is methoxy or ethoxy and R^{24} is lower alkoxy; or R^4 is methoxy or ethoxy and R^{24} is lower alkyl.

[0047] In some embodiments of compounds of Formula Ib, R^{24} and R^{25} are not lower alkyl; or R^{24} is H and R^{25} is not lower alkyl; or R^{25} is H and R^{24} is not lower alkyl.

[0048] In some embodiments, the invention involves compounds of Forumula II as follows:

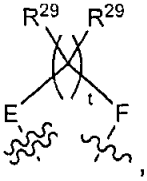


Formula II

all salts, prodrugs, tautomers and isomers thereof,

wherein:

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$; or

R^{30} and R^{31} combine to form a fused ring, wherein the combined R^{30} and R^{31} are of the formula 

, wherein  indicates the point of attachment of R^{30} to the indole ring and  indicates the point of attachment of R^{31} to the indole ring;

E and F are independently selected from the group consisting of $CR^{29}R^{29}$, O, $S(O)_2$ and NR^{44};

R^{29} at each occurrence is independently selected from the group consisting of hydrogen, fluoro, optionally fluoro substituted lower alkyl, optionally fluoro substituted lower alkoxy, and optionally fluoro substituted lower alkylthio;

R^{44} is hydrogen or lower alkyl;

t is 1 or 2;

R^{32} is selected from the group consisting of $-C(O)OR^{26}$, $-C(O)NR^{27}R^{28}$, and a carboxylic acid isostere;

R^{33} is L-R^{42} or heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -OH, $-NO_2$, -CN, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

L is $-(CR^{51}R^{52})_m-$ or $-CR^{55}=CR^{56}-$;

D is $-CR^{51}R^{52}-$ or $-S(O)_2-$;

R^{34} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{34} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the O of $-OR^{34}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{34} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the O of $-OR^{34}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, and $-C(Z)NR^{38}R^{39}$;

R^{35} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{35} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the S of $-SR^{35}$ or the O of $-OR^{35}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{35} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the S of $-SR^{35}$ or the O of $-OR^{35}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{36} and R^{37} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{36} and/or R^{37} are optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{36}R^{37}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{36} and/or R^{37} are optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{36}R^{37}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_nR^{41}$, and $-S(O)_2NR^{38}R^{39}$;

R^{38} and R^{39} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{38} and/or R^{39} are optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $NR^{38}R^{39}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{38} and/or R^{39} are optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $NR^{38}R^{39}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{40} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{40} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to -C(Z)-, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{40} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to -C(Z)-, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, and $-OR^{35}$;

R^{41} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{41} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to $-S(O)_n-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{41} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to $-S(O)_n-$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally optionally substituted aryl, and optionally substituted heteroaryl;

R^{42} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -OH, $-NO_2$, -CN, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

R^{51} and R^{52} are independently selected from the group consisting of hydrogen, fluoro, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

or any two of R^{51} and R^{52} on the same carbon or on adjacent carbons may be combined to form an optionally substituted 3-7 membered monocyclic cycloalkyl or optionally substituted 5-7 membered monocyclic heterocycloalkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{55} and R^{56} combine to form an optionally substituted 5-7 membered monocyclic cycloalkyl or optionally substituted 5-7 membered monocyclic heterocycloalkyl;

R^{60} and R^{61} are each hydrogen, or R^{60} and R^{61} combine to form optionally substituted 3-7 membered monocyclic cycloalkyl;

R^{26} is selected from the group consisting of hydrogen, lower alkyl, phenyl, 5-7 membered monocyclic heteroaryl, 3-7 membered monocyclic cycloalkyl, and 5-7 membered monocylic heterocycloalkyl, wherein phenyl, monocyclic heteroaryl, monocyclic cycloalkyl and monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio, and wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio and fluoro substituted lower alkylthio, provided, however, that when R^{26} is lower alkyl, any substitution on the lower alkyl carbon bound to the O of OR^{26} is fluoro;

R^{27} and R^{28} are independently selected from the group consisting of hydrogen, lower alkyl, phenyl, 5-7 membered monocyclic heteroaryl, 3-7 membered monocyclic cycloalkyl, and 5-7 membered monocylic heterocycloalkyl, wherein phenyl, monocyclic heteroaryl, monocyclic cycloalkyl and monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio, and wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio and fluoro substituted lower alkylthio, provided, however, that when R^{27} and/or R^{28} is lower

alkyl, any substitution on the lower alkyl carbon bound to the N of $NR^{27}R^{28}$ is fluoro; or

R^{27} and R^{28} together with the nitrogen to which they are attached form a 5-7 membered monocyclic heterocycloalkyl or a 5 or 7 membered nitrogen containing monocyclic heteroaryl, wherein the monocyclic heterocycloalkyl or monocyclic nitrogen containing heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;

n is 1, or 2;

m is 1, 2, or 3; and

Z is O or S, provided, however, that when D is $-S(O)_2-$, R^{30} is $-OCH_3$, R^{31} is H, and R^{32} is -COOH or $-COOCH_3$, R^{33} is not unsubstituted thiophenyl

[0049] In one embodiment of compounds of Formula II, R^{33} is not unsubstituted thiophenyl. In another embodiment, R^{33} is substituted heteroaryl. In another embodiment, R^{33} is heteroaryl substituted with one or more substituents selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$, wherein one of R^{36} and R^{37} is selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$, and $-S(O)_2NR^{38}R^{39}$, and the other of R^{36} and R^{37} is hydrogen or lower alkyl, one of R^{38} and R^{39} is selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, and the other of R^{38} and R^{39} is hydrogen or lower alkyl, and wherein R^{34}, R^{35}, R^{40}, and R^{41} are independently selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted aryl or

optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

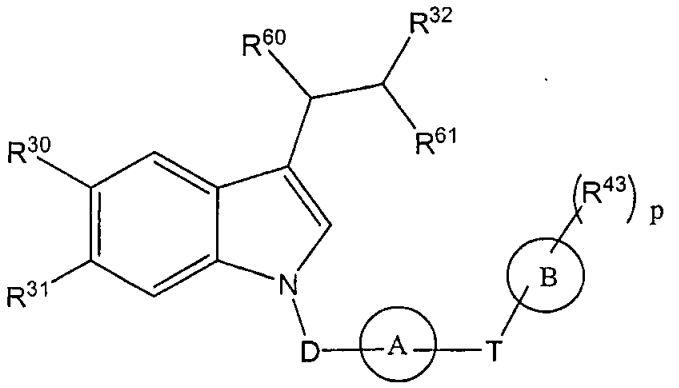
[0050] In one embodiment of compounds of Formula II, R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl, or R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen. In one embodiment, R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, and optionally substituted lower alkoxy, preferably wherein R^{31} is hydrogen and R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy.

[0051] In one embodiment of compounds of Formula II, D is $-CR^{51}R^{52}-$, wherein each R^{51} and R^{52} are independently halogen or optionally substituted lower alkyl, or any two of R^{51} and R^{52} on the same carbon or on adjacent carbons combine to form an optionally substituted 3-7 membered monocyclic cycloalkyl or optionally substituted 3-7 membered monocyclic heterocycloalkyl, R^{33} is substituted heteroaryl, and R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, and optionally substituted lower alkoxy, preferably wherein D is $-CH_2-$, R^{31} is hydrogen and R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy.

[0052] In one embodiment of compounds of Formula II, D is $-S(O)_2-$, R^{33} is substituted heteroaryl, and R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, and optionally substituted lower alkoxy, preferably wherein R^{31} is hydrogen and R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy.

[0053] Further to any of the above embodiments of compounds of Formula II, R^{60} and R^{61} are hydrogen and R^{32} is $-C(O)OR^{26}$, preferably -COOH.

[0054] In some embodiments, the invention involves compounds of Formula III as follows:



Formula III

all salts, prodrugs, tautomers and isomers thereof,

wherein:

D, R^{30}, R^{31}, R^{32}, R^{60}, and R^{61} are as defined in Formula II;

A is arylene or heteroarylene, wherein arylene or heteroarylene are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, lower alkyl, lower alkoxy, and lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, lower alkoxy, and lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro;

T is a covalent bond or is selected from the group consisting of $-(CR^{51}R^{52})_m-$, $-(CR^{51}R^{52})_qO(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{53}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(O)_n(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}S(O)_2(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(O)_2NR^{54}(CR^{51}R^{52})_r-$, and $-(CR^{51}R^{52})_qNR^{54}S(O)_2NR^{54}(CR^{51}R^{52})_r-$, wherein R^{51}, R^{52} and m are as defined in Formula II above;

q and r are independently 0, 1, or 2;

B is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R^{43} at each occurence is independently selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted

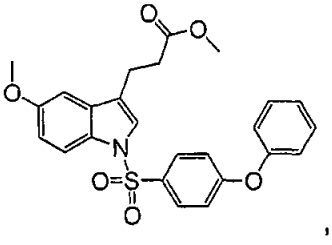
heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

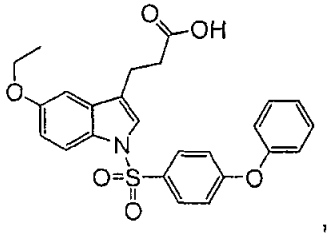
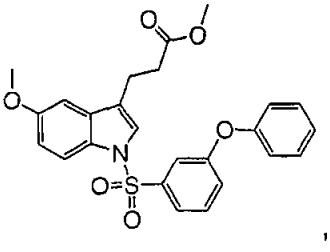
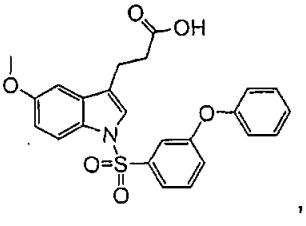
R^{53} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{53} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{53}-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{53} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{53}-$, optionally substituted cycloalkyl, optionally substituted heterocyclyoalkyl, optionally substituted aryl, optionally substituted heteroaryl,$-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_2R^{41}$;

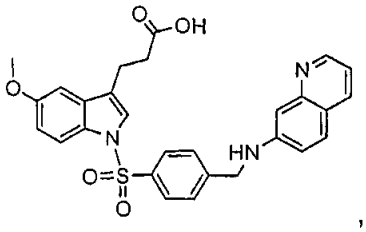
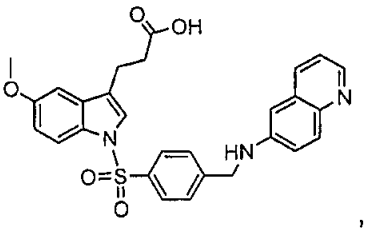
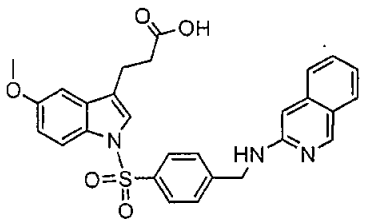
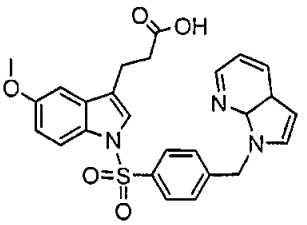
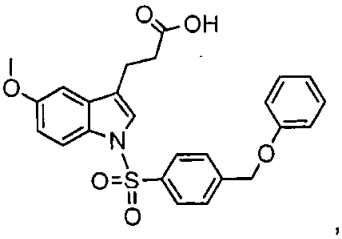
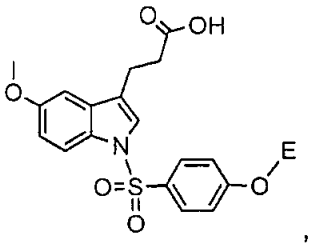
R^{54} at each occurrence is independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{54} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{54}-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{54} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{54}-$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

p is 0, 1, 2 or 3; and

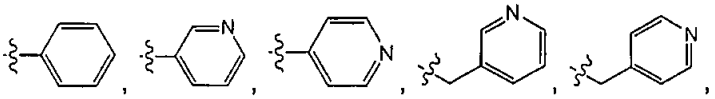
n, Z, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, and R^{41} are as defined for Formula II above,

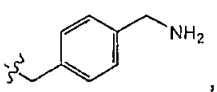
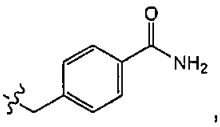
provided, however, the compound is not  ,

 ,  ,  ,

or ,

wherein E is 

 , or  , wherein indicates the point of attachment of E to O.

[0055] In one embodiment of compounds of Formula III, when A is phenyl, T is meta or para to D, and B is phenyl, pyridinyl, 7-azaindolyl, or quinolinyl, then p is 1, 2 or 3, provided, however, that when T is $-OCR^{51}R^{52}-$ and para to D, B is phenyl, p is 1, and R^{43} is para to T, R^{43} is not CH_2NH_2 or $C(O)NH_2$. In another embodiment, A is other than phenyl. In another embodiment, B is other than phenyl, pyridinyl, 7-azaindolyl, or quinolinyl.

[0056] In one embodiment of compounds of Formula III, A is heteroaryl optionally substituted with halogen, -OH, lower alkyl, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro.

In one embodiment R^{43} is selected from the group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$, wherein R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} and R^{41} are not optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or lower alkyl substituted with optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, A is heteroaryl optionally substituted with halogen, -OH, lower alkyl, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, and R^{43} is selected from the group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$, wherein R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} and R^{41} are not optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or lower alkyl substituted with optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0057] In one embodiment of compounds of Formula III, R^{30} and R^{31} are selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl, or R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen. In one embodiment, R^{30} and R^{31} are independently optionally substituted lower alkoxy, or R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen. In one embodiment, R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, and optionally substituted lower alkoxy, preferably wherein R^{31} is hydrogen and R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy.

[0058] In another embodiment of compounds of Formula III, A is phenyl and T-B is ortho to D. In one embodiment, A is heteroaryl optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro. In one embodiment, A is phenyl optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy or lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, and T-B is ortho to D.

[0059] In another embodiment of compounds of Formula III, R^{53} and R^{54} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted aryl, and optionally substituted heteroaryl. In another embodiment, R^{53} and R^{54} are independently hydrogen or optionally substituted lower alkyl, where lower alkyl is preferably optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that substitution of the carbon that is bound to the N of $-NR^{53}-$ or $-NR^{54}-$ is fluoro.

[0060] In one embodiment of compounds of Formula III, D is $-S(O)_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, and T is a covalent bond, -O-, or $-NCH_3-$. In one embodiment, D is $-S(O)_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, T is a covalent bond, -O-, or $-NCH_3-$, and each R^{43} is independently selected from the

group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkoxy, and optionally substituted lower alkylthio, preferably halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro.

[0061] In one embodiment of compounds of Formula III, D is $-S(O)_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl, wherein phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl are optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, T is a covalent bond, -O-, or $-NCH_3-$, and B is phenyl, pyridinyl, pyrazolyl, or isoxazolyl. In one embodiment, D is $-S(O)_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl, wherein phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl are optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, T is a covalent bond, -O-, or $-NCH_3-$, B is phenyl, pyridinyl, pyrazolyl, or isoxazolyl, and each R^{43} is independently selected from the group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkoxy, and optionally substituted lower alkylthio, preferably halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro.

[0062] In one embodiment of compounds of Formula III, D is $-S(O)_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy,

preferably lower alkoxy, A is phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl, wherein phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl are optionally substituted with fluoro, chloro, optionally fluoro substituted lower alkyl, or optionally fluoro substituted lower alkoxy, T is a covalent bond, -O-, or $-NCH_3-$, B is phenyl, pyridinyl, pyrazolyl, or isoxazolyl, and each R^{43} is independently selected from the group consisting of fluoro, chloro, optionally fluoro substituted lower alkyl, and optionally fluoro substituted lower alkoxy.

[0063] In one embodiment of compounds of Formula III, D is $-CR^{51}R^{52}-$, preferably $-CH_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, and T is a covalent bond, -O-, or $-NCH_3-$. In one embodiment, D is $-CR^{51}R^{52}-$, preferably $-CH_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, T is a covalent bond, -O-, or $-NCH_3-$, and each R^{43} is independently selected from the group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkoxy, and optionally substituted lower alkylthio, preferably halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro.

[0064] In one embodiment of compounds of Formula III, D is $-CR^{51}R^{52}-$, preferably $-CH_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl, wherein phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl are

optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, T is a covalent bond, -O-, or $-NCH_3-$, and B is phenyl, pyridinyl, pyrazolyl, or isoxazolyl. In one embodiment, D is $-CR^{51}R^{52}-$, preferably $-CH_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl, wherein phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl are optionally substituted with halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro, T is a covalent bond, -O-, or $-NCH_3-$, B is phenyl, pyridinyl, pyrazolyl, or isoxazolyl, and each R^{43} is independently selected from the group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkoxy, and optionally substituted lower alkylthio, preferably halogen, lower alkyl, -OH, lower alkoxy, or lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with fluoro, -OH, lower alkoxy, or lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro.

[0065] In one embodiment of compounds of Formula III, D is $-CR^{51}R^{52}-$, preferably $-CH_2-$, R^{60} and R^{61} are hydrogen, R^{31} is hydrogen, R^{30} is halogen or optionally fluoro substituted lower alkoxy, preferably lower alkoxy, A is phenyl, thiophenyl, pyridinyl, thiazolyl, or oxazolyl optionally substituted with fluoro, chloro, optionally fluoro substituted lower alkyl, or optionally fluoro substituted lower alkoxy, T is a covalent bond, -O-, or $-NCH_3-$, B is phenyl, pyridinyl, pyrazolyl, or isoxazolyl, and each R^{43} is independently selected from the group consisting of fluoro, chloro, optionally fluoro substituted lower alkyl, and optionally fluoro substituted lower alkoxy.

[0066] Further to any of the above embodiments of compounds of Formula III, R^{32} is $-C(O)OR^{26}$, preferably -COOH.

[0067] In some embodiments of the above compounds, compounds are excluded where N (except where N is a heteroaryl ring atom), O, or S is bound to a carbon that is also

bound to N (except where N is a heteroaryl ring atom), O, or S; or where N (except where N is a heteroaryl ring atom), O, C(S), C(O), or $S(O)_n$ (n is 0-2) is bound to an alkene carbon of an alkenyl group or bound to an alkyne carbon of an alkynyl group; accordingly, in some embodiments compounds that include linkages such as the following are excluded from the present invention: $-NR-CH_2-NR-$, $-O-CH_2-NR-$, $-S-CH_2-NR-$, $-NR-CH_2-O-$, $-O-CH_2-O-$, $-S-CH_2-O-$, $-NR-CH_2-S-$, $-O-CH_2-S-$, $-S-CH_2-S-$, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, $-S(O)_{0-2}-CH=CH-$, $-CH=CH-S(O)_{0-2}-$, $-S(O)_{0-2}-C≡C-$, $-C≡C-S(O)_{0-2}-$, -C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)-, or -C(S)-C≡C-.

[0068] Reference to compounds of Formulae I, II and III herein includes specific reference to sub-groups and species of compounds of Formulae I, II and III described herein (including all embodiments as described above, e.g. reference to Formula I includes reference to Formulae Ia and Ib) unless indicated to the contrary. In specifying a compound or compounds of Formulae I, II, or III, unless clearly indicated to the contrary, specification of such compound(s) includes pharmaceutically acceptable salts of the compound(s).

[0069] Another aspect of the invention relates to novel use of compounds of Formulae I, Ia, Ib, II, or III for the treatment of diseases associated with PPARs.

[0070] Another aspect of this invention provides compositions that include a therapeutically effective amount of a compound of Formulae II or III and at least one pharmaceutically acceptable carrier, excipient, and/or diluent. The composition can include a plurality of different pharmacalogically active compounds, including one or more compounds of Formulae I, II or III.

[0071] In another aspect, compounds of Formulae II or III can be used in the preparation of a medicament for the treatment of a PPAR-mediated disease or condition or a disease or condition in which modulation of a PPAR provides a therapeutic benefit. In a further aspect, the disease or condition is selected from the group consisting of weight disorders (e.g. obesity, overweight condition, bulimia, and anorexia nervosa), lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and

low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), cardiovascular disease (e.g. hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease), inflammatory diseases (e.g. autoimmune diseases such as vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, and multiple sclerosis, diseases involving airway inflammation such as asthma and chronic obstructive pulmonary disease, and inflammation in other organs, such as polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), skin disorders (e.g. epithelial hyperproliferative diseases such as eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and chronic dermatitis, and impaired wound healing), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and demyelinating disease, including acute disseminated encephalomyelitis and Guillain-Barre syndrome), coagulation disorders (e.g. thrombosis), gastrointestinal disorders (e.g. infarction of the large or small intestine), genitourinary disorders (e.g. renal insufficiency, erectile dysfunction, urinary incontinence, and neurogenic bladder), ophthalmic disorders (e.g. ophthalmic inflammation, macular degeneration, and pathologic neovascularization), infections (e.g. HCV, HIV, and Helicobacter pylori), neuropathic or inflammatory pain, infertility, and cancer. In some embodiments, the disease or condition is selected from the group consisting of obesity, overweight condition, bulimia, anorexia nervosa, hyperlipidemia, dyslipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, a diabetic complication of neuropathy, nephropathy, retinopathy, cataracts, hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, asthma, chronic obstructive pulmonary disease, eczema, psoriasis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, thrombosis, macular degeneration, infertility, and cancer. In some embodiments, the disease or condition is selected from the group

consisting of vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome, infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic pain, inflammatory pain, and infertility. In some embodiments, the disease or condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

[0072] In another aspect, the invention provides kits that include a compound or composition as described herein. In some embodiments, the compound or composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the compound or composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal,e.g., a human; the compound or composition is approved for administration to a mammal, e.g., a human for a PPAR-mediated disease or condition; the kit includes written instructions or other indication that the compound or composition is suitable or approved for administration to a mammal, e.g., a human, for a PPAR-mediated disease or condition; the compound or composition is packaged in unit does or single dose form, e.g., single dose pills, capsules, or the like. In some embodiments, the compound or composition of the kits of the invention are approved for a medical indication selected from the group consisting of obesity, overweight condition, bulimia, anorexia nervosa, hyperlipidemia, dyslipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, low HDL, Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, a diabetic complication of neuropathy, nephropathy, retinopathy, diabetic foot ulcer or cataracts, hypertension, coronary heart

disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease, vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, eczema, psoriasis, dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome, thrombosis, infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic or inflammatory pain, infertility, and cancer. In some embodiments, the compound or composition of the kits of the invention are approved for a medical indication selected from the group consisting of obesity, overweight condition, bulimia, anorexia nervosa, hyperlipidemia, dyslipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, a diabetic complication of neuropathy, nephropathy, retinopathy, cataracts, hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, asthma, chronic obstructive pulmonary disease, eczema, psoriasis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, thrombosis, macular degeneration, infertility, and cancer. In some embodiments, the compound or composition of the kits of the invention are approved for a medical indication selected from the group consisting of vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome,

infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic pain, inflammatory pain, and infertility. In some embodiments, the compound or composition of the kits of the invention are approved for a medical indication selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

[0073] In another aspect, the invention provides a method of treating or prophylaxis of a disease or condition in an animal subject, e.g., a PPAR-mediated disease or condition or a disease or condition in which modulation of a PPAR provides a therapeutic benefit, by administering to the subject a therapeutically effective amount of a compound of Formulae I, II, or III, a prodrug of such compound, or a pharmaceutically acceptable salt of such compound or prodrug. The compound can be administered alone or can be administered as part of a composition. In one aspect, the method involves administering to the subject an effective amount of a compound of Formulae I, II, or III, in combination with one or more other therapies for the disease or condition.

[0074] In another aspect, the invention provides a method of treating or prophylaxis of a PPAR-mediated disease or condition or a disease or condition in which modulation of a PPAR provides a therapeutic benefit, wherein the method involves administering to the subject a therapeutically effective amount of a composition including a compound of Formulae I, II or III.

[0075] In aspects and embodiments involving treatment or prophylaxis of a disease or condition, the disease or condition is selected from the group consisting of weight disorders (e.g. obesity, overweight condition, bulimia, and anorexia nervosa), lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), cardiovascular disease (e.g.

hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease), inflammatory diseases (e.g. autoimmune diseases such as vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, and multiple sclerosis, diseases involving airway inflammation such as asthma and chronic obstructive pulmonary disease, and inflammation in other organs, such as polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), skin disorders (e.g. epithelial hyperproliferative diseases such as eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and chronic dermatitis, and impaired wound healing), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and demyelinating disease, including acute disseminated encephalomyelitis and Guillain-Barre syndrome), coagulation disorders (e.g. thrombosis), gastrointestinal disorders (e.g. infarction of the large or small intestine), genitourinary disorders (e.g. renal insufficiency, erectile dysfunction, urinary incontinence, and neurogenic bladder), ophthalmic disorders (e.g. ophthalmic inflammation, macular degeneration, and pathologic neovascularization), infections (e.g. HCV, HIV, and Helicobacter pylori), neuropathic or inflammatory pain, infertility, and cancer. In some embodiments, the disease or condition is selected from the group consisting of obesity, overweight condition, bulimia, anorexia nervosa, hyperlipidemia, dyslipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, a diabetic complication of neuropathy, nephropathy, retinopathy, cataracts, hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, asthma, chronic obstructive pulmonary disease, eczema, psoriasis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, thrombosis, macular degeneration, infertility, and cancer. In some embodiments, the disease or condition is selected from the group consisting of vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease,

systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome, infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic pain, inflammatory pain, and infertility. In some embodiments, the disease or condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

[0076] In certain aspects and embodiments, compounds of Formulae II or III are used in the treatment or prophylaxis of a disease or condition selected from the group consisting of weight disorders (e.g. obesity, overweight condition, bulimia, and anorexia nervosa), lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), cardiovascular disease (e.g. hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease), inflammatory diseases (e.g. autoimmune diseases such as vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, and multiple sclerosis, diseases involving airway inflammation such as asthma and chronic obstructive pulmonary disease, and inflammation in other organs, such as polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), skin disorders (e.g. epithelial hyperproliferative diseases such as eczema and psoriasis, dermatitis, including atopic

dermatitis, contact dermatitis, allergic dermatitis and chronic dermatitis, and impaired wound healing), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and demyelinating disease, including acute disseminated encephalomyelitis and Guillain-Barre syndrome), coagulation disorders (e.g. thrombosis), gastrointestinal disorders (e.g. infarction of the large or small intestine), genitourinary disorders (e.g. renal insufficiency, erectile dysfunction, urinary incontinence, and neurogenic bladder), ophthalmic disorders (e.g. ophthalmic inflammation, macular degeneration, and pathologic neovascularization), infections (e.g. HCV, HIV, and Helicobacter pylori), neuropathic or inflammatory pain, infertility, and cancer. In some embodiments, the disease or condition is selected from the group consisting of obesity, overweight condition, bulimia, anorexia nervosa, hyperlipidemia, dyslipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, a diabetic complication of neuropathy, nephropathy, retinopathy, cataracts, hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, asthma, chronic obstructive pulmonary disease, eczema, psoriasis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, thrombosis, macular degeneration, infertility, and cancer. In some embodiments, the disease or condition is selected from the group consisting of vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome, infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic pain, inflammatory pain, and infertility. In some embodiments, the disease or condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome,

Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

[0077] In certain aspects and embodiments, compounds of Formulae I, Ia, Ib, II, or III are used in the treatment or prophylaxis of a disease or condition selected from the group consisting of inflammatory diseases (e.g. autoimmune diseases such as vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, and multiple sclerosis, diseases involving airway inflammation such as asthma and chronic obstructive pulmonary disease, and inflammation in other organs, such as polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), skin disorders (e.g. dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and chronic dermatitis, and impaired wound healing), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and demyelinating disease, including acute disseminated encephalomyelitis and Guillain-Barre syndrome), gastrointestinal disorders (e.g. infarction of the large or small intestine), genitourinary disorders (e.g. renal insufficiency, erectile dysfunction, urinary incontinence, and neurogenic bladder), ophthalmic disorders (e.g. ophthalmic inflammation, macular degeneration, and pathologic neovascularization), infections (e.g. HCV, HIV, and Helicobacter pylori), neuropathic or inflammatory pain, and infertility. In some aspects and embodiments, PPAR modulators with chemical structure of Formulae I, Ia, or Ib are used in the treatment or prophylaxis of a disease or condition selected from the group consisting of neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

[0078] In some embodiments of aspects involving compounds of Formulae I, II, or III the compound is specific for any one or any two of PPARα, PPARγ and PPARδ, e.g. specific for PPARα; specific for PPARδ; specific for PPARγ; specific for PPARα and PPARδ; specific for PPARα and PPARγ; or specific for PPARδ and PPARγ. Such specificity means that the compound has at least 5-fold greater activity (preferably at least

5-, 10-, 20-, 50-, or 100-fold or more greater activity) on the specific PPAR(s) than on the other PPAR(s), where the activity is determined using a biochemical assay suitable for determining PPAR activity, e.g., any assay known to one skilled in the art or as described herein. In another embodiment, compounds have significant activity on all three of PPARα, PPARδ, and PPARγ.

[0079] In some embodiments, a compound of Formulae I, II, or III will have an EC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to at least one of PPARα, PPARγ and PPARδ as determined in a generally accepted PPAR activity assay. In one embodiment, a compound of any of Formulae I, II, or III will have an EC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to at least any two of PPARα, PPARγ and PPARδ. In one embodiment, a compound of any of Formulae I, II, or III will have an EC_{50} of less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to all three of PPARα, PPARγ and PPARδ. Further to any of the above embodiments, a compound of the invention may be a specific agonist of any one of PPARα, PPARγ and PPARδ, or any two of PPARα, PPARγ and PPARδ. A specific agonist of one of PPARα, PPARγ and PPARδ is such that the EC_{50} for one of PPARα, PPARγ and PPARδ will be at least about 5-fold, also 10-fold, also 20-fold, also 50-fold, or at least about 100-fold less than the EC_{50} for the other two of PPARα, PPARγ and PPARδ. A specific agonist of two of PPARα, PPARγ and PPARδ is such that the EC_{50} for each of two of PPARα, PPARγ and PPARδ will be at least about 5-fold, also 10-fold, also 20-fold, also 50-fold, or at least about 100-fold less than the EC_{50} for the other of PPARα, PPARγ and PPARδ.

[0080] In some embodiments of the invention, the compounds of Formulae I, II, or III active on PPARs also have desireable pharmacologic properties. In some embodiments the desired pharmacologic property is PPAR pan-activity, PPAR selectivity for any individual PPAR (PPARα, PPARδ, or PPARγ), selectivity on any two PPARs (PPARα and PPARδ, PPARα and PPARγ, or PPARδ and PPARγ), or any one or more of serum half-life longer than 2 hr, also longer than 4 hr, also longer than 8 hr, aqueous solubility, and oral bioavailability more than 10%, also more than 20%.

[0081] Additional embodiments will be apparent from the Detailed Description and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0082] As indicated in the Summary above, the present invention concerns the peroxisome proliferator-activated receptors (PPARs), which have been identified in humans and other mammals. A group of compounds have been identified, corresponding to Formulae I, II, or III, that are active on one or more of the PPARs, in particular compounds that are active on one or more human PPARs. Such compounds can be used for a variety of applications, e.g., as agonists on PPARs, including agonists of at least one of PPARα, PPARδ, and PPARγ, as well as dual PPAR agonists and pan-agonist, such as agonists of both PPARα and PPARγ, both PPARα and PPARδ, both PPARγ and PPARδ, or agonists of PPARα, PPARγ and PPARδ.

[0083] As used herein the following definitions apply unless otherwise indicated:

[0084] "Halogen" - alone or in combination refers to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0085] "Hydroxyl" or "hydroxy" refer to the group -OH.

[0086] "Thiol" refers to the group -SH.

[0087] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. "Substituted lower alkyl" denotes lower alkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$,

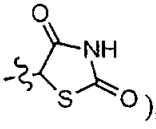
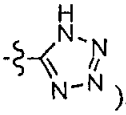
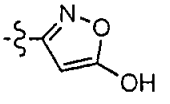
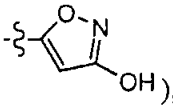
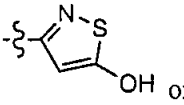
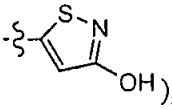
$-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^c$, and $-R^f$. Furthermore, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formulae I, II, or III, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkyl" denotes a lower alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions are attached at any available atom to produce a stable compound, when optionally substituted lower alkyl is an R group of a moiety such as -OR (e.g. lower alkoxy), -SR (e.g. lower alkylthio), -NHR (e.g. mono-alkylamino), -C(O)NHR, and the like, substitution of the lower alkyl R group is such that substitution of the lower alkyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the lower alkyl carbon bound to any O, S, or N of the moiety.

[0088] "Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be contained within either a straight chain or branched portion. Examples of lower alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and the like. "Substituted lower alkenyl" denotes lower alkenyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^d$, and $-R^f$. Further, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formulae I, II, or III, attached at any available atom to produce a stable compound. It is understood that substitutions are attached at any available atom to produce a stable compound, substitution of lower alkenyl groups are such that F, C(O), C(S), C(NH), S(O), $S(O)_2$, O, S, or N (except where N is a heteroaryl ring atom), are not bound to an alkene carbon thereof. Further, where lower alkenyl is a substituent of another moiety or an R group of a moiety

such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any C(O), C(S), S(O), $S(O)_2$, O, S, or N thereof (except where N is a heteroaryl ring atom) are not bound to an alkene carbon of the lower alkenyl substituent or R group. Further, where lower alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the lower alkenyl R group is such that substitution of the lower alkenyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the lower alkenyl carbon bound to any O, S, or N of the moiety. An "alkenyl carbon" refers to any carbon within a lower alkenyl group, whether saturated or part of the carbon to carbon double bond. An "alkene carbon" refers to a carbon within a lower alkenyl group that is part of a carbon to carbon double bond. "C_{3-6} alkenyl" denotes lower alkenyl containing 3-6 carbon atoms. A "substituted C_{3-6} alkenyl" denotes optionally substituted lower alkenyl containing 3-6 carbon atoms.

[0089] "Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. Examples of lower alkynyl groups include ethynyl, propynyl, butynyl, and the like. "Substituted lower alkynyl" denotes lower alkynyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of -F, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^d$, and $-R^f$. Further, possible substitutions include subsets of these substitutions, such as are indicated herein, for example, in the description of compounds of Formulae I, II, or III, attached at any available atom to produce a stable compound. It is understood that substitutions are attached at any available atom to produce a stable compound, substitution of lower alkynyl groups are such that F, C(O), C(S), C(NH), S(O), $S(O)_2$, O, S, or N (except where N is a heteroaryl ring atom) are not bound to an alkyne carbon thereof. Further, where lower alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any C(O), C(S), S(O), $S(O)_2$, O, S, or N

thereof (except where N is a heteroaryl ring atom) are not bound to an alkyne carbon of the lower alkynyl substituent or R group. Further, where lower alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the lower alkynyl R group is such that substitution of the lower alkynyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the lower alkynyl carbon bound to any O, S, or N of the moiety. An "alkynyl carbon" refers to any carbon within a lower alkynyl group, whether saturated or part of the carbon to carbon triple bond. An "alkyne carbon" refers to a carbon within a lower alkynyl group that is part of a carbon to carbon triple bond. "C_{3-6} alkynyl" denotes lower alkynyl containing 3-6 carbon atoms. A "substituted C_{3-6} alkynyl" denotes optionally substituted lower alkynyl containing 3-6 carbon atoms.

[0090] "Carboxylic acid isostere" refers to a moiety selected from the group consisting of thiazolidine dione (i.e. ), hydroxamic acid (i.e. -C(O)NHOH), acyl-cyanamide (i.e. -C(O)NHCN), tetrazole (i.e. ), 3- or 5- hydroxy isoxazole (i.e.  or ), 3- or 5- hydroxy isothiazole (i.e.  or ), sulphonate (i.e. -S(O)$_2$OH), and sulfonamide (i.e. -S(O)$_2$NH$_2$). In functional terms, carboxylic acid isosteres mimic carboxylic acids by virtue of similar physical properties, including but not limited to molecular size, charge distribution or molecular shape. 3- or 5- hydroxy isoxazole or 3- or 5- hydroxy isothiazole may be optionally substituted with lower alkyl or lower alkyl substituted with 1, 2 or 3 substituents selected from the group consisting of fluoro, aryl and heteroaryl, wherein aryl or heteroaryl may further be optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio. The nitrogen of the sulfonamide may be optionally substituted with a

substituent selected from the group consisting of lower alkyl, fluoro substituted lower alkyl, acetyl (i.e. $-C(O)CH_3$), aryl and heteroaryl, wherein aryl or heteroaryl may further be optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio.

[0091] "Aryl" alone or in combination refers to a monocyclic or bicyclic ring system containing aromatic hydrocarbons such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl or heterocycloalkyl of preferably 5-7, more preferably 5-6, ring members. "Arylene" refers to a divalent aryl.

[0092] "Heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinoxalinyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. "Heteroarylene" refers to a divalent heteroaryl.

[0093] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like.

[0094] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members. Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which one of the ring carbons is oxo substituted, i.e. the

ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl.

[0095] "Optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted cycloalkyl", and "optionally substituted heterocycloalkyl", refers to aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups, respectively, which are optionally independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^d$, $-R^e$, and $-R^f$.

[0096] The variables as used in the description of optional substituents for lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are defined as follows:

$-R^a$, $-R^b$, and $-R^c$ at each occurrence are independently selected from the group consisting of hydrogen, $-R^d$, $-R^e$, and $-R^f$, provided, however, that R^a bound to S, S(O), $S(O)_2$, C(S) or C(O) is not hydrogen, or

$-R^b$ and $-R^c$ combine with the nitrogen to which they are attached form a 5-7 membered heterocycloalkyl or a 5 or 7 membered nitrogen containing heteroaryl, wherein the 5-7 membered heterocycloalkyl or 5 or 7 membered nitrogen containing heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, cycloalkylamino, $-NO_2$, -CN, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-R^m$, and $-R^o$;

$-R^d$ at each occurrence is independently lower alkyl optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, $-OR^g$, $-SR^g$, $-NR^gR^g$, $-C(O)R^g$, $-C(S)R^g$, $-S(O)R^g$, $-S(O)_2R^g$,

$-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NR^gR^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NR^gS(O)_2R^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, and $-R^f$;

$-R^e$ at each occurrence is independently selected from the group consisting of lower alkenyl and lower alkynyl, wherein lower alkenyl or lower alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of fluoro, $-OR^g$, $-SR^g$, $-NR^gR^g$, $-C(O)R^g$, $-C(S)R^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NR^gR^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NR^gS(O)_2R^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-R^d$, and $-R^f$;

$-R^f$ at each occurrence is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2 or 3 substituents selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^g$, $-SR^g$, $-NR^gR^g$, $-C(O)R^g$, $-C(S)R^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NR^gR^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NR^gS(O)_2R^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-R^m$, and $-R^o$;

$-R^g$ at each occurrence is independently selected from the group consisting of hydrogen, $-R^h$, $-R^i$, and $-R^j$, provided, however, that R^g bound to S, S(O), $S(O)_2$, C(S) or C(O) is not hydrogen;

$-R^h$ at each occurrence is independently lower alkyl optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of fluoro, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-C(O)R^k$, $-C(S)R^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NR^kR^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NR^kS(O)_2R^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, and $-R^o$, provided, however, that any substitution on the lower alkyl carbon bound to any O, S, or N of any OR^h, SR^h, or NR^h is selected from the group consisting of fluoro and $-R^o$;

$-R^i$ at each occurrence is independently selected from the group consisting of C_{3-6} alkenyl and C_{3-6} alkynyl, wherein C_{3-6} alkenyl or C_{3-6} alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of fluoro, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-C(O)R^k$, $-C(S)R^k$, $-S(O)R^k$, $-S(O)_2R^k$ $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NR^kR^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$,

$-NR^kS(O)_2R^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, $-R^m$ and $-R^o$, provided, however, that any substitution on the alkenyl or alkynyl carbon bound to any O, S, or N of any OR^i, SR^i, or NR^i is selected from the group consisting of fluoro, $-R^m$ and $-R^o$;

R^j at each occurrence is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-C(O)R^k$, $-C(S)R^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NR^kR^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NR^kS(O)_2R^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, $-R^m$, and $-R^o$;

$-R^m$ at each occurrence is independently selected from the group consisting of lower alkyl, lower alkenyl and lower alkynyl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of $-R^o$, fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein lower alkenyl or lower alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of $-R^o$, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino;

$-R^k$ at each occurrence is independently selected from the group consisting of hydrogen, $-R^n$, and $-R^o$, provided, however, that R^k bound to S, S(O), $S(O)_2$, C(S) or C(O) is not hydrogen;

$-R^n$ at each occurrence is independently selected from the group consisting of lower alkyl, C_{3-6} alkenyl and C_{3-6} alkynyl, wherein lower alkyl is optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of $-R^o$, fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of

the lower alkyl carbon bound to the O of OR^n, S of SR^n, or N of any NR^n is fluoro or $-R^o$, and wherein C_{3-6} alkenyl or C_{3-6} alkynyl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of $-R^o$, fluoro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, provided, however, that any substitution of the C_{3-6} alkenyl or C_{3-6} alkynyl carbon bound to the the O of OR^n, S of SR^n, or N of any NR^n is fluoro, lower alkyl, fluoro substituted lower alkyl, or $-R^o$;

$-R^o$ at each occurrence is independently selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally substituted with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents selected from the group consisting of halogen, -OH, $-NH_2$, $-NO_2$, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino.

[0097] "Lower alkoxy" denotes the group $-OR^p$, where R^p is lower alkyl. "Optionally substituted lower alkoxy" denotes lower alkoxy in which R^p is optionally substituted lower alkyl. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkoxy" denotes lower alkoxy in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on lower alkoxy are attached at any available atom to produce a stable compound, substitution of lower alkoxy is such that O, S, or N (except where N is a heteroaryl ring atom), are not bound to the lower alkyl carbon bound to the lower alkoxy O. Further, where lower alkoxy is described as a substituent of another moiety, the lower alkoxy oxygen is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0098] "Aryloxy" denotes the group $-OR^q$, where R^q is aryl. "Optionally substituted aryloxy" denotes aryloxy in which R^q is optionally substituted aryl. "Heteroaryloxy"

denotes the group $-OR^r$, where R^r is heteroaryl. "Optionally substituted heteroaryloxy" denotes heteroaryloxy in which R^r is optionally substituted heteroaryl.

[0099] "Lower alkylthio" denotes the group $-SR^s$, where R^s is lower alkyl. "Substituted lower alkylthio" denotes lower alkylthio in which R^s is optionally substituted lower alkyl. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylthio" denotes lower alkylthio in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylthio is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. It is understood that substitutions on lower alkylthio are attached at any available atom to produce a stable compound, substitution of lower alkylthio is such that O, S, or N (except where N is a heteroaryl ring atom), are not bound to the lower alkyl carbon bound to the lower alkylthio S. Further, where lower alkylthio is described as a substituent of another moiety, the lower alkylthio sulfur is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0100] "Amino" or "amine" denotes the group $-NH_2$. "Mono-alkylamino" denotes the group $-NHR^t$ where R^t is lower alkyl. "Di-alkylamino" denotes the group $-NR^tR^u$, where R^t and R^u are independently lower alkyl. "Cycloalkylamino" denotes the group $-NR^vR^w$, where R^v and R^w combine with the nitrogen to form a 5-7 membered heterocycloalkyl, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as O, N, or S, and may also be further substituted with lower alkyl. Examples of cycloalkylamino include, but are not limited to, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine. It is understood that when mono-alkylamino, di-alkylamino, or cycloalkylamino are substituents on other moieties that are attached at any available atom to produce a stable compound, the nitrogen of mono-alkylamino, di-alkylamino, or cycloalkylamino as substituents is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom) or to an alkene or alkyne carbon of the other moiety.

[0101] As used herein in connection with PPAR modulating compound, binding compounds or ligands, the term "specific for PPAR" and terms of like import mean that a particular compound binds to a PPAR to a statistically greater extent than to other biomolecules that may be present in or originally isolated from a particular organism, e.g.,

at least 2, 3, 4, 5, 10, 20, 50, 100, or 1000-fold greater binding. Also, where biological activity other than binding is indicated, the term "specific for PPAR" indicates that a particular compound has greater biological activity associated with binding to a PPAR than to other biomolecules (e.g., at a level as indicated for binding specificity). Similarly, the specificity can be for a specific PPAR with respect to other PPARs that may be present in or originally isolated from a particular organism.

[0102] Also in the context of compounds binding to a biomolecular target, the term "greater specificity" indicates that a compound binds to a specified target to a greater extent than to another biomolecule or biomolecules that may be present under relevant binding conditions, where binding to such other biomolecules produces a different biological activity than binding to the specified target. In some cases, the specificity is with reference to a limited set of other biomolecules, *e.g.*, in the case of PPARs, in some cases the reference may be other receptors, or for a particular PPAR, it may be other PPARs. In some embodiments, the greater specificity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, or 1000-fold greater specificity. In the context of ligands interacting with PPARs, the terms "activity on", "activity toward," and like terms mean that such ligands have IC_{50} EC_{50} less than 10 μM, less than 1 μM, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to at least one PPAR as determined in a generally accepted PPAR activity assay.

[0103] The term "composition" or "pharmaceutical composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes. The formulation includes a therapeutically significant quantity (i.e. a therapeutically effective amount) of at least one active compound and at least one pharmaceutically acceptable carrier or excipient, which is prepared in a form adapted for administration to a subject. Thus, the preparation is "pharmaceutically acceptable", indicating that it does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. In many cases, such a pharmaceutical composition is a sterile preparation, e.g. for injectibles.

[0104] The term "PPAR-mediated" disease or condition and like terms refer to a disease or condition in which the biological function of a PPAR affects the development and/or course of the disease or condition, and/or in which modulation of PPAR alters the

development, course, and/or symptoms of the disease or condition. Similarly, the phrase "PPAR modulation provides a therapeutic benefit" indicates that modulation of the level of activity of PPAR in a subject indicates that such modulation reduces the severity and/or duration of the disease, reduces the likelihood or delays the onset of the disease or condition, and/or causes an improvement in one or more symptoms of the disease or condition. In some cases the disease or condition may be mediated by any one or more of the PPAR isoforms, e.g., PPARγ, PPARα, PPARδ, PPARγ and PPARα, PPARγ and PPARδ, PPARα and PPARδ, or PPARγ, PPARα, and PPARδ.

[0105] The term "therapeutically effective" or "effective amount" indicates that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[0106] The term "PPAR" refers to a peroxisome proliferator-activated receptor as recognized in the art. As indicated above, the PPAR family includes PPARα (also referred to as PPARa or PPARalpha), PPARδ (also referred to as PPARd or PPARdelta), and PPARγ (also referred to as PPARg or PPARgamma). The individual PPARs can be identified by their sequences, where exemplary reference sequence accession numbers are as follows:

Receptor	Sequence	Accession No.	SEQ ID NO:
hPPARa	cDNA	NM_005036	
hPPARa	protein	NP_005027	
hPPARg isoform 2	cDNA	NM_015869	
hPPARg isoform 2	protein	NP_056953	
hPPARd	cDNA	NM_006238	
hPPARd	protein	NP_006229	

One of ordinary skill in the art will recognize that sequence differences will exist due to allelic variation, and will also recognize that other animals, particularly other mammals have corresponding PPARs, which have been identified or can be readily identified using sequence alignment and confirmation of activity. Such homologous PPARs can also be used in the present invention, which homologous PPARs have sequence identity of, for example, at least 50%, 60%, 70%, 80%, 90%, 95%, 99%, or even 100%, over a region

spanning 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, or even more amino acids or nucleotides for proteins or nucleic acids, respectively. One of ordinary skill in the art will also recognize that modifications can be introduced in a PPAR sequence without destroying PPAR activity. Such modified PPARs can also be used in the present invention, e.g., if the modifications do not alter the binding site conformation to the extent that the modified PPAR lacks substantially normal ligand binding.

[0107] As used herein in connection with the design or development of ligands, the term "bind" and "binding" and like terms refer to a non-convalent energetically favorable association between the specified molecules (i.e., the bound state has a lower free energy than the separated state, which can be measured calorimetrically). For binding to a target, the binding is at least selective, that is, the compound binds preferentially to a particular target or to members of a target family at a binding site, as compared to non-specific binding to unrelated proteins not having a similar binding site. For example, BSA is often used for evaluating or controlling for non-specific binding. In addition, for an association to be regarded as binding, the decrease in free energy going from a separated state to the bound state must be sufficient so that the association is detectable in a biochemical assay suitable for the molecules involved.

[0108] By "assaying" is meant the creation of experimental conditions and the gathering of data regarding a particular result of the experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. Likewise, for example, a compound or ligand can be assayed based on its ability to bind to a particular target molecule or molecules and/or to modulate an activity of a target molecule.

[0109] By "background signal" in reference to a binding assay is meant the signal that is recorded under standard conditions for the particular assay in the absence of a test compound, molecular scaffold, or ligand that binds to the target molecule. Persons of ordinary skill in the art will realize that accepted methods exist and are widely available for determining background signal.

[0110] By "clog P" is meant the calculated log P of a compound, "P" referring to the partition coefficient of the compound between a lipophilic and an aqueous phase, usually between octanol and water.

[0111] In the context of compounds binding to a target, the term "greater affinity" indicates that the compound binds more tightly than a reference compound, or than the same compound in a reference condition, i.e., with a lower dissociation constant. In some embodiments, the greater affinity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, or 10,000-fold greater affinity.

[0112] By binding with "moderate affinity" is meant binding with a K_D of from about 200 nM to about 1 μM under standard conditions. By "moderately high affinity" is meant binding at a K_D of from about 1 nM to about 200 nM. By binding at "high affinity" is meant binding at a K_D of below about 1 nM under standard conditions. The standard conditions for binding are at pH 7.2 at 37 °C for one hour. For example, typical binding conditions in a volume of 100 μl/well would comprise a PPAR, a test compound, HEPES 50 mM buffer at pH 7.2, NaCl 15 mM, ATP 2 μM, and bovine serum albumin (1 ug/well), at 37°C for one hour.

[0113] Binding compounds can also be characterized by their effect on the activity of the target molecule. Thus, a "low activity" compound has an inhibitory concentration (IC_{50}) (for inhibitors or antagonists) or effective concentration (EC_{50}) (applicable to agonists) of greater than 1 μM under standard conditions. By "moderate activity" is meant an IC_{50} or EC_{50} of 200 nM to 1 μM under standard conditions. By "moderately high activity" is meant an IC_{50} or EC_{50} of 1 nM to 200 nM. By "high activity" is meant an IC_{50} or EC_{50} of below 1 nM under standard conditions. The IC_{50} (or EC_{50}) is defined as the concentration of compound at which 50% of the activity of the target molecule (*e.g.*, enzyme or other protein) activity being measured is lost (or gained) relative to activity when no compound is present. Activity can be measured using methods known to those of ordinary skill in the art, *e.g.*, by measuring any detectable product or signal produced by occurrence of an enzymatic reaction, or other activity by a protein being measured. For PPAR agonists, activities can be determined as described in the Examples, or using other such assay methods known in the art.

[0114] By "protein" is meant a polymer of amino acids. The amino acids can be naturally or non-naturally occurring. Proteins can also contain modfications, such as being glycosylated, phosphorylated, or other common modifications.

[0115] By "protein family" is meant a classification of proteins based on structural and/or functional similarities. For example, kinases, phosphatases, proteases, and similar groupings of proteins are protein families. Proteins can be grouped into a protein family based on having one or more protein folds in common, a substantial similarity in shape among folds of the proteins, homology, or based on having a common function. In many cases, smaller families will be specified, e.g., the PPAR family.

[0116] By "specific biochemical effect" is meant a therapeutically significant biochemical change in a biological system causing a detectable result. This specific biochemical effect can be, for example, the inhibition or activation of an enzyme, the inhibition or activation of a protein that binds to a desired target, or similar types of changes in the body's biochemistry. The specific biochemical effect can cause alleviation of symptoms of a disease or condition or another desirable effect. The detectable result can also be detected through an intermediate step.

[0117] By "standard conditions" is meant conditions under which an assay is performed to obtain scientifically meaningful data. Standard conditions are dependent on the particular assay, and can be generally subjective. Normally the standard conditions of an assay will be those conditions that are optimal for obtaining useful data from the particular assay. The standard conditions will generally minimize background signal and maximize the signal sought to be detected.

[0118] By "standard deviation" is meant the square root of the variance. The variance is a measure of how spread out a distribution is. It is computed as the average squared deviation of each number from its mean. For example, for the numbers 1, 2, and 3, the mean is 2 and the variance is:

$$\sigma^2 = \frac{(1-2)^2 + (2-2)^2 + (3-2)^2}{3} = 0.667 .$$

[0119] In the context of this invention, by "target molecule" is meant a molecule that a compound, molecular scaffold, or ligand is being assayed for binding to. The target molecule has an activity that binding of the molecular scaffold or ligand to the target molecule will alter or change. The binding of the compound, scaffold, or ligand to the target molecule can preferably cause a specific biochemical effect when it occurs in a biological system. A "biological system" includes, but is not limited to, a living system

such as a human, animal, plant, or insect. In most but not all cases, the target molecule will be a protein or nucleic acid molecule.

[0120] By "pharmacophore" is meant a representation of molecular features that are considered to be responsible for a desired activity, such as interacting or binding with a receptor. A pharmacophore can include 3-dimensional (hydrophobic groups, charged/ionizable groups, hydrogen bond donors/acceptors), 2D (substructures), and 1D (physical or biological) properties.

[0121] As used herein in connection with numerical values, the terms "approximately" and "about" mean ±10% of the indicated value.

I. Applications of PPAR Agonists

[0122] The PPARs have been recognized as suitable targets for a number of different diseases and conditions. Some of those applications are described briefly below. Additional applications are known and the present compounds can also be used for those diseases and conditions.

(a) Insulin resistance and diabetes

[0123] In connection with insulin resistance and diabetes, PPARγ is necessary and sufficient for the differentiation of adipocytes *in vitro* and *in vivo*. In adipocytes, PPARγ increases the expression of numerous genes involved in lipid metabolism and lipid uptake. In contrast, PPARγ down-regulates leptin, a secreted, adipocyte-selective protein that has been shown to inhibit feeding and augment catabolic lipid metabolism. This receptor activity could explain the increased caloric uptake and storage noted *in vivo* upon treatment with PPARγ agonists. Clinically, TZDs, including troglitazone, rosiglitazone, and pioglitazone, and non-TZDs, including farglitazar, have insulin-sensitizing and antidiabetic activity. (Berger et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

[0124] PPARγ has been associated with several genes that affect insulin action. TNFα, a proinflammatory cytokine that is expressed by adipocytes, has been associated with insulin resistance. PPARγ agonists inhibit expression of TNFα in adipose tissue of obese rodents, and ablate the actions of TNFα in adipocytes *in vitro*. PPARγ agonists were

shown to inhibit expression of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD-1), the enzyme that converts cortisone to the glucocorticoid agonist cortisol, in adipocytes and adipose tissue of type 2 diabetes mouse models. This is noteworthy since hypercorticosteroidism exacerbates insulin resistance. Adipocyte Complement-Related Protein of 30 kDa (Acrp30 or adiponectin) is a secreted adipocyte-specific protein that decreases glucose, triglycerides, and free fatty acids. In comparison to normal human subjects, patients with type 2 diabetes have reduced plasma levels of Acrp30. Treatment of diabetic mice and nondiabetic human subjects with PPARγ agonists increases plasma levels of Acrp30. Induction of Acrp30 by PPARγ agonists might therefore also play a key role in the insulin-sensitizing mechanism of PPARγ agonists in diabetes. (Berger et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

[0125] PPARγ is expressed predominantly in adipose tissue. Thus, it is believed that the net *in vivo* efficacy of PPARγ agonists involves direct actions on adipose cells with secondary effects in key insulin responsive tissues such as skeletal muscle and liver. This is supported by the lack of glucose-lowering efficacy of rosiglitazone in a mouse model of severe insulin resistance where white adipose tissue was essentially absent. Furthermore, *in vivo* treatment of insulin resistant rats produces acute (<24 h) normalization of adipose tissue insulin action whereas insulin-mediated glucose uptake in muscle was not improved until several days after the initiation of therapy. This is consistent with the fact that PPARγ agonists can produce an increase in adipose tissue insulin action after direct *in vitro* incubation, whereas no such effect could be demonstrated using isolated *in vitro* incubated skeletal muscles. The beneficial metabolic effects of PPARγ agonists on muscle and liver may be mediated by their ability to (a) enhance insulin-mediated adipose tissue uptake, storage (and potentially catabolism) of free fatty acids; (b) induce the production of adipose-derived factors with potential insulin sensitizing activity (e.g., Acrp30); and/or (c) suppress the circulating levels and/or actions of insulin resistance-causing adipose-derived factors such as TNFα or resistin. (Berger et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

(b) Dyslipidemia and atherosclerosis

[0126] In connection with dyslipidemia and atherosclerosis, PPARα has been shown to play a critical role in the regulation of cellular uptake, activation, and β-oxidation of fatty acids. Activation of PPARα induces expression of fatty acid transport proteins and

enzymes in the peroxisomal β-oxidation pathway. Several mitochondrial enzymes involved in the energy-harvesting catabolism of fatty acids are robustly upregulated by PPARα agonists. Peroxisome proliferators also activate expression of the CYP4As, a subclass of cytochrome P450 enzymes that catalyze the ω-hydroxylation of fatty acids, a pathway that is particularly active in the fasted and diabetic states. In sum, it is clear that PPARα is an important lipid sensor and regulator of cellular energy-harvesting metabolism. (Berger et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

[0127] Atherosclerosis is a very prevalent disease in Westernized societies. In addition to a strong association with elevated LDL cholesterol, "dyslipidemia" characterized by elevated triglyceride-rich particles and low levels of HDL cholesterol is commonly associated with other aspects of a metabolic syndrome that includes obesity, insulin resistance, type 2 diabetes, and an increased risk of coronary artery disease. Thus, in 8,500 men with known coronary artery disease, 38% were found to have low HDL (<35 mg/dL) and 33% had elevated triglycerides (>200 mg/dL). In such patients, treatment with fibrates resulted in substantial triglyceride lowering and modest HDL-raising efficacy. More importantly, a recent large prospective trial showed that treatment with gemfibrozil produced a 22% reduction in cardiovascular events or death. Thus PPARα agonists can effectively improve cardiovascular risk factors and have a net benefit to improve cardiovascular outcomes. In fact, fenofibrate was recently approved in the United States for treatment of type IIA and IIB hyper-lipidemia. Mechanisms by which PPARα activation cause triglyceride lowering are likely to include the effects of agonists to suppress hepatic apo-CIII gene expression while also stimulating lipoprotein lipase gene expression. Dual PPARγ/α agonists, including KRP-297 and DRF 2725, possess potent lipid-altering efficacy in addition to antihyperglycemic activity in animal models of diabetes and lipid disorders.

[0128] The presence of PPARα and/or PPARγ expression in vascular cell types, including macrophages, endothelial cells, and vascular smooth muscle cells, suggests that direct vascular effects might contribute to potential antiatherosclerosis efficacy. PPARα and PPARα activation have been shown to inhibit cytokine-induced vascular cell adhesion and to suppress monocyte-macrophage migration. Several additional studies have also shown that PPARγ-selective compounds have the capacity to reduce arterial lesion size and attenuate monocyte-macrophage homing to arterial lesions in animal models of

atherosclerosis. PPARγ is present in macrophages in human atherosclerotic lesions, and may play a role in regulation of expression of matrix metalloproteinase-9 (MMP-9), which is implicated in atherosclerotic plaque rupture (Marx et al., *Am J Pathol.* 1998, 153(1):17-23). Downregulation of LPS induced secretion of MMP-9 was also observed for both PPARα and PPARγ agonists, which may account for beneficial effects observed with PPAR agonists in animal models of atherosclerosis (Shu et al., *Biochem Biophys Res Commun.* 2000, 267(1):345-9). PPARγ is also shown to have a role in intercellular adhesion molecule-1 (ICAM-1) protein expression (Chen et al., *Biochem Biophys Res Commun.* 2001, 282(3):717-22) and vascular cell adhesion molecule-1 (VCAM-1) protein expression (Jackson et al., *Arterioscler Thromb Vasc Biol.* 1999, 19(9):2094-104) in endothelial cells, both of which play a role in the adhesion of monocytes to endothelial cells. In addition, two recent studies have suggested that either PPARα or PPARγ activation in macrophages can induce the expression of a cholesterol efflux "pump" protein.

[0129] It has been found that relatively selective PPARδ agonists produce minimal, if any, glucose- or triglyceride-lowering activity in murine models of type 2 diabetes in comparison with efficacious PPARγ or PPARα agonists. Subsequently, a modest increase in HDL-cholesterol levels was detected with PPARδ agonists in db/db mice. Recently, Oliver et al. (*supra*) reported that a potent, selective PPARδ agonist could induce a substantial increase in HDL-cholesterol levels while reducing triglyceride levels and insulin resistance in obese rhesus monkeys.

[0130] Thus, via multifactorial mechanisms that include improvements in circulating lipids, systemic and local antiinflammatory effects, and, inhibition of vascular cell proliferation, PPARα, PPARγ, and PPARδ agonists can be used in the treatment or prevention of atherosclerosis (Berger et al., *supra*).

(c) Inflammation

[0131] Monocytes and macrophages are known to play an important part in the inflammatory process through the release of inflammatory cytokines and the production of nitric oxide by inducible nitric oxide synthase. Rosiglitazone has been shown to induce apoptosis of macrophages at concentrations that parallel its affinity for PPARγ. This ligand has also been shown to block inflammatory cytokine synthesis in colonic cell lines.

This latter observation suggests a mechanistic explanation for the observed anti-inflammatory actions of TZDs in rodent models of colitis.

[0132] Additional studies have examined the relationship between macrophages, cytokines and PPARγ and agonists thereof (Jiang et al., *Nature* 1998, 391(6662):82-6., Ricote et al., *Nature* 1998, 391(6662):79-82, Hortelano et al., *J Immunol.* 2000, 165(11):6525-31, and Chawla et al., *Nat Med.* 2001, 7(1):48-52) suggesting a role for PPARγ agonists in treating inflammatory responses, for example in autoimmune diseases.

[0133] The migration of monocytes and macrophages plays a role in the development of inflammatory responses as well. PPAR ligands have been shown to have an effect on a variety of chemokines. Monocyte chemotactic protein-1 (MCP-1) directed migration of monocytes is attenuated by PPARγ and PPARα ligands in a monocytic leukemia cell line (Kintscher et al., *Eur J Pharmacol.* 2000, 401(3):259-70). MCP-1 gene expression was shown to be suppressed by PPARγ ligand 15-deoxy-Delta(12,14)PGJ2 (15d-PGJ2) in two monocytic cell lines, which also showed induction of IL-8 gene expression (Zhang et al., *J Immunol.* 2001, 166(12):7104-11).

[0134] Anti-inflammatory actions have been described for PPARα ligands that can be important in the maintenance of vascular health. Treatment of cytokine-activated human macrophages with PPARα agonists induced apoptosis of the cells. It was reported that PPARα agonists inhibit activation of aortic smooth muscle cells in response to inflammatory stimuli. (Staels et al., 1998, *Nature* 393:790-793.) In hyperlipidemic patients, fenofibrate treatment decreases the plasma concentrations of the inflammatory cytokine interleukin-6.

[0135] Anti-inflammatory pathways in airway smooth muscle cells were investigated with respect to PPARα and PPARγ (Patel et al., 2003, *The Journal of Immunology*, 170:2663-2669). This study demonstrated and anti-inflammatory effect of a PPARγ ligand that may be useful in the treatment of COPD and steroid-insensitive asthma.

[0136] The anti-inflammatory effects of PPAR modulators have also been studied with respect to autoimmune diseases, such as chronic inflammatory bowel syndrome, arthritis, Crohn's disease and multiple sclerosis, and in neuronal diseases such as Alzheimer's disease and Parkinson's disease.

(d) Hypertension

[0137] Hypertension is a complex disorder of the cardiovascular system that has been shown to be associated with insulin resistance. Type 2 diabetes patients demonstrate a 1.5-2-fold increase in hypertension in comparison with the general population. Troglitazone, rosiglitazone, and pioglitazone therapy have been shown to decrease blood pressure in diabetic patients as well as troglitazone therapy in obese, insulin-resistant subjects. Since such reductions in blood pressure were shown to correlate with decreases in insulin levels, they can be mediated by an improvement in insulin sensitivity. However, since TZDs also lowered blood pressure in one-kidney one-clip Sprague Dawley rats, which are not insulin resistant, it was proposed that the hypotensive action of PPARγ agonists is not exerted solely through their ability to improve insulin sensitivity. Other mechanisms that have been invoked to explain the antihypertensive effects of PPARγ agonists include their ability to (a) downregulate expression of peptides that control vascular tone such as PAI-I, endothelin, and type-c natriuretic peptide C or (b) alter calcium concentrations and the calcium sensitivity of vascular cells (Berger et al., *supra*).

(e) Cancer

[0138] PPAR modulation has also been correlated with cancer treatment. (Burstein et al.; *Breast Cancer Res. Treat.* 2003 79(3):391-7; Alderd et al.; *Oncogene*, 2003, 22(22):3412-6).

(f) Weight Control

[0139] Administration of PPARα agonists can induce satiety, and thus are useful in weight loss or maintenance. Such PPARα agonists can act preferentially on PPARα, or can also act on another PPAR, or can be PPAR pan-agonists. Thus, the satiety inducing effect of PPARα agonists can be used for weight control or loss.

(g) Autoimmune diseases

[0140] PPAR agonists may provide benefits in the treatment of autoimmune diseases. Agonists of PPAR isoforms may be involved in T cell and B cell trafficking or activity, the altering of oligodendrocyte function or differentiation, the inhibition of macrophage

activity, the reduction of inflammatory responses, and neuroprotective effects, some or all of which may be important in a variety of autoimmune diseases.

[0141] Multiple sclerosis (MS) is a neurodegenerative autoimmune disease that involves the demyelination of axons and formation of plaques. PPARδ mRNA has been shown to be strongly expressed in immature oligodendrocytes (Granneman et al., *J Neurosci Res.* 1998, 51(5):563-73). PPARδ selective agonists or pan- agonists were shown to accelerate differentiation of oligodendrocytes, with no effect on differentiation observed with a PPARγ selective agonist. An alteration in the myelination of corpus callosum was observed in PPARδ null mice (Peters et al., *Mol Cell Biol.* 2000, 20(14):5119-28). It was also shown that PPARδ mRNA and protein is expressed throughout the brain in neurons and oligodendrocytes, but not in astrocytes (Woods et al., *Brain Res.* 2003, 975(1-2):10-21). These observations suggest that PPARδ has a role in myelination, where modulation of such a role could be used to treat multiple sclerosis by altering the differentiation of oligodendrocytes, which may result in slowing of the demyelination, or even promoting the remyelination of axons. It has also been shown that oligodendrocyte-like B12 cells, as well as isolated spinal cord oligodendrocytes from rat, are affected by PPARγ agonists. Alkyl-dihydroxyacetone phosphate synthase, a key peroxisomal enzyme involved in the synthesis of plasmologens, which are a key component of myelin, is increased in PPARγ agonist treated B12 cells, while the number of mature cells in isolated spinal cord oligodendrocytes increases with PPARγ agonist treatment.

[0142] The role of PPAR in the regulation of B and T cells may also provide therapeutic benefits in diseases such as MS. For example, it has been shown that PPARγ agonists can inhibit the secretion of IL-2 by T cells (Clark et al., *J Immunol.* 2000, 164(3):1364-71) or may induce apoptosis in T cells (Harris et al., *Eur J Immunol.* 2001, 31(4):1098-105), suggesting an important role in cell-mediated immune responses. An antiproliferative and cytotoxic effect on B cells by PPARγ agonists has also been observed (Padilla et al., *Clin Immunol.* 2002, 103(1):22-33).

[0143] The anti-inflammatory effects of PPAR modulators, as discussed herein, may also be useful in treating MS, as well as a variety of other autoimmune diseases such as Type-1 diabetes mellitus, psoriasis, vitiligo, uveitis, Sjogren's disease, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's

disease, Hashimoto's disease, chronic graft-versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, and Crohn's disease. Using a mouse model, the PPARα agonists gemfibrozil and fenofibrate were shown to inhibit clinical signs of experimental autoimmune encephalomyelitis, suggesting that PPARα agonists may be useful in treating inflammatory conditions such as multiple sclerosis (Lovett-Racke et al., *J Immunol.* 2004, 172(9):5790-8).

[0144] Neuroprotective effects that appear to be associated with PPARs may also aid in the treatment of MS. The effects of PPAR agonists on LPS induced neuronal cell death were studied using cortical neuron-glial co-cultures. PPARγ agonists 15d-PGJ2, ciglitazone and troglitazone were shown to prevent the LPS-induced neuronal cell death, as well as abolish NO and PGE2 release and a reduction in iNOS and COX-2 expression (Kim et al., *Brain Res.* 2002, 941(1-2):1-10).

[0145] Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that results in the destruction of joints. In addition to chronic inflammation and joint damage due in part to mediators such as IL-6 and TNF-alpha, osteoclast differentiation is also implicated in damage to the joints. PPAR agonists may regulate these pathways, providing therapeutic benefits in treatment of RA. In studies using PPARγ agonist troglitazone in fibroblast-like synovial cells (FLS) isolated from patients with rheumatoid arthritis, an inhibition of cytokine mediated inflammatory responses was observed (Yamasaki et al., *Clin Exp Immunol.*, 2002, 129(2):379-84). PPARγ agonists have also demonstrated beneficial effects in a rat or mouse model of RA (Kawahito et al., *J Clin Invest.* 2000, 106(2):189-97; Cuzzocrea et al., *Arthritis Rheum.* 2003, 48(12):3544-56). The effects of the PPARα ligand fenofibrate on rheumatoid synovial fibroblasts from RA patients also showed inhibition of cytokine production, as well as NF-KappaB activation and osteoclast differentiation. Fenofibrate was also shown to inhibit the development of arthritis in a rat model (Okamoto et al., *Clin Exp Rheumatol.* 2005, 23(3):323-30).

[0146] Psoriasis is a T cell mediated autoimmune disease, where T cell activation leads to release of cytokines and resulting proliferation of keratinocytes. In addition to anti-inflammatory effects, the differentiation of keratinocytes may also be a therapeutic target for PPAR agonists. Studies in a PPARδ null mouse model suggest using PPARδ ligand to selectively induce keratinocyte differentiation and inhibit cell proliferation (Kim et al., *Cell Death Differ.* 2005). Thiazolidinedione ligands of PPARγ have been shown to inhibit

the proliferation of psoriatic keratinocytes in monolayer and organ culture, and when applied topically inhibit epidermal hyperplasia of human psoriatic skin transplanted to SCID mice (Bhagavathula et al., *J Pharmacol Exp Ther.* 2005,315(3):996-1004).

(h) Neurodegenerative diseases:

[0147] The modulation of the PPARs may provide benefits in the treatment of neuronal diseases. For example, the anti-inflammatory effects of PPAR modulators discussed herein have also been studied with respect to neuronal diseases such as Alzheimer's disease and Parkinson's disease.

[0148] In addition to inflammatory processes, Alzheimer's disease is characterized by deposits of amyloid-beta (Abeta) peptides and neurofibrillary tangles. A decrease in the levels of Abeta peptide in neuronal and non-neuronal cells was observed with induced expression of PPARγ, or by activation of PPARγ using a thiazolidinedione (Camacho et al., *J Neurosci.* 2004, 24(48):10908-17). Treatment of APP7171 mice with PPARγ agonist pioglitazone showed several beneficial effects, including reduction in activated microglia and reactive astrocytes in the hippocampus and cortex, reduction in proinflammatory cyclooxygenase 2 and inducible nitric oxide synthase, decreased β-secretase-1 mRNA and protein levels, and a reduction in the levels of soluble Abeta1-42 peptide (Heneka et al., *Brain.* 2005, 128(Pt 6):1442-53).

[0149] Regions of degeneration of dopamine neurons in Parkinson's disease have been associated with increased levels of inflammatory cytokines (Nagatsu et al., *J Neural Transm Suppl.* 2000;(60):277-90). The effect of PPARγ agonist pioglitazone on dopaminergic nerve cell death and glial activation was studied in an MPTP mouse model of Parkinson's disease, wherein orally administered pioglitazone resulted in reduced glial activation as well as prevention of dopaminergic cell loss (Breidert et al. *Journal of Neurochemistry*, 2002, 82: 615).

(i) Other indications

[0150] PPARγ modulators have shown inhibition of VEGF-induced choroidal angiogenesis as well as repression of choroidal neovascularization effects, suggesting potential for treatment of retinal disorders. PPARδ has been shown to be expressed in implantation sites and in decidual cells in rats, suggesting a role in pregnancy, such as to

enhance fertility. These studies were reviewed in Kota et al., 2005, *Pharmacological Research* 51: 85-94.

[0151] The management of pain, either neuropathic or inflammatory, is also suggested as a possible target for PPAR modulators. Burstein, S., Life Sci. 2005, 77(14):1674-84, suggests that PPARγ provides a receptor function for the activity of some cannabinoids. Lo Verme et al., *Mol Pharmacol.* 2005, 67(1):15-9, identifies PPARα as a target responsible for pain and inflammation reducing effects of palmitoylethanolamide (PEA). PEA selectively activates PPARα *in vitro*, and induces expression of PPARα mRNA when applied topically to mice. In animal models of carrageenan-induced paw edema and phorbol ester-induced ear edema, inflammation in wild type mice is attenuated by PEA, which has no effect in PPARα deficient mice. PPARα agonists OEA, GW7647 and Wy-14643 demonstrate similar effects. Benani et al., *Neurosci Lett.* 2004, 369(1):59-63, uses a model of inflammation in rats to assess the PPAR response in the rat spinal cord following injection of complete Freund's adjuvant into the hind paw. It was shown that PPARα was activated, suggesting a role in pain pathways.

[0152] PPARs are also involved in some infections, and may be targeted in treating such infections. Dharancy et al. report that HCV infection is related to altered expression and function of the anti-inflammatory nuclear receptor PPARalpha, and identify hepatic PPARalpha as one mechanism underlying the pathogenesis of HCV infection, and as a new therapeutic target in traditional treatment of HCV-induced liver injury (Dharancy et al., Gastroenterology 2005, 128(2):334-42). J Raulin reports that among other effects, HIV infection induces alteration of cellular lipids, including deregulation of PPARγ (J. Raulin, Prog Lipid Res 2002, 41(1):27-65). Slomiany and Slomiany report that PPARgamma activation leading to the impedance of Helicobacter pylori lipopolysaccharide (LPS) inhibitory effect on salivary mucin synthesis requires epidermal growth factor receptor (EGFR) participation. Further, they showed the impedance by ciglitazone was blunted in a concentration dependent fashion by a PPAR gamma agonist. (Slomiany and Slomiany, *Inflammopharmacology* 2004, 12(2):177-88).

[0153] Muto et al. (*Human Molecular Genetics* 2002, 11(15):1731-1742) showed that molecular defects observed in $Pkd1^{-/-}$ embryos contribute to the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD)and that thiazolidindiones have a compensatory effect on the pathway affected by the loss of polycystin-1. Thus pathways

activated by thiazolidinediones may provide new therapeutic targets in ADPKD (Muto et al., *supra*). Glintborg et al. show an increase in growth hormone levels in subjects with polycystic ovary syndrome treated with pioglitazone (Glintborg et al., *J Clin Endocrinol Metab* 2005, 90(10):5605-12).

[0154] In accordance with the description above, isoforms of the PPAR family of nuclear receptors are clearly involved in the systemic regulation of lipid metabolism and serve as "sensors" for fatty acids, prostanoid metabolites, eicosanoids and related molecules. These receptors function to regulate a broad array of genes in a coordinate fashion. Important biochemical pathways that regulate insulin action, lipid oxidation, lipid synthesis, adipocyte differentiation, peroxisome function, cell apoptosis, and inflammation can be modulated through the individual PPAR isoforms. Strong therapeutic effects of PPARα and PPARγ agonists to favorably influence systemic lipid levels, glucose homeostasis, and atherosclerosis risk (in the case of PPARα activation in humans) have recently been discovered. PPARα and PPARγ agonists are presently used clinically to favorably alter systemic lipid levels and glucose homeostasis, respectively. Recent observations made using PPARS ligands suggest that this isoform is also an important therapeutic target for dyslipidemia and insulin resistance, as well.

[0155] Thus, PPAR modulators, such as those described herein, can be used in the prophylaxis and/or therapeutic treatment of a variety of different disease and conditions, such as weight disorders (e.g. obesity, overweight condition, bulimia, and anorexia nervosa), lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), cardiovascular disease (e.g. hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease), inflammatory diseases (e.g. autoimmune diseases such as vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease,

systemic lupus erythematosis, Sjogren's Syndrome, and multiple sclerosis, diseases involving airway inflammation such as asthma and chronic obstructive pulmonary disease, and inflammation in other organs, such as polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), skin disorders (e.g. epithelial hyperproliferative diseases such as eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and chronic dermatitis, and impaired wound healing), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and demyelinating disease, including acute disseminated encephalomyelitis and Guillain-Barre syndrome), coagulation disorders (e.g. thrombosis), gastrointestinal disorders (e.g. infarction of the large or small intestine), genitourinary disorders (e.g. renal insufficiency, erectile dysfunction, urinary incontinence, and neurogenic bladder), ophthalmic disorders (e.g. ophthalmic inflammation, macular degeneration, and pathologic neovascularization), infections (e.g. HCV, HIV, and Helicobacter pylori), neuropathic or inflammatory pain, infertility, and cancer.

II. PPAR Active Compounds

[0156] As indicated in the Summary and in connection with applicable diseases and conditions, a number of different PPAR agonists have been identified. In addition, the present invention provides PPAR agonist compounds described by Formulae I, Ia, Ib, II, or III as provided in the Summary above. Included within Formula I are sub-groups and compounds described in US Patent Application Serial Number 10/937,791, the disclosure of which is hereby incorporated by reference herein in its entirety. These compounds can be used in the treatment or prophylaxis of a disease or condition selected from the group consisting of inflammatory diseases (e.g. autoimmune diseases such as vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, and multiple sclerosis, diseases involving airway inflammation such as asthma and chronic obstructive pulmonary disease, and inflammation in other organs, such as polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), skin disorders (e.g. dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and chronic dermatitis, and

impaired wound healing), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, and demyelinating disease, including acute disseminated encephalomyelitis and Guillain-Barre syndrome), gastrointestinal disorders (e.g. infarction of the large or small intestine), genitourinary disorders (e.g. renal insufficiency, erectile dysfunction, urinary incontinence, and neurogenic bladder), ophthalmic disorders (e.g. ophthalmic inflammation, macular degeneration, and pathologic neovascularization), infections (e.g. HCV, HIV, and Helicobacter pylori), neuropathic or inflammatory pain, and infertility, preferably neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, autoimmune diseases such as rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease and multiple sclerosis, infertility, diseases involving airway smooth muscle cells such as asthma and chronic obstructive pulmonary disease, and angiogenesis related conditions, such as macular degeneration. Compounds of Formulae II or III may also be used in the treatment of these diseases, as well as in the treatment or prophylaxis of a disease or condition selected from the group consisting of weight disorders (e.g. obesity, overweight condition, bulimia, and anorexia nervosa), lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), cardiovascular disease (e.g. hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease), skin disorders (e.g. epithelial hyperproliferative diseases such as eczema and psoriasis, coagulation disorders (e.g. thrombosis), and cancer. Exemplary compounds described by Formulae II and III are provided in the Examples below. Additional compounds within Formulae I, Ia, Ib, II, or III can also be prepared and tested to confirm activity using conventional methods and the guidance provided herein.

[0157] The activity of the compounds can be assessed using methods known to those of skill in the art, as well as methods described herein. Screening assays may include controls for purposes of calibration and confirmation of proper manipulation of the

components of the assay. Blank wells that contain all of the reactants but no member of the chemical library are usually included. As another example, a known inhibitor (or activator) of an enzyme for which modulators are sought, can be incubated with one sample of the assay, and the resulting decrease (or increase) in the enzyme activity used as a comparator or control. It will be appreciated that modulators can also be combined with the enzyme activators or inhibitors to find modulators which inhibit the enzyme activation or repression that is otherwise caused by the presence of the known the enzyme modulator. Similarly, when ligands to a target are sought, known ligands of the target can be present in control/calibration assay wells.

(a) Enzymatic Activity Assays

[0158] A number of different assays can be utilized to assess activity of PPAR modulators and/or determine specificity of a modulator for a particular PPAR. In addition to the assays mentioned in the Examples below, one of ordinary skill in the art will know of other assays that can be utilized and can modify an assay for a particular application. For example, the assay can utilize AlphaScreen (*a*mplified *l*uminescent *p*roximity *h*omogeneous *a*ssay) format, e.g., AlphaScreening system (Packard BioScience). AlphaScreen is generally described in Seethala and Prabhavathi, *Homogenous Assays: AlphaScreen*, Handbook of Drug Screening, Marcel Dekkar Pub. 2001, pp. 106-110. Applications of the technique to PPAR receptor ligand binding assays are described, for example, in Xu, et al., *Nature,* 2002, 415:813-817.

(b) Assessment of efficacy of compounds in disease model systems.

[0159] The utility of compounds of Formula I for the treatment of diseases such as autoimmune diseases and neurological diseases can be readily assessed using model systems known to those of skill in the art. For example, efficacy of PPAR modulators in models of Alzheimer's disease can be tested by mimicking inflammatory injury to neuronal tissues and measuring recovery using molecular and pharmacological markers (Heneka, et al., *J. Neurosci.*,2000, 20:6862–6867). Efficacy of PPAR modulators in multiple sclerosis has been monitored using the accepted model of experimental autoimmune encephalomyelitis (EAE) (Storer, et al., *J. Neuroimmunol.,* 2004, 161:113-122. See also: Niino, et al., *J. Neuroimmunol.*, 2001, 116:40–48; Diab, et al. *J. Immunol.*,

2002, 168:2508–2515; Natarajan, et al., *Genes Immun.*, 2002, 3, 59–70; Feinstein, et al., *Ann. Neurol.*, 2002, 51:694–702.)

(c) Isomers, Prodrugs, and Active Metabolites

[0160] Compounds contemplated herein are described with reference to both generic formulae and specific compounds. In addition, the invention compounds may exist in a number of different forms or derivatives, all within the scope of the present invention. These include, for example, tautomers, stereoisomers, racemic mixtures, regioisomers, salts, prodrugs (e.g., carboxylic acid esters), solvated forms, different crystal forms or polymorphs, and active metabolites.

(d) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms

[0161] It is understood that some compounds may exhibit tautomerism. In such cases, the formulae provided herein expressly depict only one of the possible tautomeric forms. It is therefore to be understood that the formulae provided herein are intended to represent any tautomeric form of the depicted compounds and are not to be limited merely to the specific tautomeric form depicted by the drawings of the formulae.

[0162] Likewise, some of the compounds according to the present invention may exist as stereoisomers, i.e. having the same atomic connectivity of covalently bonded atoms yet differing in the spatial orientation of the atoms. For example, compounds may be optical stereoisomers, which contain one or more chiral centers, and therefore, may exist in two or more stereoisomeric forms (e.g. enantiomers or diastereomers). Thus, such compounds may be present as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. As another example, stereoisomers include geometric isomers, such as *cis*- or *trans*- orientation of substituents on adjacent carbons of a double bond. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Unless specified to the contrary, all such steroisomeric forms are included within the formulae provided herein.

[0163] In some embodiments, a chiral compound of the present invention is in a form that contains at least 80% of a single isomer (60% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), or at least 85% (70% e.e. or d.e.), 90% (80% e.e. or d.e.),

95% (90% e.e. or d.e.), 97.5% (95% e.e. or d.e.), or 99% (98% e.e. or d.e.). As generally understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. In some embodiments, the compound is present in optically pure form.

[0164] For compounds in which synthesis involves addition of a single group at a double bond, particularly a carbon-carbon double bond, the addition may occur at either of the double bond-linked atoms. For such compounds, the present invention includes both such regioisomers.

[0165] Additionally, the formulae are intended to cover solvated as well as unsolvated forms of the identified structures. For example, the indicated structures include both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with a suitable solvent, such as isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

(e) Prodrugs and Metabolites

[0166] In addition to the present formulae and compounds described herein, the invention also includes prodrugs (generally pharmaceutically acceptable prodrugs), active metabolic derivatives (active metabolites), and their pharmaceutically acceptable salts.

[0167] Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Prodrugs include, without limitation, esters, amides, carbamates, carbonates, ureides, solvates, or hydrates of the active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more advantageous handling, administration, and/or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. In this context, a common example is an alkyl ester of a carboxylic acid.

[0168] As described in *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. Generally, bioprecursor prodrugs are compounds that are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically, the formation of active drug compound involves a metabolic process or reaction that is one of the follow types:

[0169] Oxidative reactions: Oxidative reactions are exemplified without limitation to reactions such as oxidation of alcohol, carbonyl, and acid functionalities, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-dealkylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

[0170] Reductive reactions: Reductive reactions are exemplified without limitation to reactions such as reduction of carbonyl functionalitites, reduction of alcohol functionalities and carbon-carbon double bonds, reduction of nitrogen-containing functional groups, and other reduction reactions.

[0171] Reactions without change in the oxidation state: Reactions without change in the state of oxidation are exemplified without limitation to reactions such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

[0172] Carrier prodrugs are drug compounds that contain a transport moiety, e.g., that improves uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, the prodrug and any release transport moiety are acceptably non-toxic. For prodrugs where the transport

moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, e.g., certain polymers or other moieties, such as cyclodextrins. (See, e.g., Cheng et al., U.S. Patent Publ. No. 20040077595, App. No. 10/656,838, incorporated herein by reference.) Such carrier prodrugs are often advantageous for orally administered drugs. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (e.g., stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxyl groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, e.g., aliphatic alcohols. Wermuth, *supra*.

[0173] Prodrugs may proceed from prodrug form to active form in a single step or may have one or more intermediate forms which may themselves have activity or may be inactive.

[0174] Metabolites, e.g., active metabolites, overlap with prodrugs as described above, e.g., bioprecursor prodrugs. Thus, such metabolites are pharmacologically active compounds or compounds that further metabolize to pharmacologically active compounds that are derivatives resulting from metabolic processes in the body of a subject. Of these, active metabolites are such pharmacologically active derivative compounds. For prodrugs, the prodrug compound is generally inactive or of lower activity than the metabolic product. For active metabolites, the parent compound may be either an active compound or may be an inactive prodrug. Metabolites of a compound may be identified using routine techniques known in the art, and their activities determined using tests such as those described herein. For example, in some compounds, one or more alkoxy groups can be metabolized to hydroxyl groups while retaining pharmacologic activity and/or carboxyl groups can be esterified, e.g., glucuronidation. In some cases, there can be more than one metabolite, where an intermediate metabolite(s) is further metabolized to provide an active metabolite. For example, in some cases a derivative compound resulting from metabolic glucuronidation may be inactive or of low activity, and can be further metabolized to provide an active metabolite.

[0175] Prodrugs and active metabolites may be identified using routine techniques known in the art. See, e.g., Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, *supra*.

(f) Pharmaceutically acceptable salts

[0176] Compounds can be formulated as or be in the form of pharmaceutically acceptable salts. Contemplated pharmaceutically acceptable salt forms include, without limitation, mono, bis, tris, tetrakis, and so on. Pharmaceutically acceptable salts are non-toxic in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

[0177] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, chloride, bromide, iodide, hydrochloride, fumarate, maleate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, sulfamate, acetate, citrate, lactate, tartrate, sulfonate, methanesulfonate, propanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, xylenesulfonates, cyclohexylsulfamate, quinate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4 dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, phenylacetate, phenylpropionate, phenylbutyrate, gamma-hydroxybutyrate, glycollate, and mandelate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid,

ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

[0178] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, t-butylamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see *Remington's Pharmaceutical Sciences*, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

[0179] Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound can be dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt can be prepared by reacting the free base and acid in an organic solvent.

[0180] Thus, for example, if the particular compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0181] Similarly, if the particular compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as L-glycine, L-lysine, and L-arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as hydroxyethylpyrrolidine, piperidine, morpholine or piperazine,

and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0182] The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[0183] Unless specified to the contrary, specification of a compound herein includes pharmaceutically acceptable salts of such compound.

(g) Polymorphic forms

[0184] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

III. Administration

[0185] The methods and compounds will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. In this context, the terms "subject", "animal subject", and the like refer to human and non-human vertebrates, e.g., mammals such as non-human primates, sports and commercial animals, e.g., bovines, equines, porcines, ovines, rodents, and pets e.g., canines and felines.

[0186] Suitable dosage forms, in part, depend upon the use or the route of administration, for example, oral, transdermal, transmucosal, inhalant, or by injection (parenteral). Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and dosage forms that retard the compound or composition from exerting its effects. Techniques and formulations generally may be found in Remington: *The Science and Practice of Pharmacy*, 21st edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (hereby incorporated by reference herein).

[0187] Compounds of the present invention (i.e. Formula I, including Formulae Ia-Im, and all sub-embodiments disclosed herein) can be formulated as pharmaceutically acceptable salts.

[0188] Carriers or excipients can be used to produce compositions. The carriers or excipients can be chosen to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution, and dextrose.

[0189] The compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, transmucosal, rectal, transdermal, or inhalant. In some embodiments, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

[0190] Pharmaceutical preparations for oral use can be obtained, for example, by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate.

[0191] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, poly-vinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0192] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin ("gelcaps"), as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0193] Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and/or subcutaneous. For injection, the compounds of the invention are formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

[0194] Administration can also be by transmucosal, topical, transdermal, or inhalant means. For transmucosal, topical or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal).

[0195] The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments, and the like by choice of appropriate carriers known in the art. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Creams for topical application are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount solvent (e.g., an oil), is admixed. Additionally, administration by transdermal means may comprise a transdermal

patch or dressing such as a bandage impregnated with an active ingredient and optionally one or more carriers or diluents known in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[0196] For inhalants, compounds of the invention may be formulated as dry powder or a suitable solution, suspension, or aerosol. Powders and solutions may be formulated with suitable additives known in the art. For example, powders may include a suitable powder base such as lactose or starch, and solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride and other additives, such as acid, alkali and buffer salts. Such solutions or suspensions may be administered by inhaling via spray, pump, atomizer, or nebulizer, and the like. The compounds of the invention may also be used in combination with other inhaled therapies, for example corticosteroids such as fluticasone proprionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as albuterol, salmeterol, and formoterol; anticholinergic agents such as ipratroprium bromide or tiotropium; vasodilators such as treprostinal and iloprost; enzymes such as DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as single or double stranded DNA or RNA, siRNA; antibiotics such as tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

[0197] The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound EC_{50}, the biological half-life of the compound, the age, size, and weight of the subject, and the disorder associated with the subject. The importance of these and other factors are well known to those of ordinary skill in the art. Generally, a dose will be between about 0.01 and 50 mg/kg, preferably 0.1 and 20 mg/kg of the subject being treated. Multiple doses may be used.

[0198] The compounds of the invention may also be used in combination with other therapies for treating the same disease. Such combination use includes administration of the compounds and one or more other therapeutics at different times, or co-administration of the compound and one or more other therapies. In some embodiments, dosage may be modified for one or more of the compounds of the invention or other therapeutics used in

combination, e.g., reduction in the amount dosed relative to a compound or therapy used alone, by methods well known to those of ordinary skill in the art.

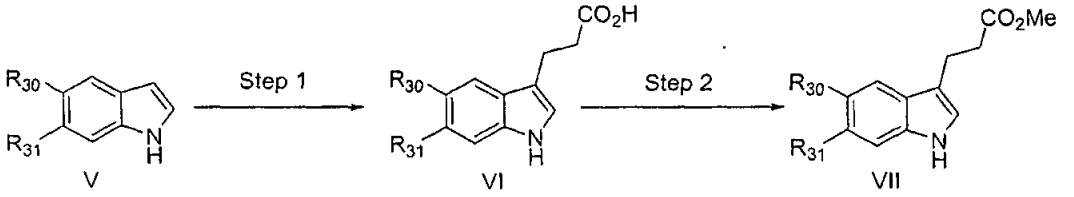
[0199] It is understood that use in combination includes use with other therapies, drugs, medical procedures etc., where the other therapy or procedure may be administered at different times (e.g. within a short time, such as within hours (e.g. 1, 2, 3, 4-24 hours), or within a longer time (e.g. 1-2 days, 2-4 days, 4-7 days, 1-4 weeks)) than a compound of the present invention, or at the same time as a compound of the invention. Use in combination also includes use with a therapy or medical procedure that is administered once or infrequently, such as surgery, along with a compound of the invention administered within a short time or longer time before or after the other therapy or procedure. In some embodiments, the present invention provides for delivery of compounds of the invention and one or more other drug therapeutics delivered by a different route of administration or by the same route of administration. The use in combination for any route of administration includes delivery of compounds of the invention and one or more other drug therapeutics delivered by the same route of administration together in any formulation, including formulations where the two compounds are chemically linked in such a way that they maintain their therapeutic activity when administered. In one aspect, the other drug therapy may be co-administered with one or more compounds of the invention. Use in combination by co-administration includes administration of co-formulations or formulations of chemically joined compounds, or administration of two or more compounds in separate formulations within a short time of each other (e.g. within an hour, 2 hours, 3 hours, up to 24 hours), administered by the same or different routes. Co-administration of separate formulations includes co-administration by delivery via one device, for example the same inhalant device, the same syringe, etc., or administration from separate devices within a short time of each other. Co-formulations of compounds of the invention and one or more additional drug therapies delivered by the same route includes preparation of the materials together such that they can be administered by one device, including the separate compounds combined in one formulation, or compounds that are modified such that they are chemically joined, yet still maintain their biological activity. Such chemically joined compounds may have a linkage that is substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.

IV. Synthesis of Compounds

[0200] Compounds with the chemical structure of Formulae I, Ia and Ib can be prepared for example, by the synthetic schemes described in US Patent Application Serial Number 10/937,791 (see also PCT publication WO 2005/009958). Compounds with the chemical structure of Formulae II and III can be prepared by a number of synthetic routes, including, for example, the synthetic schemes described herein. Additional synthetic routes can be utilized by one skilled in chemical synthesis.

[0201] One method to prepare the indole precursor with 3-propionic acid side chain (VII) involves the use of indole with Meldrum's acid to afford the propionic acid ester through a two step process in one pot as shown in Scheme I.

Scheme I:



Step 1: Preparation of the indole-3-propionic acid, VI

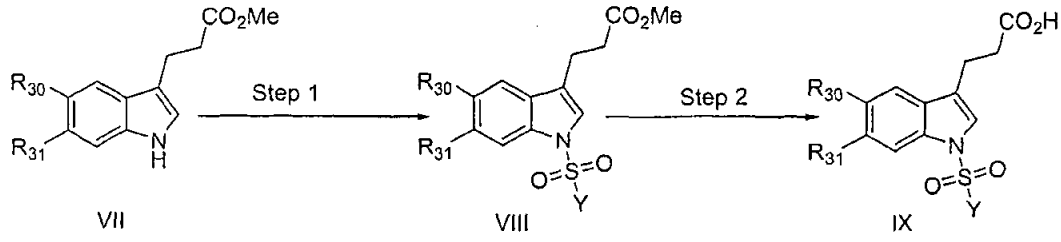
[0202] Into a microwave vessel, indole (1 equivalent), paraformaldehyde (1.1 equivalent), 2,2-dimethyl-1,3-dioxane-4,6-dione (1.1 equivalent), triethylamine (1.1 equivalent) are dissolved in acetonitrile (2 ml/mmol). The reaction is heated at 150°C for 3 minutes in a microwave reactor. The reaction is then diluted with acidified water (pH ~ 5 with acetic acid), and the aqueous layer was extracted with ethyl acetate. The organic layer is then washed with water, brine, and then dried over magnesium sulfate. Evaporation of solvent leads to a solid. The crude product is then purified via flash chromatography with step gradient of 2, 4, and 6% methanol in chloroform on silica to obtain the desired compound, **VI**, as an oil.

Step 2: Preparation of Compound VII.

[0203] Compound **VI** is stirred at ambient temperature with aqueous HCl (4M), with methanol and dioxane (1:1 equivalent) for 1 hour. The reaction mixture is then extracted with xylenes. The organic layer is evaporated, and compound **VII** is purified via flash chromatography on silica eluting with chloroform to obtain a solid.

[0204] The resulting propionic acid ester can be used to prepare the 1-sulfone substituted indole IX in two steps as shown in Scheme II.

Scheme II



VII VIII IX

Step 1: Preparation of Compound VIII

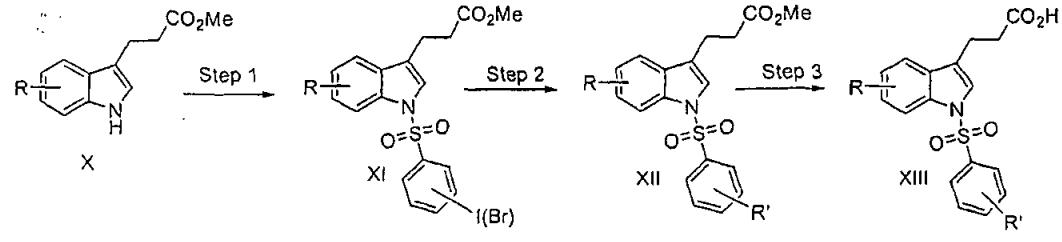
[0205] Compound **VII** (1mmol) in THF (5 ml), is combined with BEMP (1.1mmol), and substituted sulfonyl chloride (1.05 mmol) and mixed at room temperature for 2 hours. The crude product **VIII** is supplied directly to the saponification step next.

Step 2: Preparation of compound IX, deprotection of the methyl ester.

[0206] Into a flask, the crude reactant **VIII** is dissolved in 1M NaOH, and stirred for 4 hours at ambient temperature. The hydrolysis can be monitored via LC-MS. Upon full transformation, the basic solution is neutralized with acetic acid. Next, solvent is removed under reduced pressure to yield a crude solid. The crude material is then taken up in DMSO, and purified via reverse phase HPLC with a 20-100% Acetonitrile gradient (12 minute gradient). The purified material is then analyzed via HPLC to identify the pure fractions. The fractions are combined and concentrated to afford the desired compound **IX** as a solid.

[0207] Compounds having an optionally substitituted aryl sulfone on the indole nitrogen can be prepared in three steps as shown in Scheme III.

Scheme III



X XI XII XIII

*Step 1: Preparation of Compound **XI***

[0208] Compound **XI** is prepared by deprotonation of the indole nitrogen of compound **X** with the use of a base, such as for example, sodium hydride, and coupling with a halogen substituted aryl sulfonyl chloride in an inert solvent such as N,N-dimethylformamide.

*Step 2: Preparation of Compound **XII***

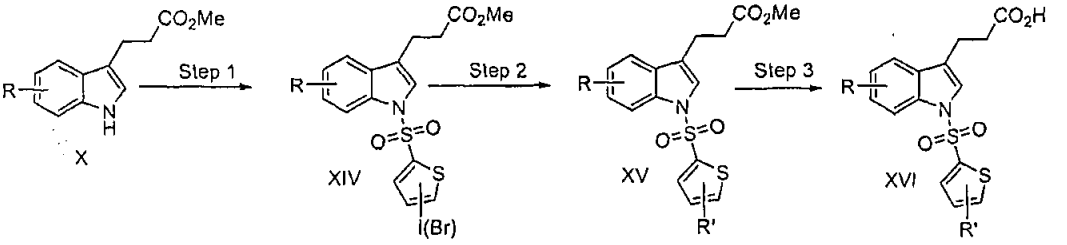
[0209] Compound **XII** is prepared through metal catalyzed (such as palladium) biaryl coupling of a boronic acid with halogen (iodo or bromo) substituted aromatic ring, under basic conditions (i.e., Suzuki Cross Coupling).

*Step 3: Preparation of Compound **XIII***

[0210] The final step of the synthesis of compound **XIII** involves the deprotection of the ester (methyl or ethyl) under saponification conditions with an aqueous hydroxide solution and an inert solvent such as tetrahydrofuran (THF).

[0211] Similarly, the Suzuki Cross Coupling reaction can also be extended to halogenated thiophenes. As illustrated in Scheme IV, bi-aryl substituted thiophenes can be generated through the same synthetic route as illustrated in Scheme III.

Scheme IV



*Step 1: Preparation of Compound **XIV***

[0212] Compound **XIV** is prepared through deprotonation of the indole nitrogen with the use of a base, such as for example, sodium hydride, and coupling with a halogen substituted thiophenyl sulfonyl chloride in an inert solvent such as N,N-dimethylformamide.

Step 2: Preparation of Compound XV

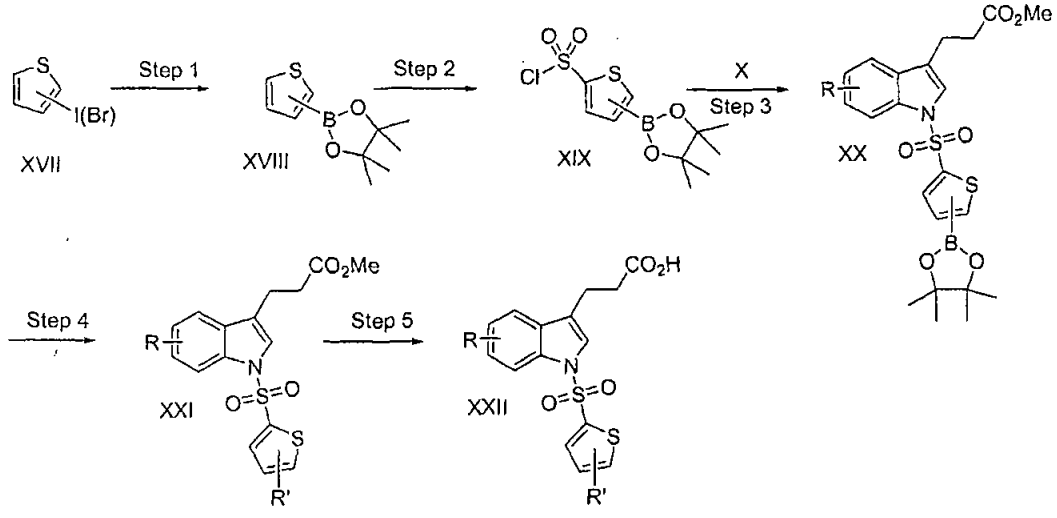
[0213] Compound **XV** is prepared through metal catalyzed (such as palladium) biaryl coupling of a boronic acid with a halogen (iodo or bromo) substituted aromatic ring, under basic conditions.

Step 3: Preparation of Compound XVI

[0214] In the final step of the synthesis of compound **XVI** the ester (methyl or ethyl) is deprotected under saponification conditions with an aqueous hydroxide solution with an inert solvent such as tetrahydrofuran (THF).

[0215] An alternative approach to generation of the biaryl linkage of the indole-1-sulfonamides contemplates reversing the order of the boronic acid/ester of the reagents. This synthetic strategy is illustrated in Scheme V using a thiophene as an example. Compounds of this type can be prepared in five synthetic steps.

Scheme V



Step 1: Preparation of Compound XVIII

[0216] From the halogenated thiophene **XVII**, a lithium exchange can occur, using reagents such as n-butyl lithium at -78 °C. The thienyl lithium can be coupled with boron trichloride. Subsequent hydrolysis of the dichloride with an alcohol or a 1,2-dihydroxyalkane, such as for example, pinacol would generate the desired boronic ester.

Step 2: Preparation of Compound XIX

[0217] Compound **XVIII** is treated with chlorosulfonic acid under cold conditions (define temperature) to add the sulfonyl chloride to the thiophene boronic ester.

Step 3: Preparation of Compound XX

[0218] Compound **XIX** is coupled to the indole **X** as described in Schemes III and IV using a base for deprotonation of the indole nitrogen, followed by coupling with the sulfonyl chloride in an inert solvent such as N,N-dimethylformamide.

Step 4: Preparation of Compound XXI

[0219] Compound **XXI** is prepared through metal catalyzed (such as palladium) biaryl coupling of a boronic acid with a halogen (Iodo or Bromo) substituted aromatic ring, under basic conditions.

Step 5: Preparation of Compound XXII

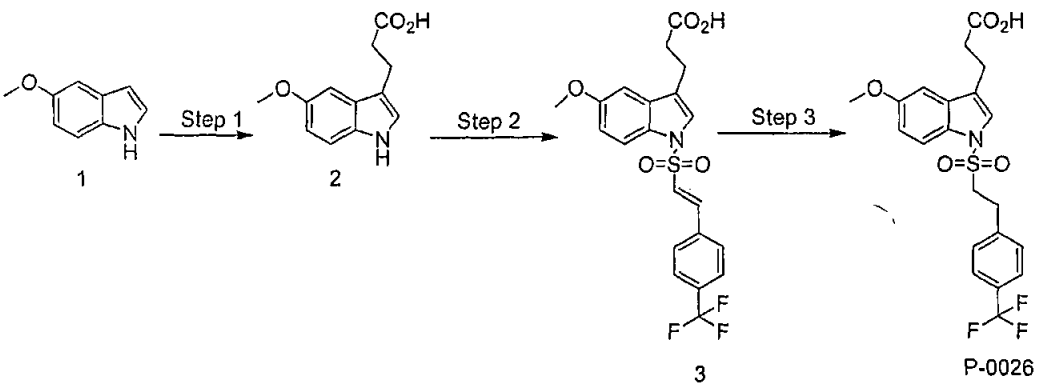
[0220] The final step of the synthesis involves the deprotection of the ester (methyl or ethyl) under saponification conditions with an aqueous hydroxide solution with an inert solvent such as tetrahydrofuran (THF).

EXAMPLES

Example 1: Synthesis of 3-{5-methoxy-1-[(E)-2-(4-trifluoromethyl-phenyl)-ethanesulfonyl]-1H-indol-3-yl}-propionic acid (P-0026).

[0221] Compound **P-0026** was synthesized in three steps from 5-methoxy indole **1** as shown in Scheme 1.

Scheme 1



Step 1: Preparation of 3-(5-methoxy-1H-indol-3-yl)-propionic acid (2)

[0222] To a solution of 5-methoxyindole (**1**, 4.00 g, 0.0272 mol) dissolved in acetic acid (13 mL, 0.22 mol) containing acetic anhydride (5 mL, 0.06 mol), acrylic acid (4.06 mL, 0.0592 mol) was added and the reaction was heated to 90 °C for 3 hrs. The reaction mixture was then concentrated, 3 ml NaOH (2M) was added and the mixture stirred for 5 min. The insoluble material was removed by filtration. The filtrate was acidified with 6M HCl. The precipitate was filtered off to yield **2** (1.95 g, 33%).

Step 2: Preparation of 3-5-Methoxy-1-[(E)-2-(4-trifluoromethyl-phenyl)-ethenesulfonyl]-1H-indol-3-yl-propionic acid (**3**)

[0223] Into a dried and argon bled round bottom flask was dissolved 3-(5-Methoxy-1H-indol-3-yl)-propionic acid (**2**, 90.0 mg, 0.000410 mol) in dry Tetrahydrofuran (4 mL, 0.06 mol). The solution was cooled to -76 °C and 2.5 M of n-Butyllithium in Hexane (328 uL) was added drop wise. After 15 minutes (E)-2-(4-Trifluoromethyl-phenyl)-ethenesulfonyl chloride (167 mg, 0.000616 mol) dissolved in 0.5 ml dry THF was added drop wise. The reaction was stirred overnight. EtOAc was added to the mixture and then acidified with HCl (1M). The mixture was stirred for 1 hour. The organic phase was separated and the aqueous phase was extracted 3 times with EtOAc. The pooled organic phase was dried (Na2SO4) and the mixture was concentrated, then put on silica and purified with flash chromatography (0.5% MeOH in DCM) to yield 33 mg, 18% of **3**.

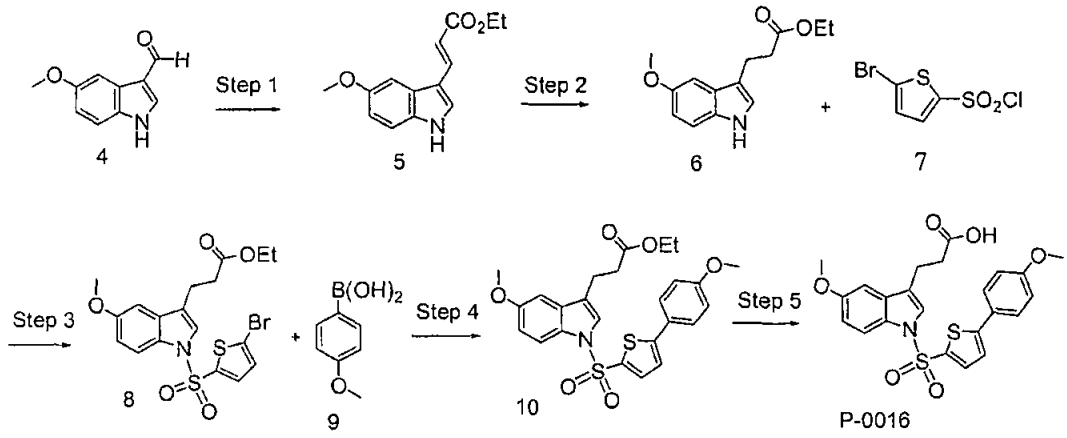
Step 3: Preparation of 3-5-Methoxy-1-[(E)-2-(4-trifluoromethyl-phenyl)-ethanesulfonyl]-1H-indol-3-yl-propionic acid. (**P-0026**)

[0224] To 3-5-Methoxy-1-[(E)-2-(4-trifluoromethyl-phenyl)-ethenesulfonyl]-1H-indol-3-yl-propionic acid (**3**, 8 mg, 0.00002 mol) dissolved in Tetrahydrofuran (2.0 mL, 0.025 mol), 5% Pd/C (5:95, Palladium:Carbon, 7 mg) was added to the solution. The mixture was stirred overnight under an atmosphere of hydrogen gas. The palladium was filtered off, and the solution evaporated to give **P-0026** (8.0 mg, 100%). Calculated molecular weight 455.45, MS (ESI) $[M+H^+]^+ = 454.0$.

Example 2: Synthesis of 3-{5-methoxy-1-[5-(4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (P-0016).

[0225] Compound **P-0016** was synthesized in five steps from 5-methoxyindole-3-carboxaldehyde **4** as shown in Scheme 2.

Scheme 2



Step 1: Preparation of 3-(5-methoxy-1H-indol-3-yl)-acrylic acid ethyl ester (**5**)

[0226] To a cold solution (ice bath) of ethyl diethylphosphonoacetate (30.11 g, 0.134 mol) in tetrahydrofuran (300 mL) under nitrogen, was added sodium hydride (6.44 g, 0.161 mol, 60%) in four portions, and stirred until hydrogen evolution ceased (caution: very vigorous evolution of gas). A solution of 5-methoxyindole-3-carboxyaldehyde (**4**,19.61 g, 0.112 mol) in 350 mL tetrahydrofuran was added over a period of 60 minutes to the phosphonate solution. The reaction mixture was heated to 55 °C for 24 hours, after which the mixture was diluted with 650 mL dichloromethane and washed with water (200 mL; 3X). The organic layer was washed once with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give a yellow-tinted oil, which was purified by filtering through a silica plug. The filtrate was evaporated to afford compound **5** as an off white solid. ^{1}H NMR is consistent with the compound structure set forth above.

Step 2 – Preparation of 3-(5-methoxy-1H-indol-3-yl)-propionic acid ethyl ester (**6**)

[0227] To a solution of 3-(5-methoxy-1*H*-indol-3-yl)-acrylic acid ethyl ester **5** in 250 mL ethyl acetate was added palladium on activated carbon (10%; 3 g). The solution was deoxygenated under vacuum and hydrogen was introduced to the reaction flask from a balloon filled with hydrogen. The process was repeated three times and the reaction mixture was stirred for 16 hours at room temperature. The mixture was filtered through celite and the filtrate was evaporated under reduced pressure to yield compound **6** as a while solid (18.9 g, 68% yield). 1H NMR is consistent with the compound structure set forth above.

Step 3: Preparation of 3-[1-(5-bromo-thiophen-2-ylmethyl)-5-methoxy-1H-indol-3-yl]-propionic acid ethyl ester (**8**)

[0228] To a dry round bottom flask, 3-(5-methoxy-1H-indol-3-yl)-propionic acid ethyl ester (**6**, 492.0 mg, 1.9 mmol) was dissolved with dichloromethane (12 mL). Tetrabutylammonium hydrogen sulfate (30 mg) and 50% KOH solution (5 mL) were added next. After about 5 minutes of stirring, 5-bromo thiophene-2-sulfonyl chloride (**7**, 774.0 mg, 2.9 mmol) was added. This reaction was allowed to stir at ambient temperature overnight, after which 50 mL water and 150 mL ethyl acetate were added to the reaction. The layers were separated and the organic layer was washed with saturated bicarbonate (3 X 75 mL) and water (2 X 75 mL) to remove the hydroxide and sulfonate salt, then washed with brine (1 X 75 mL) and dried over anhydrous sodium sulfate. Evaporation under reduced pressure afforded compound **8** as a brown oil. (820 mg, 87%). ^{1}H NMR is consistent with the compound structure set forth above.

Step 4: Preparation of 3-{5-methoxy-1-[5-(4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid ethyl ester (**10**)

[0229] Into a 50 mL oven dried round bottom flask, 3-[1-(5-bromo-thiophen-2-ylmethyl)-5-methoxy-1H-indol-3-yl]-propionic acid ethyl ester (**8**, 300 mg, 0.064 mmol) was dissolved in dry tetrahydrofuran (8 mL) under an argon flow. 4-Methoxy-phenyl boronic acid (**9**, 24.0 mg, 0.16 mmol), tetrakis(triphenylphosphine) palladium(0) (7.2 mg, 0.006 mmol) and 1 N K_2CO_3 (0.4 mL) were added. A condenser equipped with argon gas line was attached and the reaction heated at 48 °C for 3 days. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel, using a gradient of 0-10% ethyl acetate/hexane to provide compound **10**. ^{1}H NMR is consistent with the compound structure set forth above.

Step 5: Synthesis of 3-{5-methoxy-1-[5-(4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0016**)

[0230] To a solution of 3-{5-methoxy-1-[5-(4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid ethyl ester **10** in tetrahydrofuran (4 mL) was added an aqueous solution of potassium hydroxide (1 mL of 1M) and stirred at room temperature overnight. The acid product was isolated by neutralizing the reaction mixture with aqueous hydrochloric acid, extracting the product with ethyl acetate, drying over anhydrous magnesium sulfate, evaporating under reduced pressure, and triturating with

diethyl ether to afford **P-0016** as a white solid (10 mg, 32%) Calculated molecular weight 471.55, MS(ESI) $[M - H^+]^-$ = 470.11).

[0231] Additional compounds were prepared following the protocol of Scheme 2, replacing 4-methoxy-phenyl boronic acid **9** with an appropriate boronic acid in Step 4. The following compounds were prepared by this method:

3-{5-Methoxy-1-[5-(4-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid ethyl ester (**P-0014**, isolated after Step 4),

3-{5-Methoxy-1-[5-(4-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0015**),

3-{1-[5-(4-Ethoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0017**),

3-{5-Methoxy-1-[5-(3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0019**),

3-{5-Methoxy-1-[5-(3-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0018**),

3-{5-Methoxy-1-[5-(4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0020**),

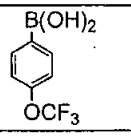
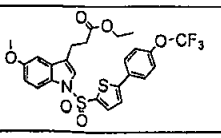
3-{5-Methoxy-1-[5-(4-propoxy-phenyl) -thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0035**),

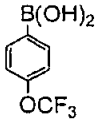
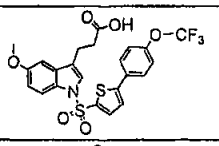
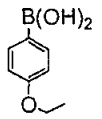
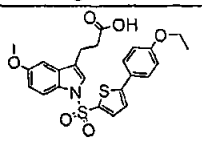
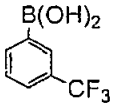
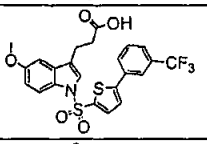
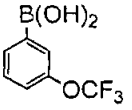
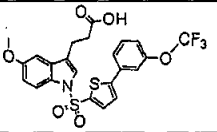
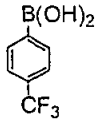
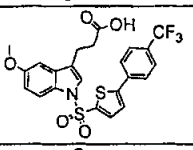
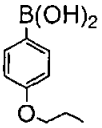
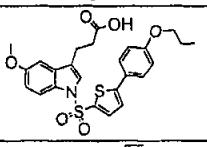
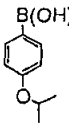
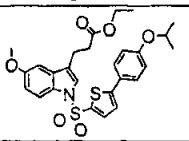
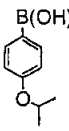
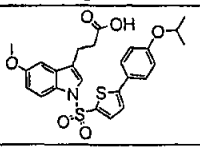
3-{1-[5-(4-Isopropoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid ethyl ester (**P-0036**, isolated after Step 4), and

3-{1-[5-(4-Isopropoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0037**).

These compounds are shown in the following Table 1, where the compound number is provided in Column 1, the boronic acid used in Step 4 in Column 2, the compound structure in Column 3, and the calculated and measured mass in Columns 4 and 5.

Table 1.

Cmpd. number	Boronic acid	Compound structure	Molecular weight	
			Calc.	Measured MS(ESI)
P-0014			525.53	$[M+H^+]^+$ = 526.16

Cmpd. number	Boronic acid	Compound structure	Molecular weight	
			Calc.	Measured MS(ESI)
P-0015			471.55	$[M - H^+]^-$ = 470.11
P-0017			485.10	$[M - H^+]^-$ = 484.17
P-0019			509.06	$[M - H^+]^-$ = 508.12
P-0018			525.05	
P-0020			509.52	$[M - H^+]^-$ = 508.12 $[M+H^+]^+$ = 510.20
P-0035			499.61	
P-0036			527.66	
P-0037			499.61	

[0232] Additional compounds were prepared following the protocol of Scheme 2, optionally replacing 5-methoxyindole-3-carboxyaldehyde **4** with an appropriate indole carboxyaldehyde in Step 1, and/or optionally replacing 5-bromo thiophene-2-sulfonyl chloride **7** with an appropriate sulfonyl chloride in Step 3, and taking the product of Step 3 directly on to Step 5 to form the propionic acid. The following compounds were prepared by this method, with the calculated molecular weight and measured mass (MS(ESI)) provided after the compound:

3-{5-Fluoro-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0002**), calculated MW 501.47, $[M - H^+]^-$ = 500.08,

3-{5-Fluoro-1-[5-(5-trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0003**), calculated MW 488.43, $[M-H^+]^-$ = 487.08,
3-{5-Chloro-1-[5-(5-trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0004**), calculated MW 504.92, $[M+H^+]^+$ = 505.48, $[M-H^+]^-$ = 503.06,
3-{1-[4-(4-Trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0006**), calculated MW 489.47, $[M+H^+]^+$ = 488.32,
3-{1-[5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0007**), calculated MW 483.49, $[M-H^+]^-$ = 482.2,
3-{5-Methoxy-1-[5-(5-trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0008**), calculated MW 500.47, $[M-H^+]^-$ = 499.1,
3-{5-Ethoxy-1-[5-(5-trifluoromethyl-isoxazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid ethyl ester (**P-0009**), calculated MW 528.52, $[M-H^+]^-$ = 527.1,
3-{5-Chloro-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0033**), calculated MW 517.0, $[M+H^+]^+$ = 518.15, $[M-H^+]^-$ = 516.07,
3-{5-Methoxy-1-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl} propionic acid (**P-0034**), calculated MW 513.53, $[M+H^+]^+$ = 514.33, $[M-H^+]^-$ = 512.24,
3-{5-Methoxy-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0047**), calculated MW 452.49, $[M+H^+]^+$ = 453.1,
3-{5-Methoxy-1-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0048**), calculated MW 481.53, $[M+H^+]^+$ = 482.3,
3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0049**), calculated MW 520.39, $[M-H^+]^-$ = 519.9,
3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0050**), calculated MW 520.39, $[M-H^+]^-$ = 519.9,
3-{5-Methoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0051**), calculated MW 519.50, $[M+H^+]^+$ = 519.9,
3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0052**), calculated MW 534.42, $[M-H^+]^-$ = 533.9,
3-{5-Ethoxy-1-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0053**), calculated MW 503.62, $[M+H^+]^+$ = 520.3,
3-{5-Ethoxy-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid

(**P-0055**), calculated MW 466.52, $[M+H^+]^+ = 467.1$,

3-{5-Ethoxy-1-[4-(pyridin-3-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0056**), calculated MW 466.52, $[M+H^+]^+ = 467.1$,

3-{5-Ethoxy-1-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0057**), calculated MW 495.56, $[M+H^+]^+ = 496.3$,

3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0058**), calculated MW 534.42, $[M-H^+]^- = 533.9$,

3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0059**), calculated MW 534.42, $[M-H^+]^- = 533.9$,

3-{5-Ethoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0060**), calculated MW 533.53, $[M+H^+]^+ = 533.9$,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0061**), calculated MW 568.96, $[M+H^+]^+ = 569.2$,

3-[5-Ethoxy-1-(4'-methoxy-biphenyl-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0062**), calculated MW 479.56, $[M+H^+]^+ = 480.3$,

3-[5-Ethoxy-1-(6-morpholin-4-yl-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0063**), calculated MW 459.53, $[M+H^+]^+ = 460.3$,

3-[5-Ethoxy-1-(6-phenoxy-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0064**), calculated MW 466.52, $[M+H^+]^+ = 467.1$,

3-[5-Ethoxy-1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0065**), calculated MW 456.54, $[M+H^+]^+ = 457.1$,

3-{5-Ethoxy-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0066**), calculated MW 527.55, $[M+H^+]^+ = 527.9$,

3-{5-Methoxy-1-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0067**), calculated MW 489.59, $[M-H^+]^- = 489.1$,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0068**), calculated MW 554.93, $[M+H^+]^+ = 555.2$,

3-{5-Methoxy-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0069**), calculated MW 513.52, $[M-H^+]^- = 512.09$,

3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0071**), calculated MW 520.39, $[M-H^+]^- = 520.3$,

3-[5-Methoxy-1-(4'-methoxy-biphenyl-4-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0072**), calculated MW 465.53, $[M+H^+]^+ = 466.3$,3-[5-Methoxy-1-(5-methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0146**), calculated MW 439.49, $[M+H^+]^+ = 440.3$,

3-{5-Methoxy-1-[3-(pyridine-2-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0150**), calculated MW 464.50, $[M+H^+]^+ = 465.1$,

3-{5-Methoxy-1-[3-(pyridine-4-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0151**), calculated MW 464.50, $[M+H^+]^+ = 465.1$,

3-[1-(Biphenyl-2-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid (**P-0152**), calculated MW 435.50, $[M+H^+]^+ = 436.3$,

3-[5-Methoxy-1-(4-pyrazol-1-yl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid (**P-0155**), calculated MW 425.47, $[M+H^+]^+ = 426.3$,

3-[5-Methoxy-1-(2-phenoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid (**P-0162**), calculated MW 451.50, $[M+H^+]^+ = 451.9$,

3-{5-Ethoxy-1-[3-(pyridine-4-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0168**), calculated MW 478.53, $[M+H^+]^+ = 479.1$,

3-[5-Methoxy-1-(6-morpholin-4-yl-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0214**), calculated MW 445.50, $[M+H^+]^+ = 446.3$,

3-[5-Methoxy-1-(6-phenoxy-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0215**), calculated MW 452.49, $[M+H^+]^+ = 453.1$,

3-[5-Methoxy-1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0216**), calculated MW 442.52, $[M+H^+]^+ = 443.5$,

3-{5-Isopropoxy-1-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0311**), calculated MW 517.46, $[M+H^+]^+ = 517.9$,

3-{5-Isopropoxy-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0316**), calculated MW 480.54, $[M+H^+]^+ = 481.1$,

3-{5-Isopropoxy-1-[4-(pyridin-4-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0317**), calculated MW 480.54, $[M+H^+]^+ = 481.1$,

3-{5-Isopropoxy-1-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0318**), calculated MW 509.98, $[M+H^+]^+ = 510.3$,

3-{5-Isopropoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0319**), calculated MW 547.55, $[M+H^+]^+ = 548.3$,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5-isopropoxy-1H-indol-3-yl}-propionic acid (**P-0320**), calculated MW 582.99, $[M+H^+]^+ = 583.2$,

3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-isopropoxy-1H-indol-3-yl}-

propionic acid (**P-0321**), calculated MW 548.45, $[M-H^+]^-$ = 547.9,
3-[5-Isopropoxy-1-(4'-methoxy-biphenyl-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0322**), calculated MW 493.58, $[M+H^+]^+$ = 494.3,
3-[5-Isopropoxy-1-(6-phenoxy-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0323**), calculated MW 480.54, $[M+H^+]^+$ = 481.1,
3-[5-Isopropoxy-1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0324**), calculated MW 470.57, $[M+H^+]^+$ = 471.1,
3-{5-Isopropoxy-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0326**), calculated MW 541.57, $[M+H^+]^+$ = 541.9,
3-[1-(Biphenyl-2-sulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid (**P-0332**), calculated MW 463.56, $[M+H^+]^+$ = 463.9,
3-[5-Isopropoxy-1-(4'-methyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0338**), calculated MW 477.58, $[M+H^+]^+$ = 478.3,
3-[5-Isopropoxy-1-(2-phenoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid (**P-0339**), calculated MW 479.56, $[M+H^+]^+$ = 479.9,
3-(5-Ethoxy-1-{4-[(morpholine-4-carbonyl)-amino]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid (**P-0342**), calculated MW 501.56, $[M+H^+]^+$ = 502.3,
3-{5-Ethoxy-1-[3-(pyridine-2-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0344**), calculated MW 478.53, $[M+H^+]^+$ = 479.1,
3-{5-Isopropoxy-1-[4-(pyridin-3-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0371**), calculated MW 480.54, $[M+H^+]^+$ = 481.1,
3-[5-Isopropoxy-1-(4-pyrazol-1-yl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid (**P-0375**), calculated MW 453.52, $[M+H^+]^+$ = 454.3,
3-[5-Ethoxy-1-(4'-methyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0386**), calculated MW 463.55, $[M+H^+]^+$ = 464.3,
3-[5-Methoxy-1-(4'-trifluoromethoxy-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0391**), calculated MW 519.49, $[M - H^+]^-$ = 518.26,
3-[5-Methoxy-1-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0392**), calculated MW 503.50, $[M - H^+]^-$ = 502.25,
3-{1-[3-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0560**), calculated MW 520.39, $[M - H^+]^-$ = 518.02,
3-{5-Methoxy-1-[3-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0561**), calculated MW 481.52, $[M - H^+]^-$ = 480.09,

3-[5-Methoxy-1-(3-p-tolyloxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid ethyl ester (**P-0562**), calculated MW 493.58, $[M+H^+]^+ = 494.2$,

3-{1-[3-(4-Chloro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid ethyl ester (**P-0563**), calculated MW 514.00, $[M+H^+]^+ = 514.9$,

3-{5-Methoxy-1-[3-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0564**), calculated MW 519.49, $[M+H^+]^+ = 520.11$, $[M-H^+]^- = 518.06$,

3-{1-[3-(4-Fluoro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid ethyl ester (**P-0565**), calculated MW 497.54, $[M+H^+]^+ = 498.2$,

3-[5-Methoxy-1-(3-p-tolyloxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid (**P-0566**), calculated MW 465.52, $[M - H^+]^- = 464.1$,

3-{1-[3-(4-Chloro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0567**), calculated MW 485.94, $[M - H^+]^- = 484.3$,

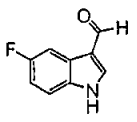
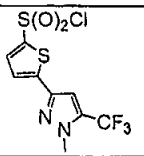
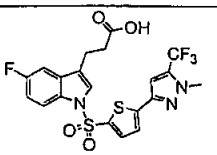
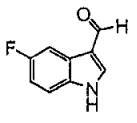
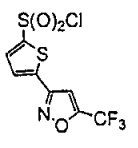
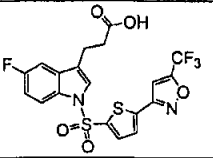
3-{1-[3-(4-Fluoro-phenoxy)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0568**), calculated MW 469.49, $[M - H^+]^- = 468.1$,

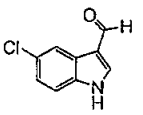
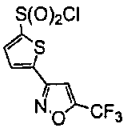
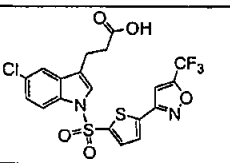
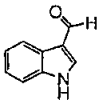
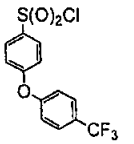
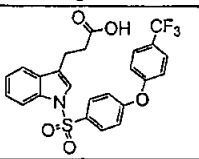
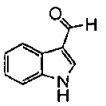
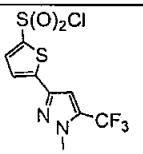
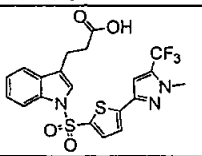
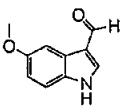
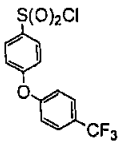
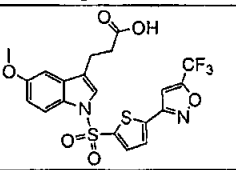
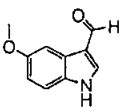
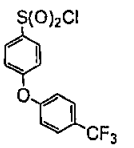
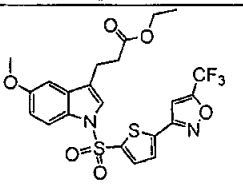
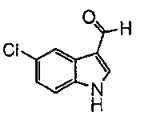
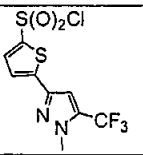
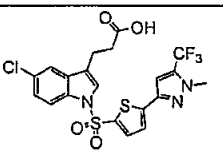
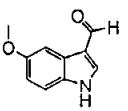
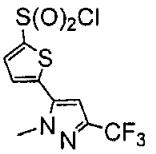
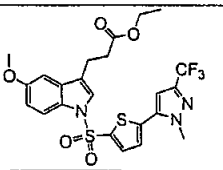
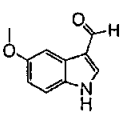
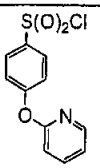
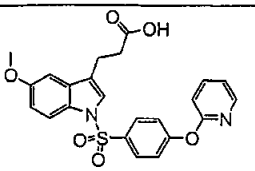
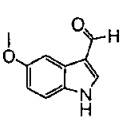
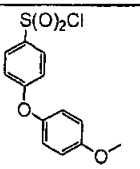
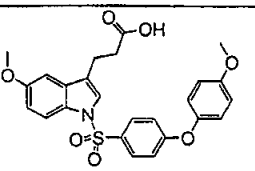
3-[5-Methoxy-1-(4'-trifluoromethyl-biphenyl-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0570**), calculated MW 503.50, and

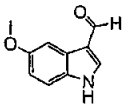
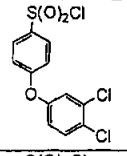
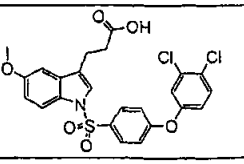
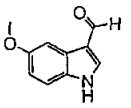
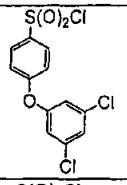
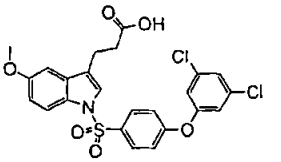
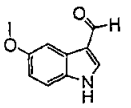
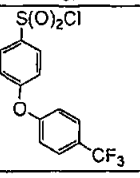
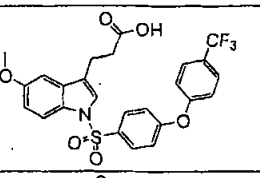
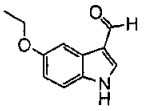
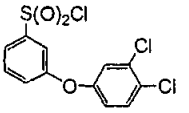
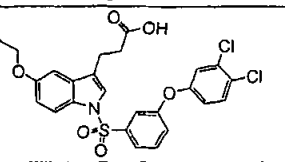
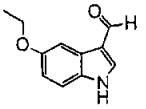
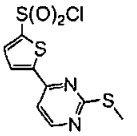
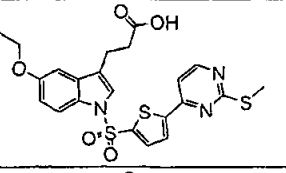
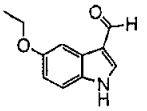
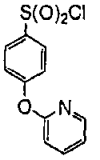
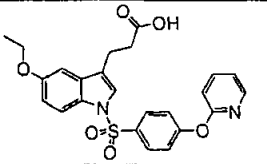
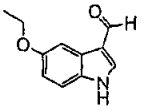
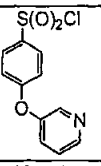
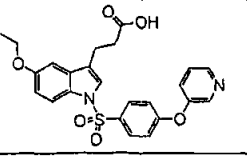
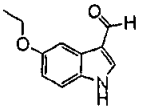
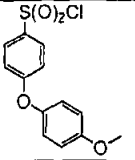
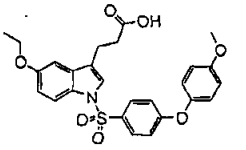
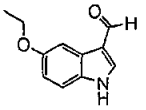
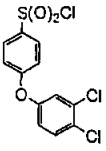
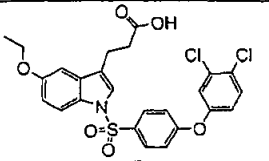
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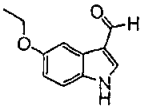
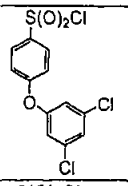
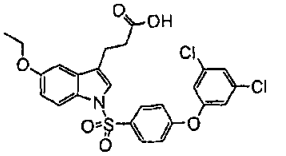
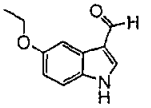
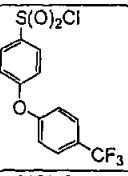
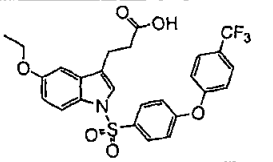
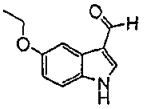
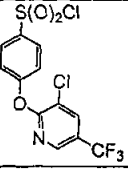
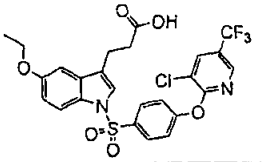
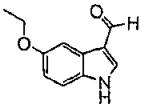
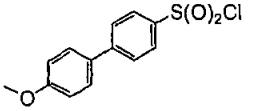
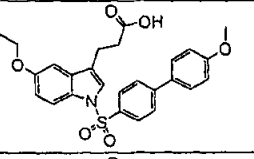
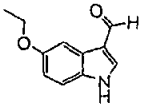
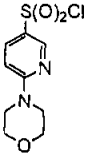
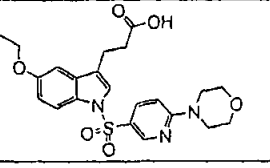
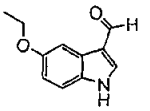
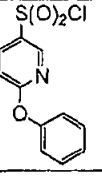
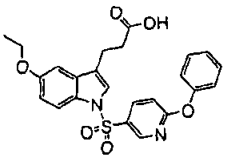
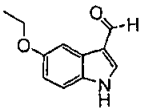
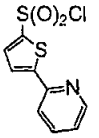
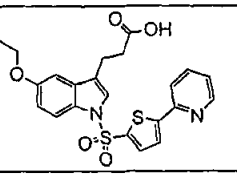
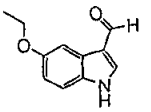
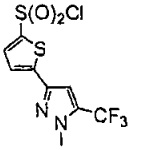
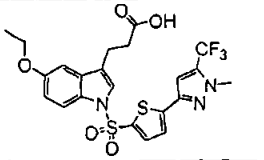
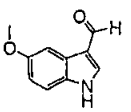
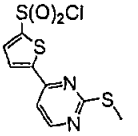
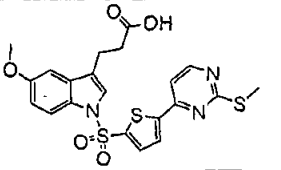
These compounds are shown in the following Table 2, where the compound number is provided in Column 1, the indole carboxyaldehyde used in Step 1 in Column 2, the sulfonyl chloride used in Step 3 in Column 3, with the compound structure in Column 4.

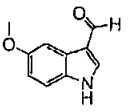
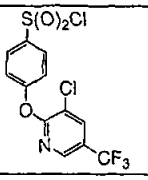
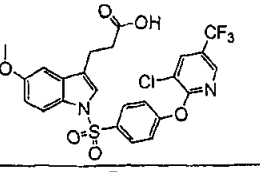
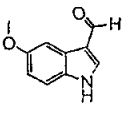
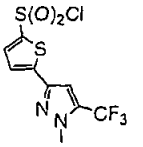
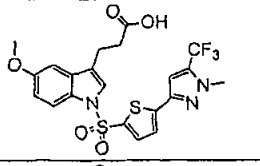
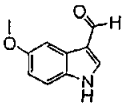
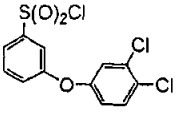
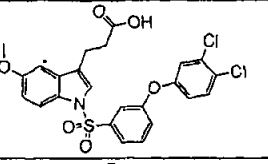
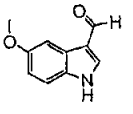
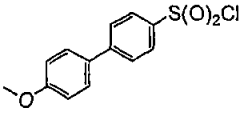
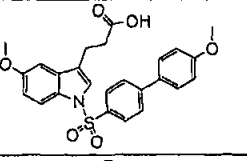
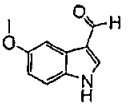
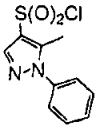
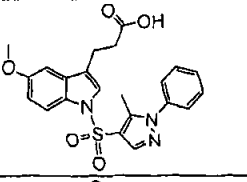
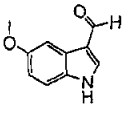
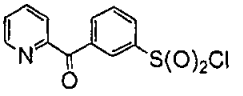
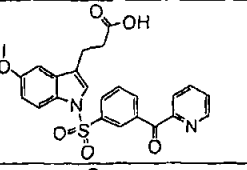
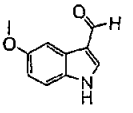
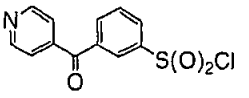
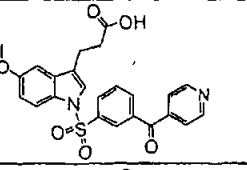
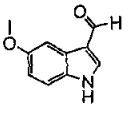
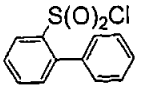
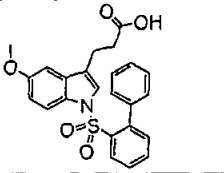
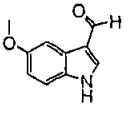
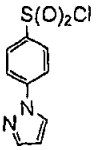
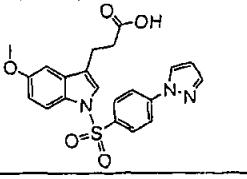
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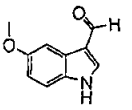
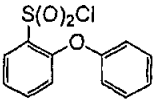
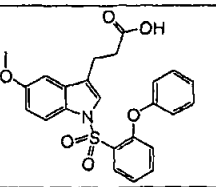
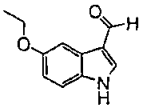
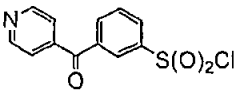
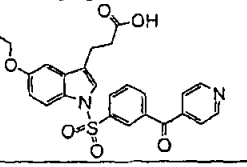
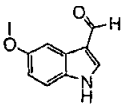
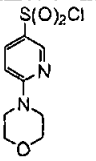
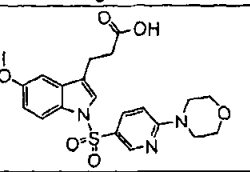
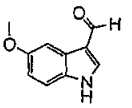
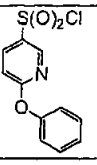
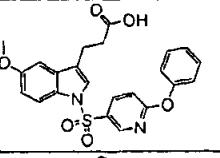
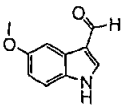
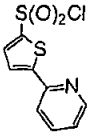
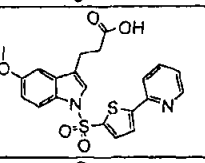
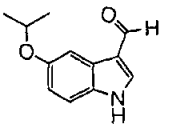
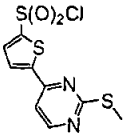
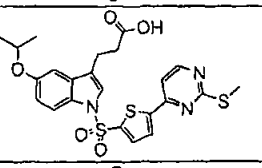
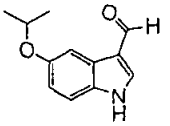
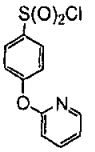
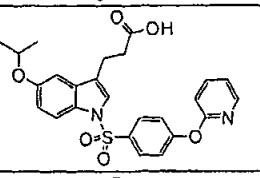
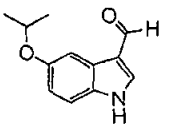
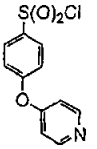
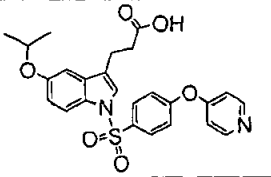
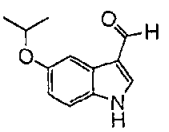
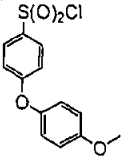
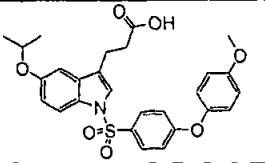
Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0002			
P-0003			

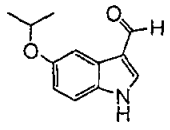
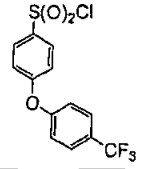
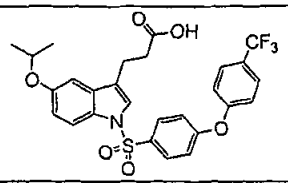
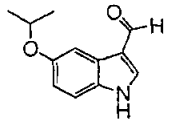
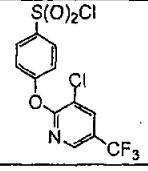
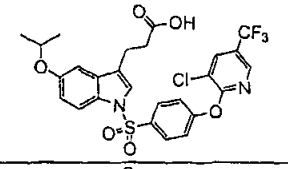
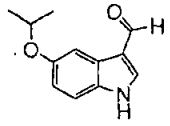
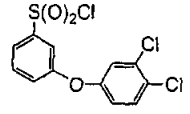
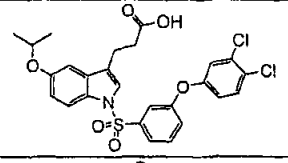
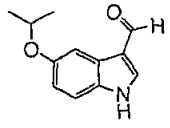
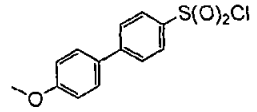
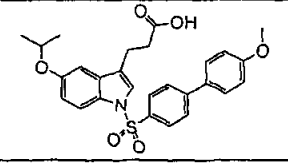
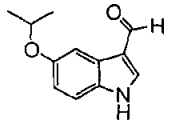
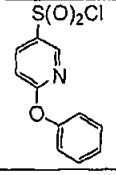
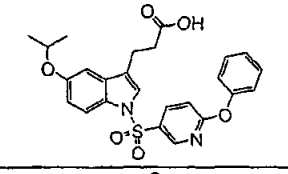
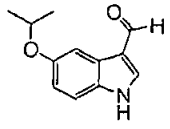
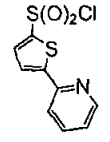
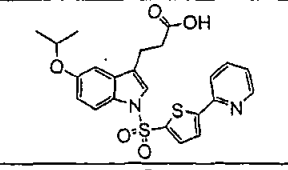
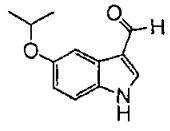
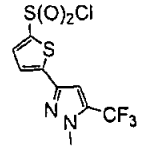
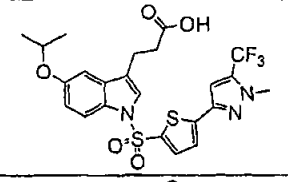
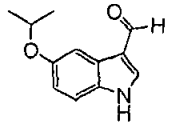
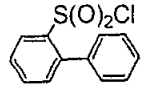
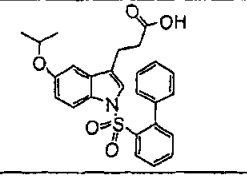
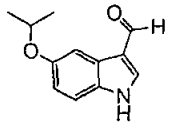
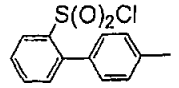
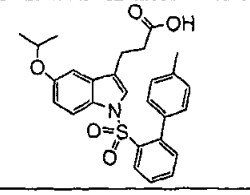
Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0004			
P-0006			
P-0007			
P-0008			
P-0009 *			
P-0033			
P-0034			
P-0047			
P-0048			

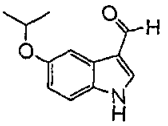
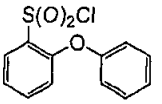
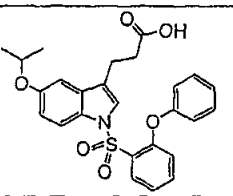
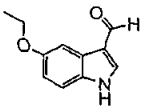
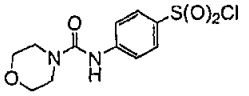
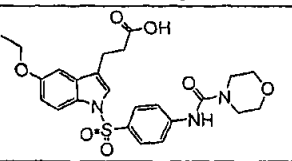
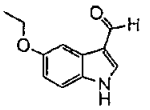
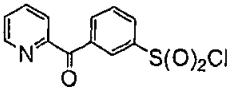
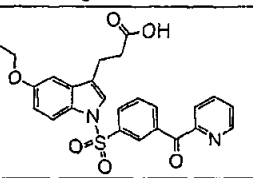
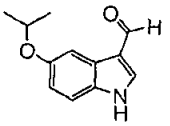
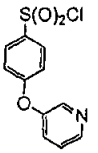
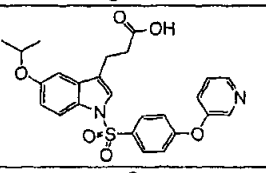
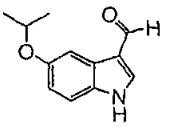
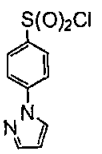
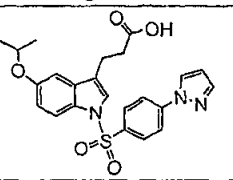
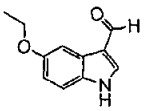
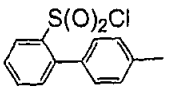
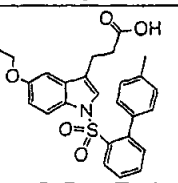
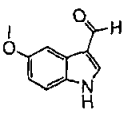
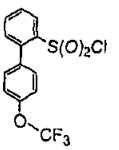
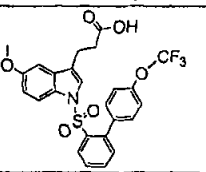
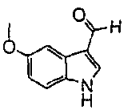
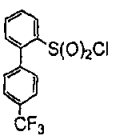
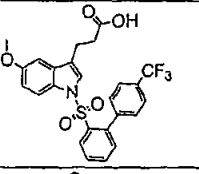
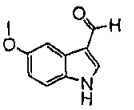
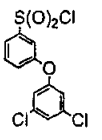
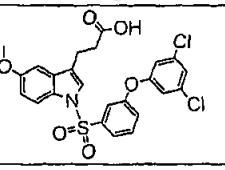
Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0049			
P-0050			
P-0051			
P-0052			
P-0053			
P-0055			
P-0056			
P-0057			
P-0058			

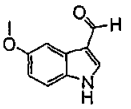
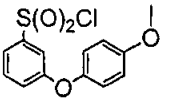
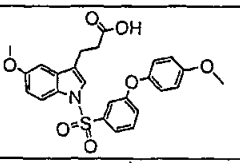
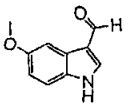
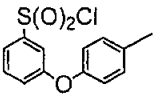
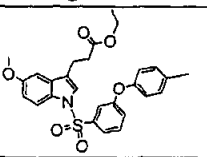
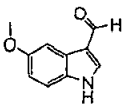
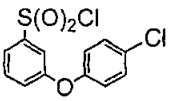
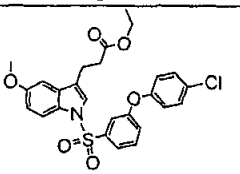
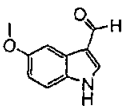
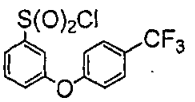
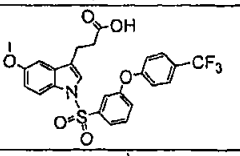
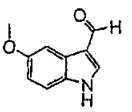
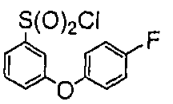
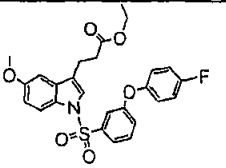
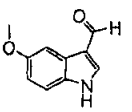
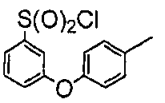
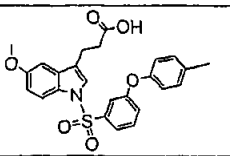
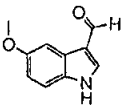
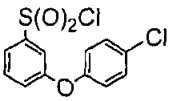
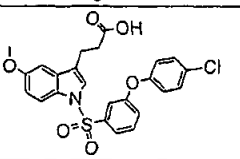
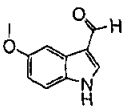
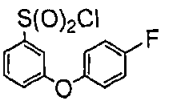
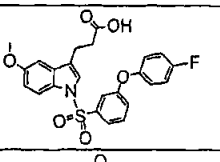
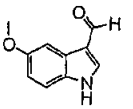
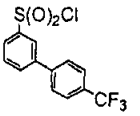
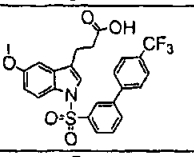
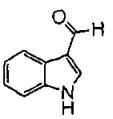
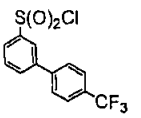
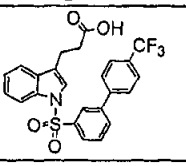
Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0059			
P-0060			
P-0061			
P-0062			
P-0063			
P-0064			
P-0065			
P-0066			
P-0067			

Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0068			
P-0069			
P-0071			
P-0072			
P-0146			
P-0150			
P-0151			
P-0152			
P-0155			

Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0162			
P-0168			
P-0214			
P-0215			
P-0216			
P-0311			
P-0316			
P-0317			
P-0318			

Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0319			
P-0320			
P-0321			
P-0322			
P-0323			
P-0324			
P-0326			
P-0332			
P-0338			

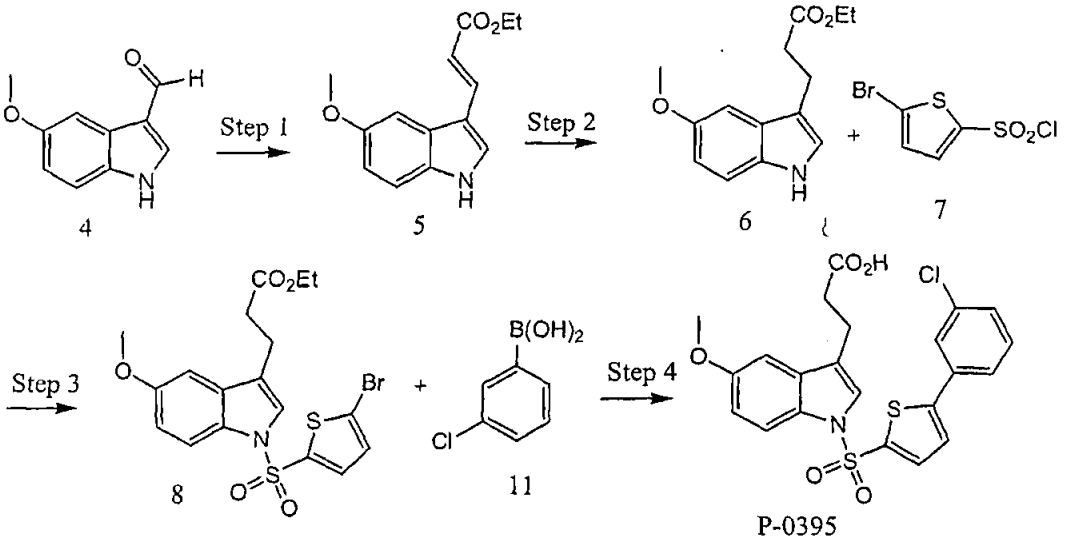
Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0339			
P-0342			
P-0344			
P-0371			
P-0375			
P-0386			
P-0391			
P-0392			
P-0560			

Cmpd. number	Indole-3-carboxyaldehyde	Sulfonyl chloride	Compound structure
P-0561			
P-0562 *			
P-0563 *			
P-0564			
P-0565 *			
P-0566			
P-0567			
P-0568			
P-0570			
P-0572			

* Isolated after Step 3.

[0233] Compounds were also prepared by an alternative route to Steps 4 and 5 as shown in Scheme 2a.

Scheme 2a



Step – 1 through Step-3: See Scheme 2 above

Step-4: Synthesis of 3-{1-[5-(3-chloro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0395**)

[0234] 10 mg of 3-[1-(5-bromo-thiophen-2-ylmethyl)-5-methoxy-1H-indol-3-yl]-propionic acid ethyl ester **8** was dissolved in 400 µL of acetonitrile and 2 equivalents of the 3-chloro-phenyl boronic acid **11** was added. 200 µL of 1M K_2CO_3 was added and 10 µL of $Pd(AOc)_2$ /di-tbutylbiphenylphosphine (0.2 M solution in toluene) was added. The reaction mixture was irradiated for 10 minutes at 160 °C in the microwave. The solution was neutralized with acetic acid and the solvents removed under vacuum. The crude material was dissolved in 500 µL of dimethyl sulfoxide and purified by reverse phase HPLC (C18 column), eluting with a water/0.1% trifluoro acetic acid and acetonitrile/0.1% trifluoro acetic acid gradient, 20-100% acetonitrile over 16 minutes. Calculated molecular weight 475.97, $[M+H^+]^+ = 475.9$.

[0235] Additional compounds were prepared following the protocol of Scheme 2a, optionally replacing 5-methoxyindole-3-carboxyaldehyde **4** with an appropriate indole-3-carboxyaldehyde in Step 1, and/or optionally replacing 3-chloro-phenyl boronic acid **11**

with an appropriate boronic acid in Step 4. The following compounds were prepared by this method, with the calculated molecular weight and measured mass (MS(ESI)) provided after the compound:

3-{1-[5-(3,5-Bis-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0001**), calculated MW 577.52, $[M-H^+]^-$ = 575.96,

3-{1-[5-(4-Trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid methyl ester (**P-0038**),

3-{1-[5-(3-Trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid methyl ester (**P-0388**), calculated MW 509.52, $[M+H^+]^+$ = 510.1,

3-{1-[5-(4-Trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0393**), calculated MW 495.50, $[M-H^+]^-$ = 494.2,

3-{1-[5-(3-Trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0394**), calculated MW 495.50, $[M-H^+]^-$ = 494.2,

3-{1-[5-(3-Chloro-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0396**), calculated MW 490.00, $[M+H^+]^+$ = 490.3,

3-{5-Chloro-1-[5-(3-chloro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0397**), calculated MW 480.39, $[M-H^+]^-$ = 476.7,

3-{1-[5-(3-Chloro-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0398**), calculated MW 463.94, $[M+H^+]^+$ = 466.3,

3-{1-[5-(4-Chloro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0399**), calculated MW 475.97, $[M+H^+]^+$ = 475.5,

3-{1-[5-(4-Chloro-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0400**), calculated MW 490.00, $[M-H^+]^-$ = 489.9,

3-{5-Chloro-1-[5-(4-chloro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0401**), calculated MW 480.39, $[M+H^+]^+$ = 481.5,

3-{1-[5-(4-Chloro-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0402**), calculated MW 463.94, $[M-H^+]^-$ = 461.1,

3-[1-(5-Furan-2-yl-thiophene-2-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid (**P-0403**), calculated MW 431.49, $[M+H^+]^+$ = 432.3,

3-[5-Ethoxy-1-(5-furan-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0404**), calculated MW 445.51, $[M+H^+]^+$ = 445.9,

3-[5-Chloro-1-(5-furan-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0405**), calculated MW 435.91, $[M+H^+]^+$ = 435.9,

3-[5-Fluoro-1-(5-furan-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0406**), calculated MW 419.45, $[M+H^+]^+$ = 419.9,

3-[1-(5-Furan-3-yl-thiophene-2-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid

(**P-0407**), calculated MW 431.49, $[M+H^+]^+$ = 432.3,

3-[5-Ethoxy-1-(5-furan-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0408**), calculated MW 445.51, $[M+H^+]^+$ = 445.9,

3-[5-Chloro-1-(5-furan-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0409**), calculated MW 435.91, $[M-H^+]^-$ = 433.9,

3-[5-Fluoro-1-(5-furan-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0410**), calculated MW 419.45, $[M+H^+]^+$ = 420.3,

3-[5-Methoxy-1-(5-pyridin-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0411**), calculated MW 442.51, $[M+H^+]^+$ = 443.1,

3-[5-Ethoxy-1-(5-pyridin-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0412**), calculated MW 456.54, $[M+H^+]^+$ = 457.1,

3-[5-Chloro-1-(5-pyridin-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0413**), calculated MW 446.93, $[M+H^+]^+$ = 447.1,

3-[5-Fluoro-1-(5-pyridin-3-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0414**), calculated MW 430.48, $[M+H^+]^+$ = 431.1,

3-[5-Ethoxy-1-(5-pyridin-4-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0415**), calculated MW 456.54, $[M+H^+]^+$ = 457.1,

3-[5-Chloro-1-(5-pyridin-4-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0416**), calculated MW 446.93, $[M+H^+]^+$ = 447.1,

3-[5-Fluoro-1-(5-pyridin-4-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid

(**P-0417**), calculated MW 430.48, $[M+H^+]^+$ = 431.1,

3-{1-[5-(3,5-Dichloro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0418**), calculated MW 510.42, $[M-H^+]^-$ = 509.9,

3-{1-[5-(3,5-Dichloro-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0419**), calculated MW 524.44, $[M+H^+]^+$ = 524.3,

3-{5-Chloro-1-[5-(3,5-dichloro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0420**), calculated MW 514.84, $[M-H^+]^-$ = 507.1,

3-{1-[5-(3,5-Dichloro-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0421**), calculated MW 498.38, $[M-H^+]^-$ = 490.3,

3-{1-[5-(3,4-Difluoro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0422**), calculated MW 477.51, $[M+H^+]^+$ = 478.3,

3-{1-[5-(3,4-Difluoro-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-

propionic acid (**P-0423**), calculated MW 491.53, $[M+H^+]^+ = 492.3$,
3-{5-Chloro-1-[5-(3,4-difluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-
propionic acid (**P-0424**), calculated MW 481.93, $[M+H^+]^+ = 481.1$,
3-{1-[5-(3,4-Difluoro-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-
propionic acid (**P-0425**), calculated MW 465.47, $[M-H^+]^- = 464.7$,
3-{1-[5-(3,4-Dimethoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-
propionic acid (**P-0426**), calculated MW 501.58, $[M+H^+]^+ = 501.9$,
3-{1-[5-(3,4-Dimethoxy-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-
propionic acid (**P-0427**), calculated MW 515.60, $[M+H^+]^+ = 516.3$,
3-{5-Chloro-1-[5-(3,4-dimethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-
propionic acid (**P-0428**), calculated MW 506.00, $[M+H^+]^+ = 507.5$,
3-{1-[5-(3,4-Dimethoxy-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-
propionic acid (**P-0429**), calculated MW 489.54, $[M-H^+]^- = 485.5$,
3-{1-[5-(4-Fluoro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic
acid (**P-0430**), calculated MW 459.52, $[M+H^+]^+ = 459.9$,
3-{5-Ethoxy-1-[5-(4-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic
acid (**P-0431**), calculated MW 473.54, $[M+H^+]^+ = 473.9$,
3-{5-Chloro-1-[5-(4-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic
acid (**P-0432**), calculated MW 463.94, $[M-H^+]^- = 458.7$,
3-{5-Fluoro-1-[5-(4-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic
acid (**P-0433**), calculated MW 447.48, $[M+H^+]^+ = 447.9$,
3-{5-Methoxy-1-[5-(4-methylsulfanyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-
propionic acid (**P-0434**), calculated MW 487.62, $[M+H^+]^+ = 487.9$,
3-{5-Ethoxy-1-[5-(4-methylsulfanyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-
propionic acid (**P-0435**), calculated MW 501.65, $[M+H^+]^+ = 501.9$,
3-{5-Chloro-1-[5-(4-methylsulfanyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-
propionic acid (**P-0436**), calculated MW 492.04, $[M-H^+]^- = 487.9$,
3-{5-Fluoro-1-[5-(4-methylsulfanyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-
propionic acid (**P-0437**), calculated MW 475.58, $[M-H^+]^- = 473.9$,
3-{1-[5-(3-Chloro-4-fluoro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-
propionic acid (**P-0438**), calculated MW 493.96, $[M+H^+]^+ = 493.9$,
3-{1-[5-(3-Chloro-4-fluoro-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-
propionic acid (**P-0439**), calculated MW 507.99, $[M+H^+]^+ = 507.5$,
3-{5-Chloro-1-[5-(3-chloro-4-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-

propionic acid (**P-0440**), calculated MW 498.38, $[M+H^+]^+ = 503.5$,
3-{1-[5-(3-Chloro-4-fluoro-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0441**), calculated MW 481.93, $[M-H^+]^- = 479.1$,
3-[5-Methoxy-1-(5-pyrimidin-5-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0442**), calculated MW 443.50, $[M+H^+]^+ = 444.3$,
3-[5-Ethoxy-1-(5-pyrimidin-5-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0443**), calculated MW 457.53, $[M+H^+]^+ = 458.3$,
3-[5-Chloro-1-(5-pyrimidin-5-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0444**), calculated MW 447.92, $[M+H^+]^+ = 447.9$,
3-[5-Fluoro-1-(5-pyrimidin-5-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0445**), calculated MW 431.47, $[M+H^+]^+ = 432.3$,
3-{5-Methoxy-1-[5-(6-methoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0446**), calculated MW 472.54, $[M+H^+]^+ = 473.1$,
3-{5-Ethoxy-1-[5-(6-methoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0447**), calculated MW 486.57, $[M+H^+]^+ = 487.1$,
3-{5-Chloro-1-[5-(6-methoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0448**), calculated MW 476.96, $[M+H^+]^+ = 477.1$,
3-{5-Fluoro-1-[5-(6-methoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0449**), calculated MW 460.50, $[M+H^+]^+ = 461.1$,
3-{5-Methoxy-1-[5-(1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0450**), calculated MW 431.49, $[M+H^+]^+ = 432.3$,
3-{5-Ethoxy-1-[5-(1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0451**), calculated MW 445.52, $[M+H^+]^+ = 445.9$,
3-{5-Chloro-1-[5-(1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0452**), calculated MW 435.91, $[M+H^+]^+ = 435.9$,
3-{5-Fluoro-1-[5-(1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0453**), calculated MW 419.46, $[M+H^+]^+ = 419.9$,
3-{5-Methoxy-1-[5-(1-methyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0454**), calculated MW 445.52, $[M+H^+]^+ = 445.9$,
3-{5-Ethoxy-1-[5-(1-methyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0455**), calculated MW 459.54, $[M+H^+]^+ = 460.3$,
3-{5-Chloro-1-[5-(1-methyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0456**), calculated MW 449.94, $[M+H^+]^+ = 449.9$,
3-{5-Fluoro-1-[5-(1-methyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-

propionic acid (**P-0457**), calculated MW 433.48, $[M+H^+]^+ = 434.3$,
3-{1-[5-(3-Dimethylamino-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0458**), calculated MW 484.59, $[M+H^+]^+ = 485.1$,
3-{1-[5-(3-Dimethylamino-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0459**), calculated MW 498.62, $[M+H^+]^+ = 499.1$,
3-{5-Chloro-1-[5-(3-dimethylamino-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0460**), calculated MW 489.01, $[M+H^+]^+ = 489.1$,
3-{1-[5-(3-Dimethylamino-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0461**), calculated MW 472.56, $[M+H^+]^+ = 473.1$,
3-{1-[5-(2,6-Dimethoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0462**), calculated MW 502.57, $[M+H^+]^+ = 503.1$,
3-{1-[5-(2,6-Dimethoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0463**), calculated MW 516.59, $[M+H^+]^+ = 517.1$,
3-{5-Chloro-1-[5-(2,6-dimethoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0464**), calculated MW 506.99, $[M+H^+]^+ = 507.1$,
3-{1-[5-(2,6-Dimethoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0465**), calculated MW 490.53, $[M+H^+]^+ = 491.1$,
3-{1-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0466**), calculated MW 503.55, $[M+H^+]^+ = 503.9$,
3-{1-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0467**), calculated MW 517.58, $[M+H^+]^+ = 517.9$,
3-{5-Chloro-1-[5-(2,4-dimethoxy-pyrimidin-5-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0468**), calculated MW 507.97, $[M+H^+]^+ = 507.9$,
3-{1-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0469**), calculated MW 491.52, $[M+H^+]^+ = 491.1$,
3-{1-[5-(6-Benzyloxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0470**), calculated MW 548.64, $[M+H^+]^+ = 549.1$,
3-{1-[5-(6-Benzyloxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0471**), calculated MW 562.66, $[M+H^+]^+ = 563.2$,
3-{1-[5-(6-Benzyloxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-chloro-1H-indol-3-yl}-propionic acid (**P-0472**), calculated MW 553.06, $[M+H^+]^+ = 553.2$,
3-{1-[5-(6-Benzyloxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0473**), calculated MW 536.60, $[M+H^+]^+ = 537.1$,
3-{5-Ethoxy-1-[5-(4-ethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic

acid (**P-0474**), calculated MW 499.61, $[M+H^+]^+ = 499.9$,
3-{5-Chloro-1-[5-(4-ethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0475**), calculated MW 490.00, $[M-H^+]^- = 489.9$,
3-{1-[5-(4-Ethoxy-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0476**), calculated MW 473.54, $[M+H^+]^+ = 473.9$,
3-{1-[5-(3-Fluoro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0477**), calculated MW 459.52, $[M+H^+]^+ = 460.3$,
3-{5-Ethoxy-1-[5-(3-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0478**), calculated MW 473.54, $[M+H^+]^+ = 473.9$,
3-{5-Chloro-1-[5-(3-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0479**), calculated MW 463.94, $[M-H^+]^- = 457.5$,
3-{5-Fluoro-1-[5-(3-fluoro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0480**), calculated MW 447.48, $[M+H^+]^+ = 447.9$,
3-{5-Ethoxy-1-[5-(3-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0481**), calculated MW 539.55, $[M+H^+]^+ = 539.9$,
3-{5-Chloro-1-[5-(3-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0482**), calculated MW 529.94, $[M+H^+]^+ = 525.9$,
3-{5-Fluoro-1-[5-(3-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0483**), calculated MW 513.49, $[M+H^+]^+ = 514.3$,
3-{1-[5-(3,4-Dichloro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0484**), calculated MW 510.42, $[M-H^+]^- = 509.9$,
3-{1-[5-(3,4-Dichloro-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0485**), calculated MW 524.44, $[M+H^+]^+ = 524.3$,
3-{5-Chloro-1-[5-(3,4-dichloro-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0486**), calculated MW 514.84, $[M+H^+]^+ = 511.9$,
3-{1-[5-(3,4-Dichloro-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0487**), calculated MW 498.38, $[M-H^+]^- = 496.3$,
3-{5-Ethoxy-1-[5-(3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0488**), calculated MW 523.55, $[M+H^+]^+ = 524.3$,
3-{5-Chloro-1-[5-(3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0489**), calculated MW 513.94, $[M-H^+]^- = 511.9$,
3-{5-Fluoro-1-[5-(3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0490**), calculated MW 497.49, $[M+H^+]^+ = 497.9$,
3-{1-[5-(4-Benzyloxy-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-

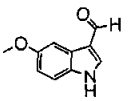
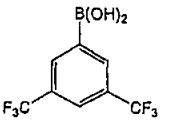
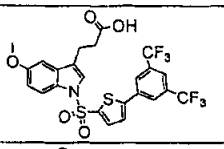
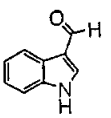
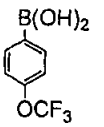
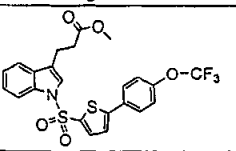
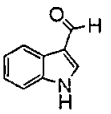
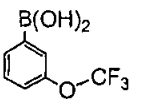
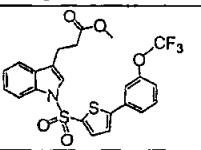
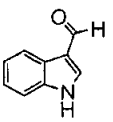
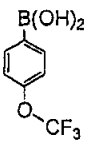
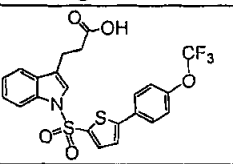
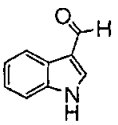
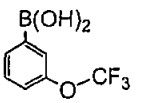
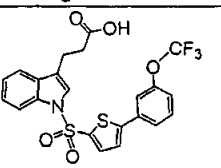
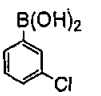
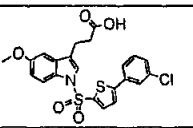
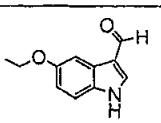
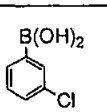
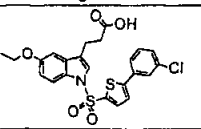
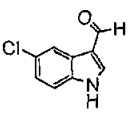
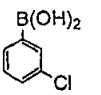
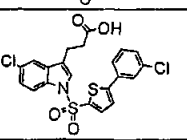
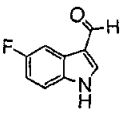
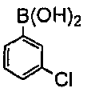
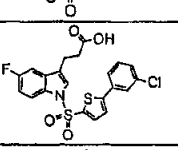
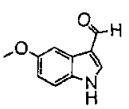
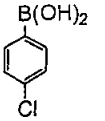
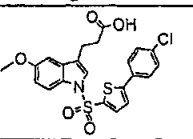
propionic acid (**P-0491**), calculated MW 561.68, $[M+H^+]^+$ = 562.0,
3-{1-[5-(4-Benzyloxy-phenyl)-thiophene-2-sulfonyl]-5-chloro-1H-indol-3-yl}-propionic acid (**P-0492**), calculated MW 552.07, $[M+H^+]^+$ = 553.6,
3-{1-[5-(4-Benzyloxy-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0493**), calculated MW 535.61, $[M+H^+]^+$ = 535.9,
3-{5-Ethoxy-1-[5-(4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0494**), calculated MW 523.55, $[M+H^+]^+$ = 524.3,
3-{5-Chloro-1-[5-(4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0495**), calculated MW 513.94, $[M-H^+]^-$ = 512.3,
3-{5-Fluoro-1-[5-(4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0496**), calculated MW 497.49, $[M-H^+]^-$ = 490.3,
3-{1-[5-(3-Fluoro-4-methoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0497**), calculated MW 489.54, $[M+H^+]^+$ = 490.3,
3-{5-Ethoxy-1-[5-(3-fluoro-4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0498**), calculated MW 503.57, $[M+H^+]^+$ = 503.9,
3-{5-Chloro-1-[5-(3-fluoro-4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0499**), calculated MW 493.96, $[M+H^+]^+$ = 497.1,
3-{5-Fluoro-1-[5-(3-fluoro-4-methoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0500**), calculated MW 477.51, $[M+H^+]^+$ = 478.3,
3-{5-Methoxy-1-[5-(5-methyl-furan-2-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0501**), calculated MW 445.51, $[M+H^+]^+$ = 445.9,
3-{5-Ethoxy-1-[5-(5-methyl-furan-2-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0502**), calculated MW 459.54, $[M+H^+]^+$ = 459.9,
3-{5-Chloro-1-[5-(5-methyl-furan-2-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0503**), calculated MW 449.93, $[M+H^+]^+$ = 449.5,
3-{1-[5-(3,5-Dimethyl-isoxazol-4-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0504**), calculated MW 460.53, $[M+H^+]^+$ = 461.1,
3-{1-[5-(3,5-Dimethyl-isoxazol-4-yl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0505**), calculated MW 474.56, $[M+H^+]^+$ = 475.1,
3-{5-Chloro-1-[5-(3,5-dimethyl-isoxazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0506**), calculated MW 464.95, $[M+H^+]^+$ = 464.7,
3-{1-[5-(3,5-Dimethyl-isoxazol-4-yl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0507**), calculated MW 448.49, $[M+H^+]^+$ = 448.7,
3-{1-[5-(4-Chloro-3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-

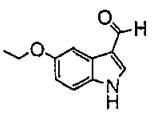
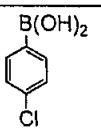
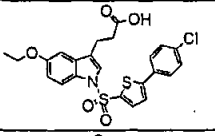
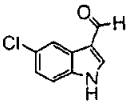
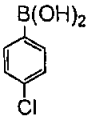
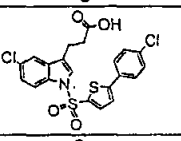
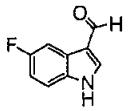
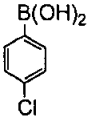
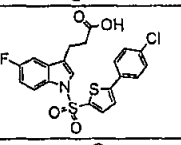
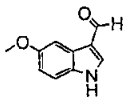
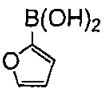
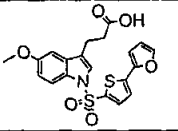
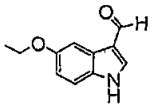
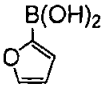
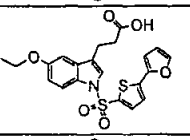
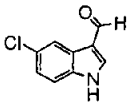
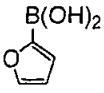
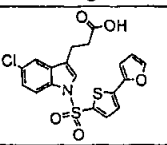
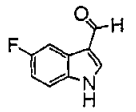
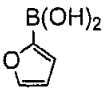
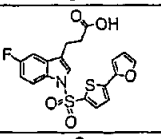
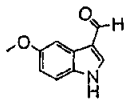
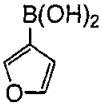
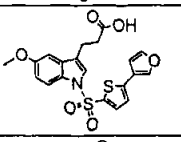
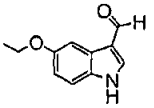
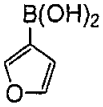
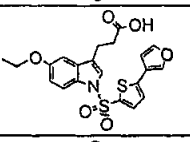
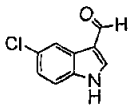
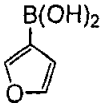
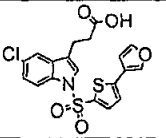
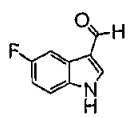
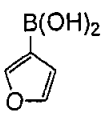
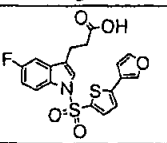
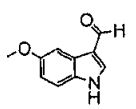
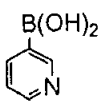
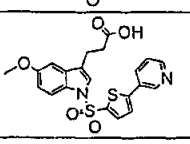
indol-3-yl}-propionic acid (**P-0508**), calculated MW 543.97, $[M+H^+]^+$ = 543.9, 3-{1-[5-(4-Chloro-3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0509**), calculated MW 558.00, $[M+H^+]^+$ = 558.0, 3-{5-Chloro-1-[5-(4-chloro-3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0510**), calculated MW 548.39, $[M-H^+]^-$ = 546.7, 3-{1-[5-(4-Chloro-3-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0511**), calculated MW 531.93, $[M+H^+]^+$ = 531.9, 3-{5-Methoxy-1-[5-(4-morpholin-4-yl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0512**), calculated MW 526.63, $[M+H^+]^+$ = 527.1, 3-{5-Ethoxy-1-[5-(4-morpholin-4-yl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0513**), calculated MW 540.66, $[M+H^+]^+$ = 541.1, 3-{5-Chloro-1-[5-(4-morpholin-4-yl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0514**), calculated MW 531.05, $[M+H^+]^+$ = 531.1, 3-{1-[5-(2-Chloro-4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid (**P-0515**), calculated MW 543.97, $[M+H^+]^+$ = 543.9, 3-{1-[5-(2-Chloro-4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0516**), calculated MW 558.00, $[M+H^+]^+$ = 558.0, 3-{5-Chloro-1-[5-(2-chloro-4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0517**), calculated MW 548.39, $[M+H^+]^+$ = 548.3, 3-{1-[5-(2-Chloro-4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-5-fluoro-1H-indol-3-yl}-propionic acid (**P-0518**), calculated MW 531.93, $[M+H^+]^+$ = 531.9, 3-{5-Methoxy-1-[5-(1-propyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0519**), calculated MW 473.57, $[M+H^+]^+$ = 473.9, 3-{5-Ethoxy-1-[5-(1-propyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0520**), calculated MW 487.60, $[M+H^+]^+$ = 487.9, 3-{5-Chloro-1-[5-(1-propyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0521**), calculated MW 477.99, $[M+H^+]^+$ = 477.9, 3-{5-Fluoro-1-[5-(1-propyl-1H-pyrazol-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0522**), calculated MW 461.54, $[M+H^+]^+$ = 462.3, and 3-(5-Methoxy-1-{5-[4-(2,2,2-trifluoro-ethoxy)-phenyl]-thiophene-2-sulfonyl}-1H-indol-3-yl)-propionic acid (**P-0523**), calculated MW 539.55, $[M-H^+]^-$ = 538.06.

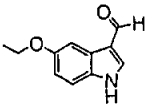
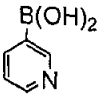
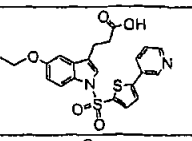
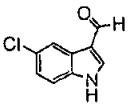
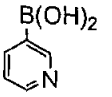
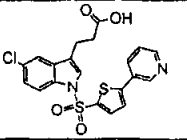
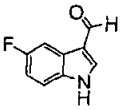
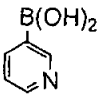
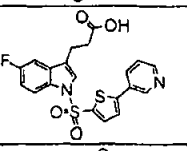
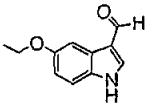
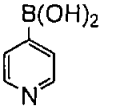
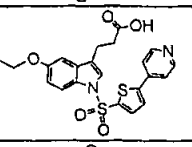
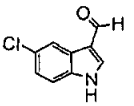
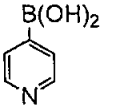
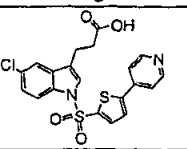
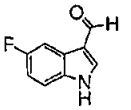
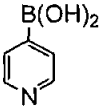
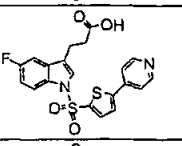
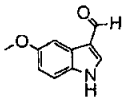
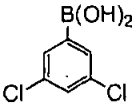
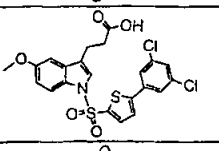
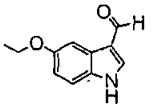
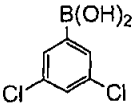
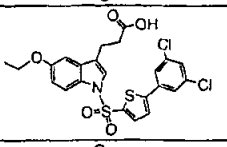
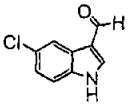
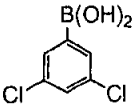
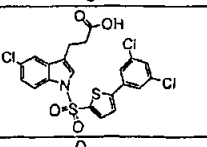
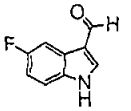
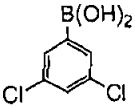
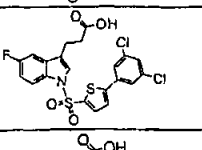
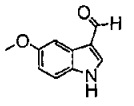
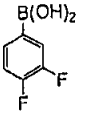
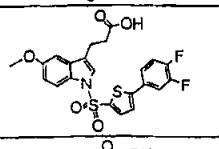
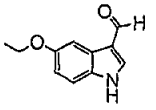
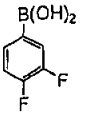
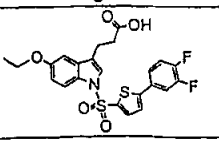
These compounds are shown in the following Table 3, indicating the indole-3-carboxyaldehyde used in Step 1 (Column 2), the boronic acid used in Step 4 (Column 3),

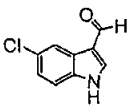
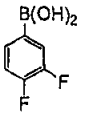
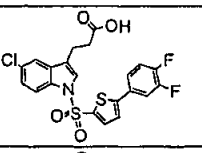
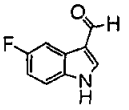
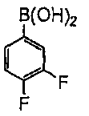
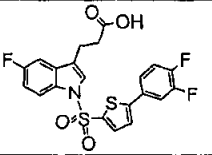
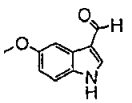
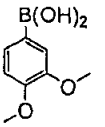
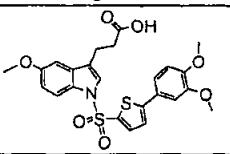
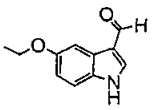
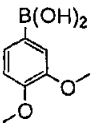
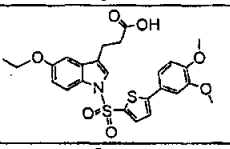
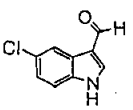
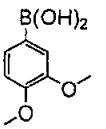
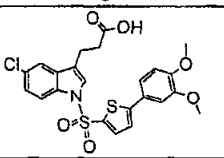
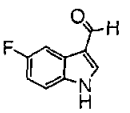
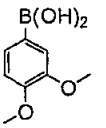
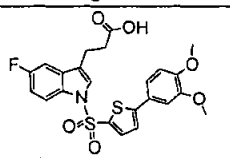
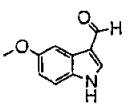
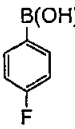
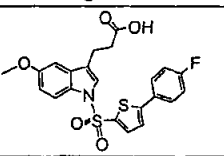
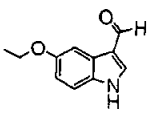
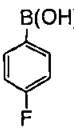
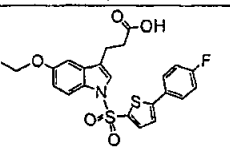
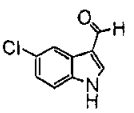
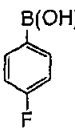
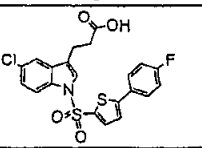
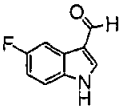
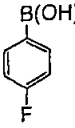
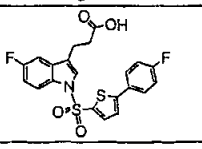
and the compound structure (Column 4), with the compound number provided in Column 1.

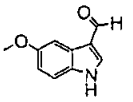
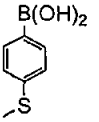
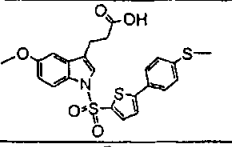
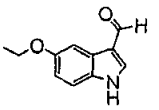
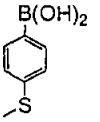
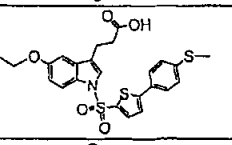
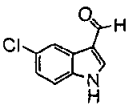
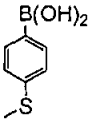
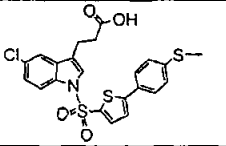
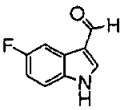
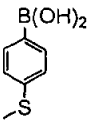
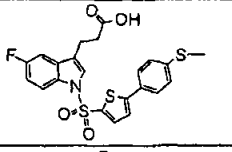
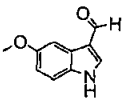
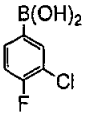
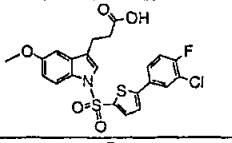
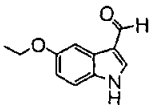
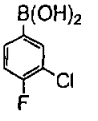
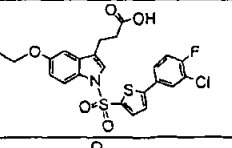
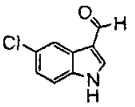
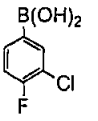
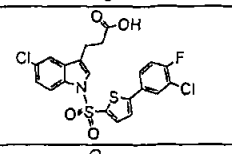
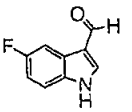
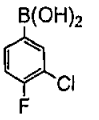
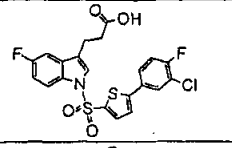
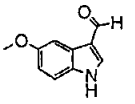
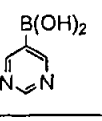
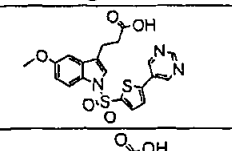
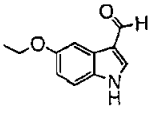
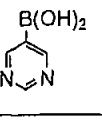
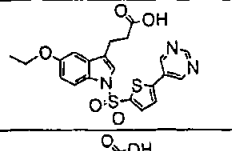
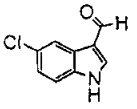
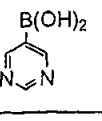
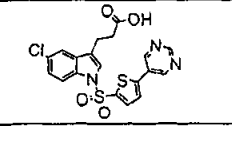
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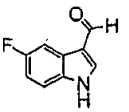
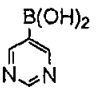
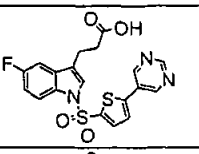
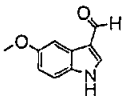
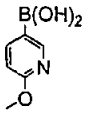
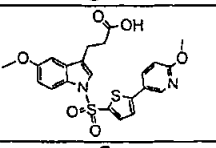
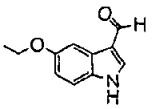
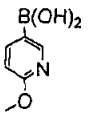
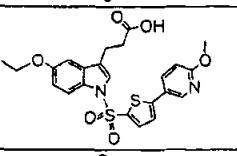
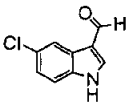
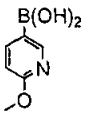
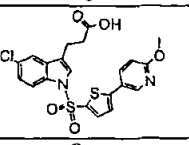
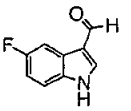
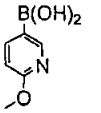
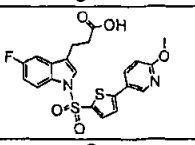
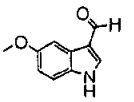
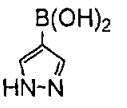
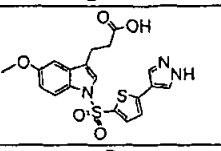
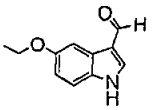
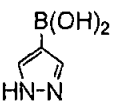
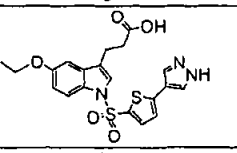
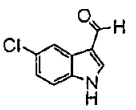
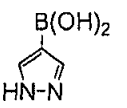
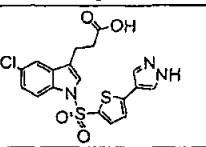
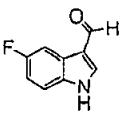
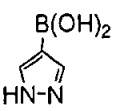
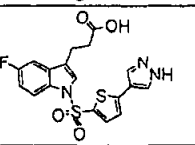
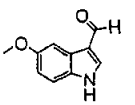
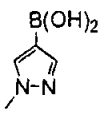
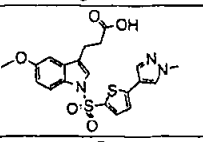
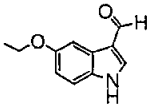
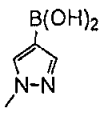
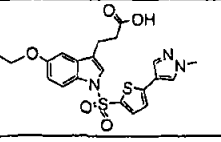
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
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P-0038			
P-0388			
P-0393			
P-0394			
P-0395			
P-0396			
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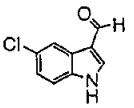
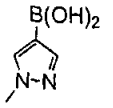
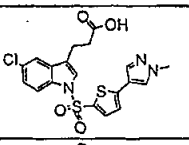
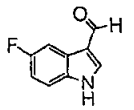
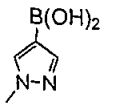
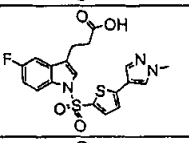
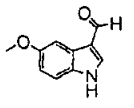
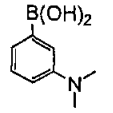
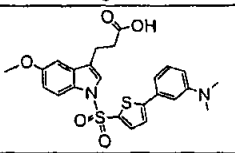
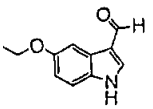
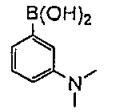
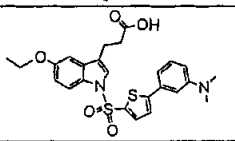
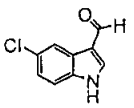
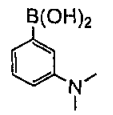
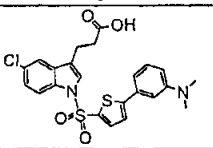
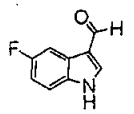
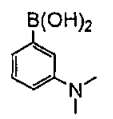
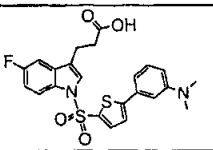
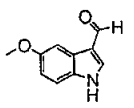
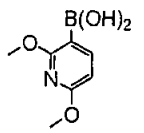
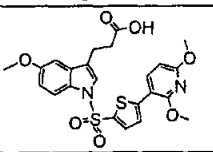
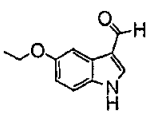
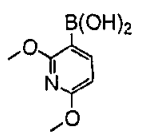
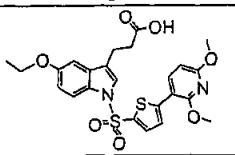
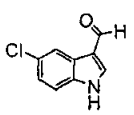
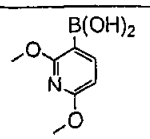
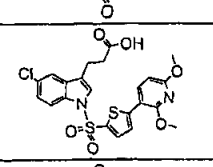
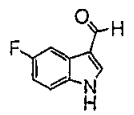
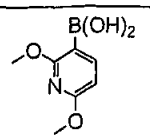
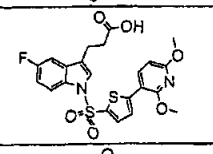
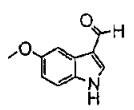
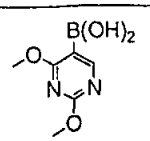
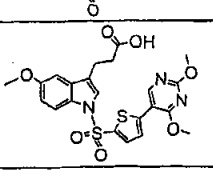
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0400			
P-0401			
P-0402			
P-0403			
P-0404			
P-0405			
P-0406			
P-0407			
P-0408			
P-0409			
P-0410			
P-0411			

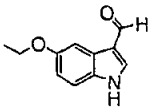
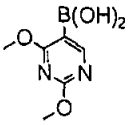
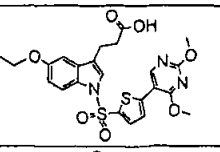
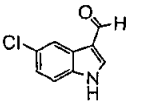
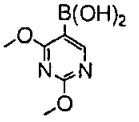
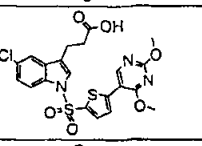
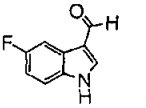
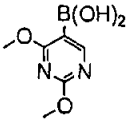
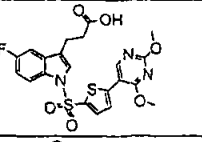
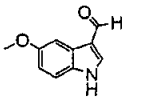
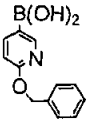
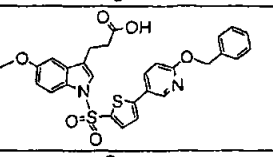
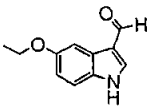
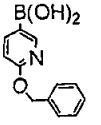
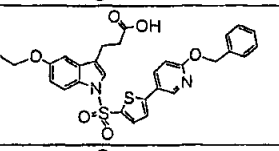
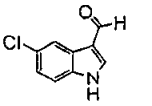
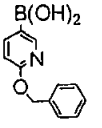
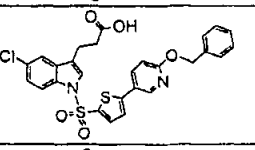
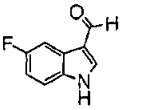
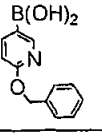
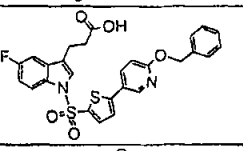
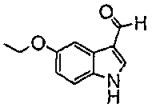
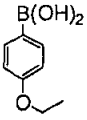
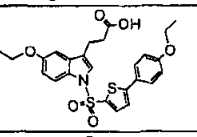
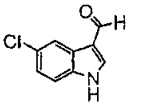
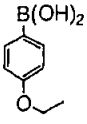
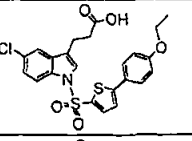
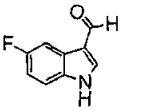
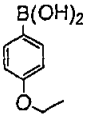
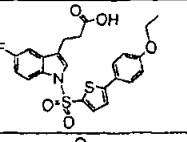
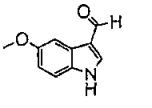
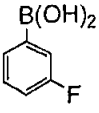
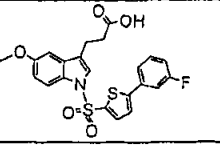
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0412			
P-0413			
P-0414			
P-0415			
P-0416			
P-0417			
P-0418			
P-0419			
P-0420			
P-0421			
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P-0423			

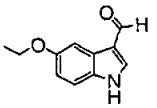
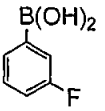
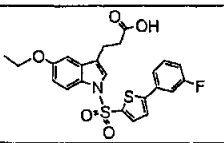
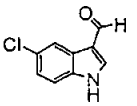
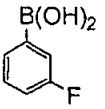
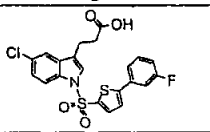
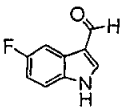
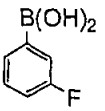
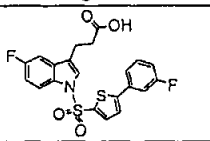
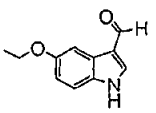
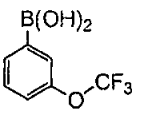
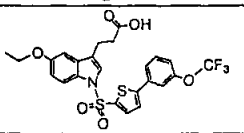
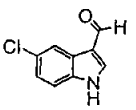
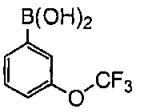
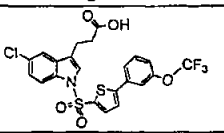
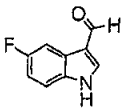
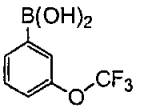
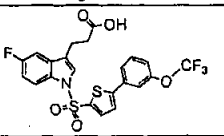
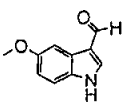
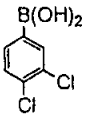
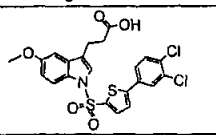
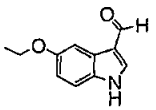
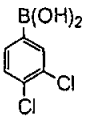
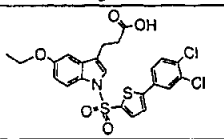
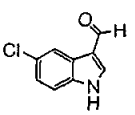
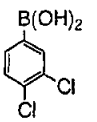
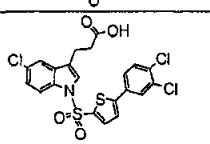
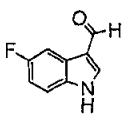
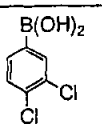
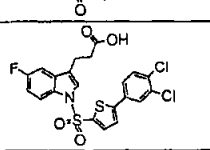
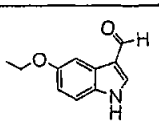
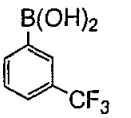
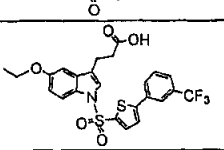
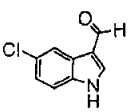
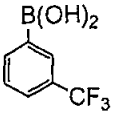
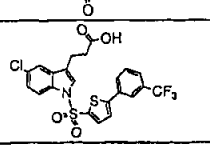
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
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P-0425			
P-0426			
P-0427			
P-0428			
P-0429			
P-0430			
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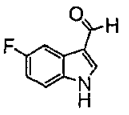
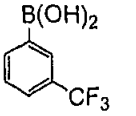
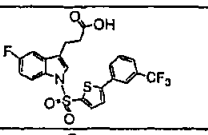
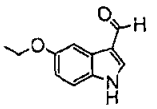
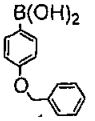
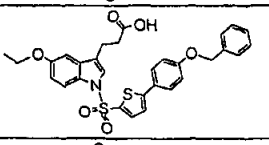
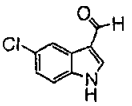
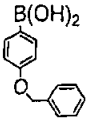
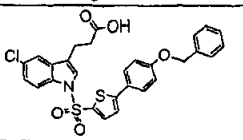
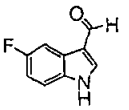
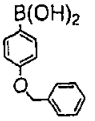
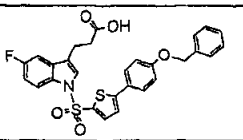
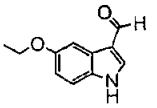
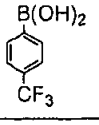
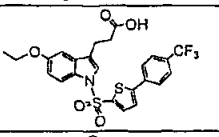
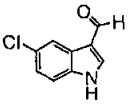
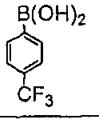
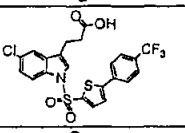
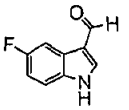
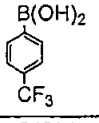
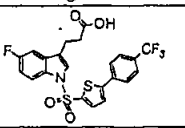
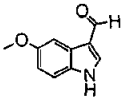
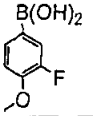
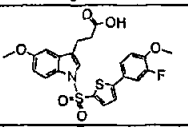
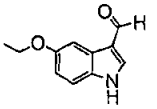
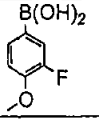
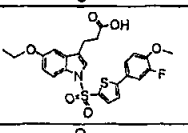
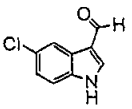
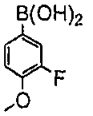
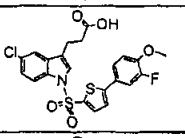
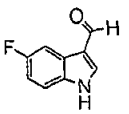
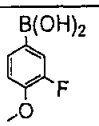
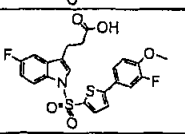
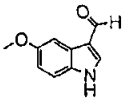
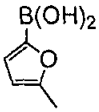
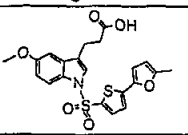
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
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P-0435			
P-0436			
P-0437			
P-0438			
P-0439			
P-0440			
P-0441			
P-0442			
P-0443			
P-0444			

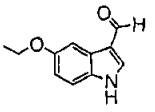
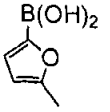
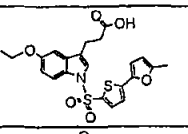
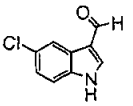
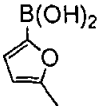
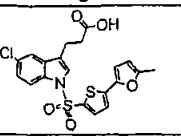
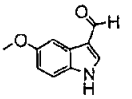
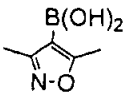
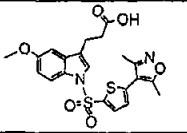
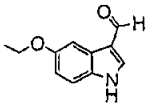
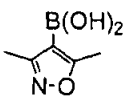
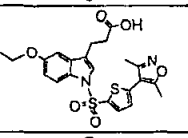
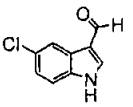
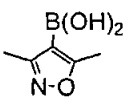
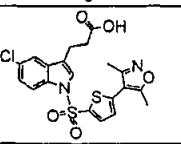
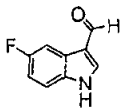
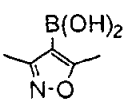
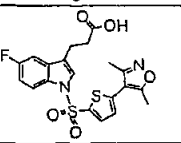
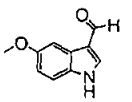
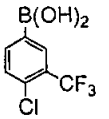
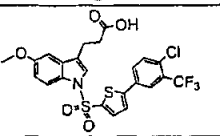
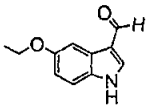
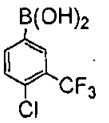
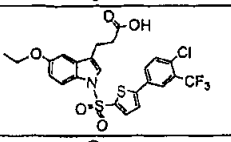
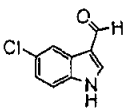
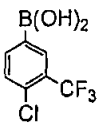
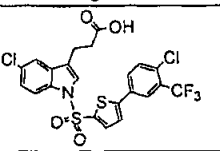
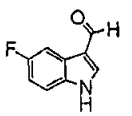
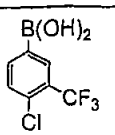
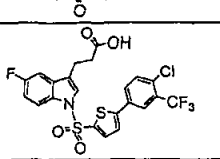
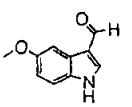
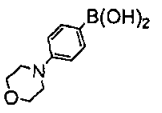
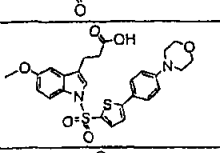
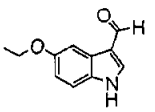
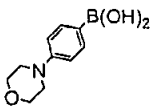
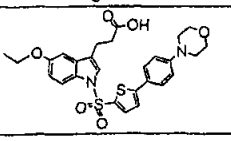
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0445			
P-0446			
P-0447			
P-0448			
P-0449			
P-0450			
P-0451			
P-0452			
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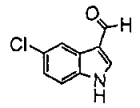
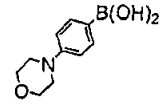
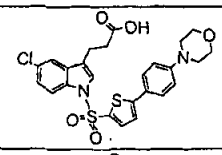
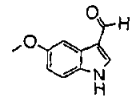
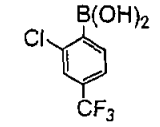
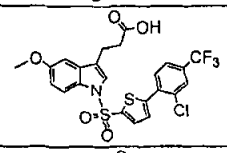
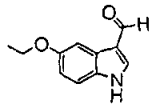
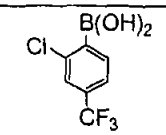
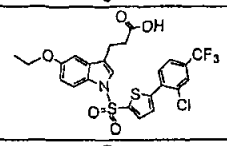
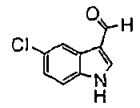
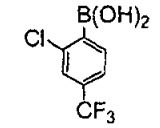
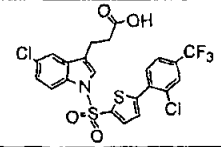
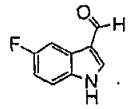
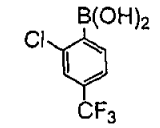
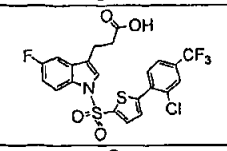
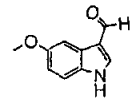
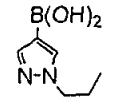
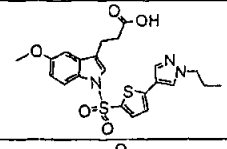
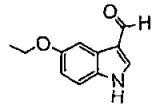
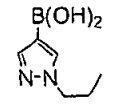
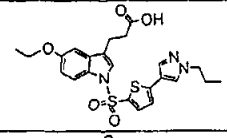
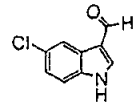
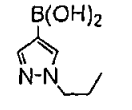
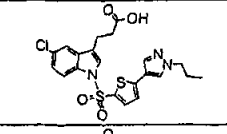
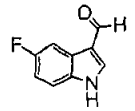
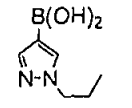
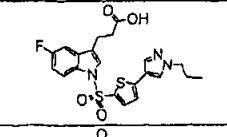
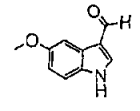
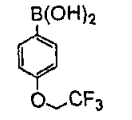
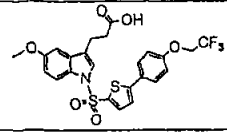
Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0456			
P-0457			
P-0458			
P-0459			
P-0460			
P-0461			
P-0462			
P-0463			
P-0464			
P-0465			
P-0466			

Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0467			
P-0468			
P-0469			
P-0470			
P-0471			
P-0472			
P-0473			
P-0474			
P-0475			
P-0476			
P-0477			

Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0478			
P-0479			
P-0480			
P-0481			
P-0482			
P-0483			
P-0484			
P-0485			
P-0486			
P-0487			
P-0488			
P-0489			

Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0490			
P-0491			
P-0492			
P-0493			
P-0494			
P-0495			
P-0496			
P-0497			
P-0498			
P-0499			
P-0500			
P-0501			

Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0502			
P-0503			
P-0504			
P-0505			
P-0506			
P-0507			
P-0508			
P-0509			
P-0510			
P-0511			
P-0512			
P-0513			

Cmpd. number	Indole-3-carboxyaldehyde	Boronic acid	Compound structure
P-0514			
P-0515			
P-0516			
P-0517			
P-0518			
P-0519			
P-0520			
P-0521			
P-0522			
P-0523			

[0236] Additional compounds were prepared similarly, replacing 5-bromo thiophene-2-sulfonyl chloride **7** with either 2-bromo-benzenesulfonyl chloride or 3-bromo-5-methyl-thiophene-2-sulfonyl chloride in Step 3 and replacing 5-methoxyindole-3-carboxyaldehyde **4** with an appropriate 5-ethoxyindole-3-carboxyaldehyde in Step 1, and

reacting the product of Step 3 with an appropriate boronic acid via a modified Step 4, wherein 10 mg of the product of Step 3 was dissolved in 400 μL of acetonitrile in a 2 mL microwave vial. To this was added 2 equivalents of the appropriate boronic acid and 3 mg of tetrakis(triphenylphosphine)palladium(0), then 400 μL of aqueous 1M potassium carbonate was added, the vial capped, and irradiate 10 minutes at 160 °C. The solution was neutralized with acetic acid and the solvents removed under vacuum. The crude material was dissolved in dimethyl sulfoxide and purified by reverse phase HPLC (C18 column), eluting with a water/0.1% trifluoro acetic acid and acetonitrile/0.1% trifluoro acetic acid gradient, 20-100% acetonitrile over 16 minutes.

[0237] The following compounds were prepared using 5-ethoxyindole-3-carboxyaldehyde in Step 1, 2-bromo-benzenesulfonyl chloride or 3-bromo-5-methyl-thiophene-2-sulfonyl chloride in Step 3, and the appropriate boronic acid in Step 4, with the calculated molecular weight and measured mass (MS(ESI)) provided after the compound:

3-[1-(2-Bromo-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid ethyl ester (**P-0528**), calculated MW 480.38, $[M+H^+]^+$ = 480.1, 482.1,

3-[1-(4'-Chloro-biphenyl-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid (**P-0529**), calculated MW 483.97, $[M+H^+]^+$ = 484.3,

3-[5-Ethoxy-1-(4'-methoxy-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0530**), calculated MW 479.55, $[M+H^+]^+$ = 479.9,

3-[5-Ethoxy-1-(4'-isopropyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0531**), calculated MW 491.61, $[M+H^+]^+$ = 492.3,

3-[5-Ethoxy-1-(4'-fluoro-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0532**), calculated MW 467.51, $[M+H^+]^+$ = 468.3,

3-[1-(4'-Dimethylamino-biphenyl-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid (**P-0533**), calculated MW 492.59, $[M+H^+]^+$ = 492.3,

3-[1-(4'-Acetyl-biphenyl-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid (**P-0534**), calculated MW 491.56, $[M+H^+]^+$ = 492.3,

3-[5-Ethoxy-1-(4'-ethoxy-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0535**), calculated MW 493.58, $[M+H^+]^+$ = 494.3,

3-[5-Ethoxy-1-(4'-trifluoromethoxy-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0536**), calculated MW 533.52, $[M+H^+]^+$ = 533.9,

3-[5-Ethoxy-1-(4'-ethyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0537**),

calculated MW 477.58, $[M+H^+]^+ = 477.9$,

3-[5-Ethoxy-1-(4'-propyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0538**), calculated MW 491.61, $[M+H^+]^+ = 492.3$,

3-[1-(4'-Amino-biphenyl-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid (**P-0539**), calculated MW 464.54, $[M+H^+]^+ = 465.1$,

3-[5-Ethoxy-1-(4'-trifluoromethyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0552**), calculated MW 517.52, $[M+H^+]^+ = 517.9$,

3-[1-(3',4'-Difluoro-biphenyl-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid (**P-0553**), calculated MW 517.52, $[M+H^+]^+ = 517.9$,

3-{5-Ethoxy-1-[2-(1H-indol-5-yl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0554**), calculated MW 488.56, $[M+H^+]^+ = 489.1$,

3-[1-(3',4'-Dimethyl-biphenyl-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid (**P-0555**), calculated MW 477.58, $[M+H^+]^+ = 478.3$,

3-[5-Ethoxy-1-(5-methyl-3-p-tolyl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0524**),

3-{1-[3-(4-Benzyloxy-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0525**),

3-{1-[3-(4-Amino-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0526**),

3-{5-Ethoxy-1-[3-(4-hydroxy-phenyl)-5-methyl-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0527**),

3-{1-[3-(4-Chloro-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0540**),

3-{5-Ethoxy-1-[3-(4-methoxy-phenyl)-5-methyl-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0541**),

3-{5-Ethoxy-1-[3-(4-isopropyl-phenyl)-5-methyl-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0542**),

3-{5-Ethoxy-1-[3-(4-fluoro-phenyl)-5-methyl-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0543**),

3-{1-[3-(4-Dimethylamino-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0544**),

3-{1-[3-(4-Acetyl-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0545**),

3-{5-Ethoxy-1-[3-(4-ethoxy-phenyl)-5-methyl-thiophene-2-sulfonyl]-1H-indol-3-yl}-

propionic acid (**P-0546**),

3-{5-Ethoxy-1-[5-methyl-3-(4-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0547**),

3-{5-Ethoxy-1-[5-methyl-3-(4-trifluoromethyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0548**),

3-{5-Ethoxy-1-[3-(4-ethyl-phenyl)-5-methyl-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0549**),

3-{5-Ethoxy-1-[5-methyl-3-(4-propyl-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0550**),

3-{1-[3-(4-Aminomethyl-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0551**),

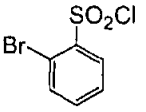
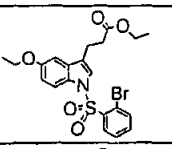
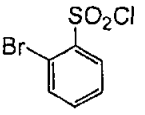
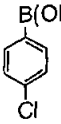
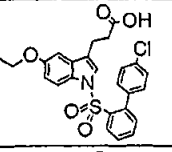
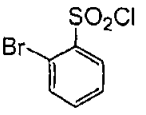
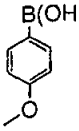
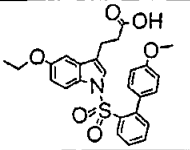
3-{1-[3-(3,4-Difluoro-phenyl)-5-methyl-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid (**P-0556**),

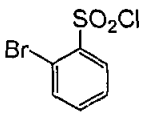
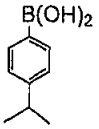
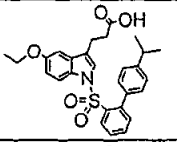
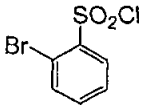
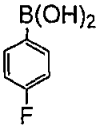
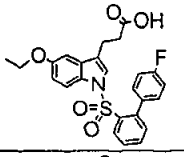
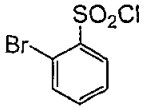
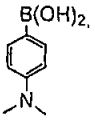
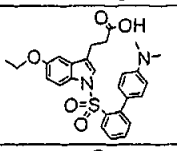
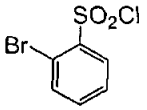
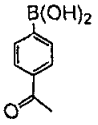
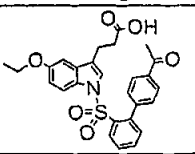
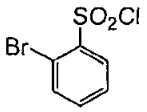
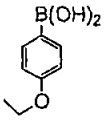
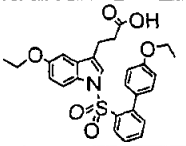
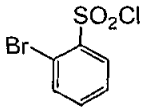
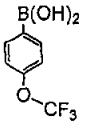
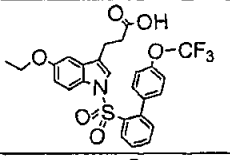
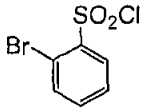
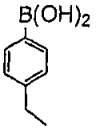
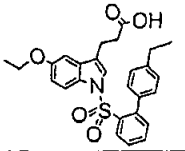
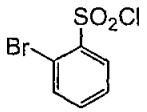
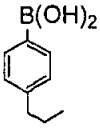
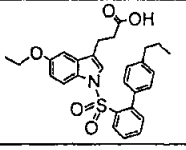
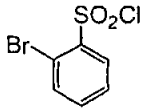
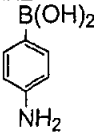
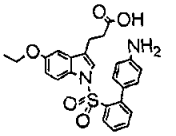
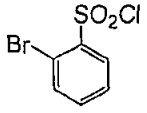
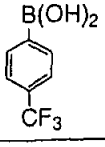
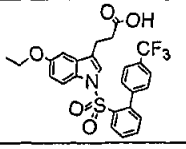
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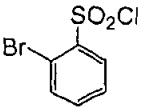
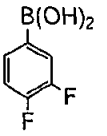
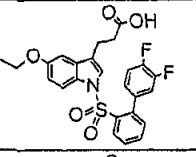
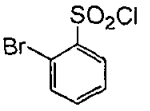
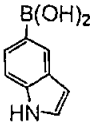
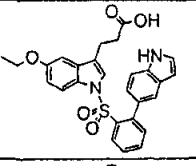
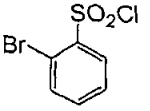
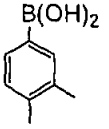
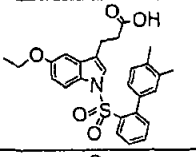
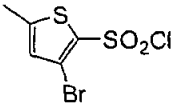
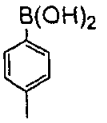
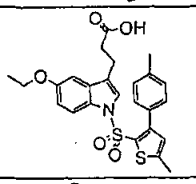
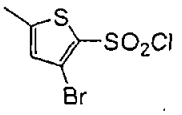
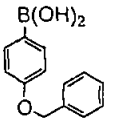
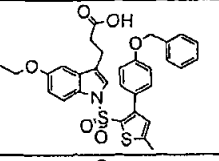
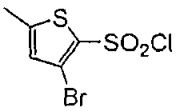
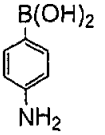
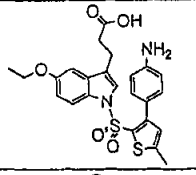
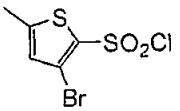
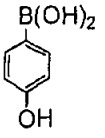
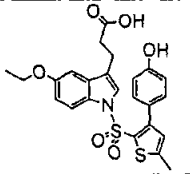
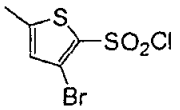
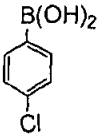
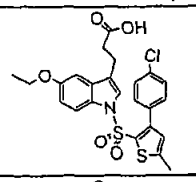
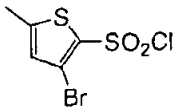
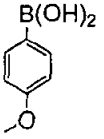
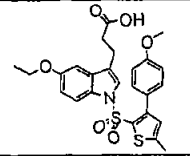
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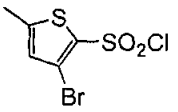
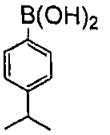
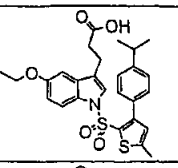
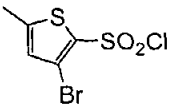
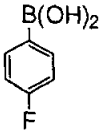
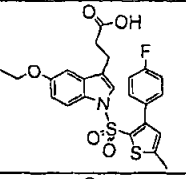
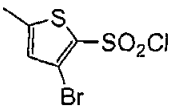
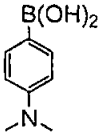
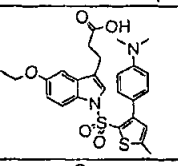
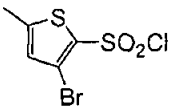
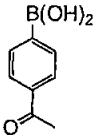
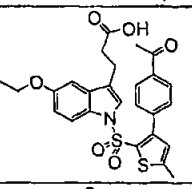
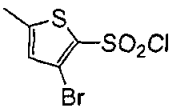
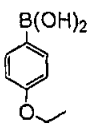
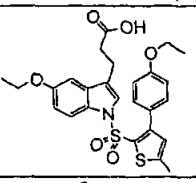
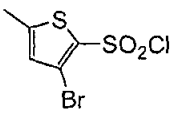
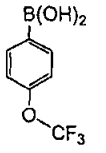
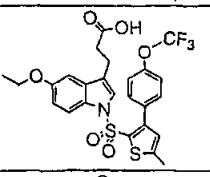
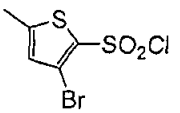
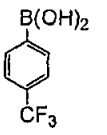
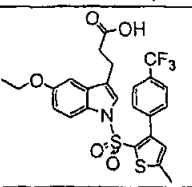
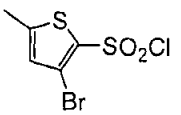
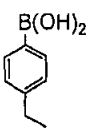
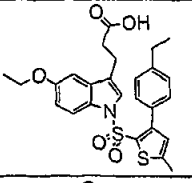
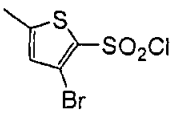
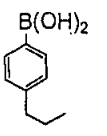
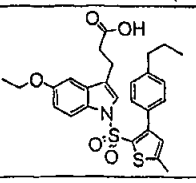
These compounds are shown in the following Table 4, indicating the sulfonyl chloride used in Step 3 (Column 2), the boronic acid used in the modified Step 4 (Column 3), and the compound structure (Column 4), with the compound number provided in Column 1.

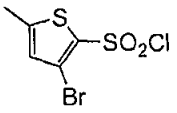
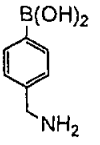
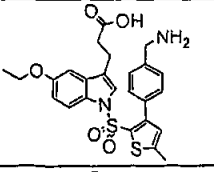
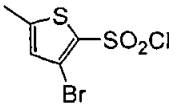
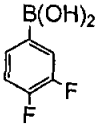
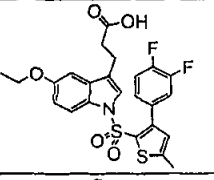
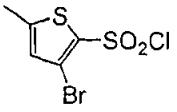
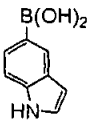
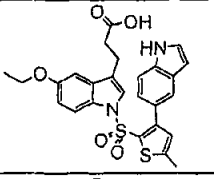
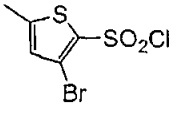
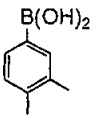
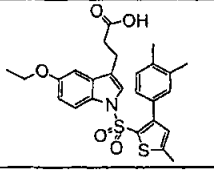
Table 4.

Cmpd. number	Sulfonyl-chloride	Boronic acid	Compound structure
P-0528 *		N/A	
P-0529			
P-0530			

Cmpd. number	Sulfonyl-chloride	Boronic acid	Compound structure
P-0531			
P-0532			
P-0533			
P-0534			
P-0535			
P-0536			
P-0537			
P-0538			
P-0539			
P-0552			

Cmpd. number	Sulfonyl-chloride	Boronic acid	Compound structure
P-0553			
P-0554			
P-0555			
P-0524			
P-0525			
P-0526			
P-0527			
P-0540			
P-0541			

Cmpd. number	Sulfonyl-chloride	Boronic acid	Compound structure
P-0542			
P-0543			
P-0544			
P-0545			
P-0546			
P-0547			
P-0548			
P-0549			
P-0550			

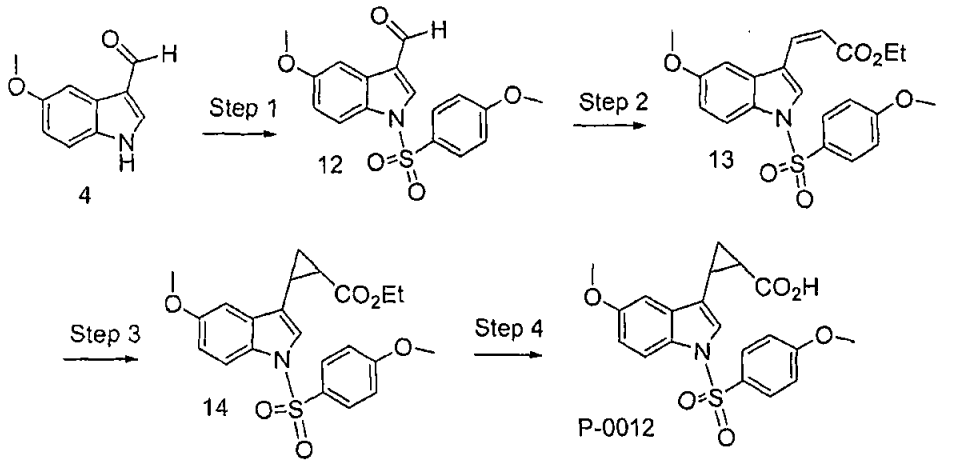
Cmpd. number	Sulfonyl-chloride	Boronic acid	Compound structure
P-0551			
P-0556			
P-0557			
P-0558			

* isolated after Step 3.

Example 3: Synthesis of 2-[5-Methoxy-1-(4-methoxy-benzenesulfonyl)-1H-Indol-3-yl)-cyclopropane carboxylic acid (P-0012).

[0238] Compound **P-0012** was synthesized in four steps as shown in Scheme 3.

Scheme 3



Step – 1: Preparation of 5-methoxy-1-(4-methoxy benzenesulfonyl)-1H-indole-3-carbaldehyde (12)

[0239] 5-methoxyindole-3-carboxyaldehyde (**4**, 263 mg) and toluene (15 mL) were combined in a dry 100 mL round bottom flask. The mixture was stirred for 5 minutes, then an aqueous solution of 50% KOH (12 mL) was added followed by tetrabutyl ammonium hydrogen sulfate (8 mg). The solution was stirred at room temperature overnight, after which the resulting solid was collected by filtration using a medium grade fritted funnel. The solid was rinsed with cold water (10 mL) and ethyl ether (2 x 15 mL) to give the desired compound (**2**, 388 mg, 75%). 1H NMR is consistent with the compound structure set forth above.

Step – 2: Preparation of (Z)-3-[5-methoxy-1-(4-methoxy-benzenesulfonyl)-1H-Indol-3-yl)-acrylic acid ethyl ester (13)

[0240] Ethyl diphenylphosphonoacetate (549 mg, 1.71 mmol) in tetrahydrofuran (2 mL) was cooled to 0 °C and sodium hydride (47.9 mg, 1.99 mmol) was added. The mixture was stirred at 0 °C for 15 min and the solution of deprotonated ethyl diphenylphosphonoacetate was added dropwise to a stirring solution of 5-methoxy-1-(4-methoxy benzenesulfonyl)-1H-indole-3-carbaldehyde (**12**, 493 mg, 1.43 mmol) in tetrahydrofuran (11 mL) at 0 °C. The reaction mixture was warmed slowly to 25 °C overnight. As conversion of **12** was incomplete, the reaction mixture was cooled to 0 °C and an additional equivalent of deprotonated ethyl diphenylphosphonoacetate was added. After slowly warming to 25 °C overnight, ethyl acetate was added to the reaction mixture and the organic layer was washed with saturated sodium bicarbonate, dried over magnesium sulfate and filtered. Concentration under reduced pressure resulted in a crude solid that was a 2:1 ratio of the Z and E isomers. The Z isomer was isolated using chromatography (gradient of hexanes to 20% ethyl acetate in hexanes) (**13**, 251 mg, 42% yield). MS(ESI) $[M + H^+]^+ = 438.2$.

Step – 3: Preparation of 2-[5-methoxy-1-(4-methoxy-benzenesulfonyl)-1H-Indol-3-yl)-cyclopropane carboxylic acid ethyl ester (14)

[0241] Trimethylsulfoxonium iodide (116 mg, 0.053 mmol) was dissolved in dimethyl sulfoxide (0.75 mL) and sodium hydride (14 mg, 0.058 mmol) was added. After 20 minutes of stirring at 25 °C, (Z)-3-[5-methoxy-1-(4-methoxy-benzenesulfonyl)-1H-Indol-3-yl)-acrylic acid ethyl ester (**13**, 200 mg, 0.048 mmol) in tetrahydrofuran (0.78 mL) was

added and the solution was heated to 60 °C under an atmosphere of nitrogen overnight. Water was added to the reaction mixture followed by the addition of ethyl acetate. The aqueous layer was washed with ethyl acetate and the organic layers were combined, dried over magnesium sulfate, filtered and concentrated at reduced pressure. Purification of the crude material was carried out using preparatory chromatography (30% ethyl acetate in hexanes) to obtain the desired compound as an off-white solid (**14**, 33 mg, 16% yield). MS(ESI) $[M+H^+]^+ = 430.4$.

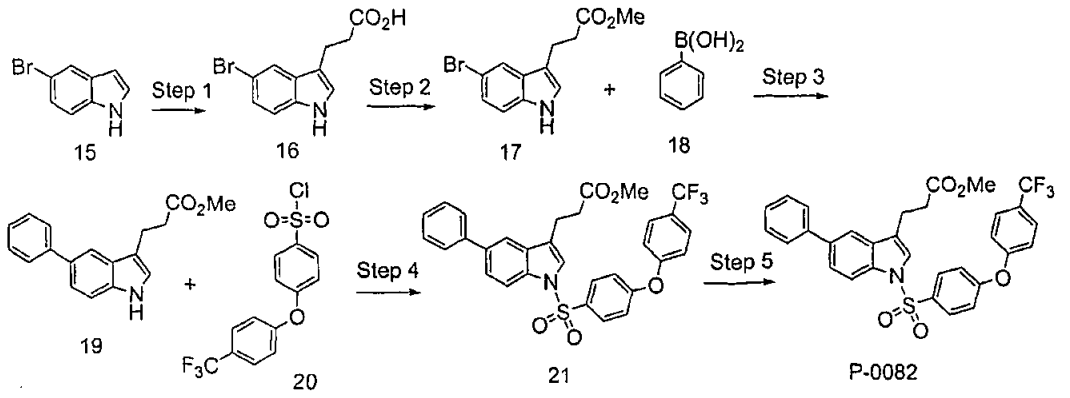
*Step – 4: Preparation of 2-[5-methoxy-1-(4-methoxy-benzenesulfonyl)-1H-Indol-3-yl)-cyclopropane carboxylic acid (**P-0012**)*

[0242] 2-[5-Methoxy-1-(4-methoxy-benzenesulfonyl)-1H-Indol-3-yl)-cyclopropane carboxylic acid ethyl ester (**14**, 25 mg, 0.006 mmol) was dissolved in tetrahydrofuran (1.0 mL) and 1M lithium hydroxide (0.25 mL) was added. After stirring for 4 days at 25 °C, ethyl acetate was added and the mixture was acidified with 1M hydrochloric acid. The organic layer was dried over magnesium sulfate, filtered and concentrated at reduced pressure to yield a red solid. The crude material was triturated with *tert*-butyl methyl ether to afford the desired compound (**P-0012**, 2.6 mg, 11% yield). Calculated molecular weight 401.43, MS(ESI) $[M - H^+]^- = 400.2$.

Example 4: Synthesis of 3-{5-phenyl-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (P-0082).

[0243] Compound **P-0082** was synthesized in five Steps as shown in Scheme 4.

Scheme 4



Step 1: preparation of 5-bromoindole-3-propionic acid (16)

[0244] Into a microwave vessel, 5-bromo-indole (**15**, 1 equivalent), paraformaldehyde (1.1 equivalent), 2,2-dimethyl-1,3-dioxane-4,6-dione (1.1 equivalent), and triethylamine (1.1 equivalent) were dissolved in acetonitrile (2 mL/mmol). The reaction was heated at 150 °C for 3 minutes in a microwave reactor. The reaction was then diluted with acidified water to pH ~ 5 with acetic acid and the aqueous layer was extracted with ethyl acetate. The organic layer was then washed with water 2X, brine 1X, and dried over magnesium sulfate. Evaporation of solvent afforded a solid. The crude solid was then purified via flash chromatography with a step gradient of 2 to 4 to 6% methanol in chloroform on silica to obtain the desired compound as a solid.

Step 2: Preparation of 5-bromoindole-3-propionic acid methyl ester (17)

[0245] The 5-bromo-indole-3-propionic acid **16** was treated with an aqueous solution of 4M HCl: methanol: dioxane (1:1:1) for 1 hour. The reaction was then re-evaporated with xylene and purified via flash chromatography on silica (chloroform) to obtain the desired compound as an off-white solid.

Step 3: Preparation of 3-(5-phenyl-1H-indol-3-yl)-propionic acid methyl ester (19)

[0246] Into a microwave tube containing intermediate 5-bromo-indole-3-propionic acid methyl ester (**17**, 0.05mmol), phenyl boronic acid (**18**, 0.1 mmol), 0.2 mL 1M K_2CO_3 (0.2 mmol), acetonitrile (0.4 ml) and a few mg of tetrakis(triphenylphosphine)palladium(0) were combined and heated in the microwave at 160 °C for 400 seconds. The crude material was then purified via flash chromatography with silica, eluting with a step gradient of 2 to 4 to 6% methanol in chloroform to isolate the desired compound as a solid.

Step 4: Preparation of 3-{5-phenyl-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid methyl ester (21)

[0247] Into a flask containing 3-(5-phenyl-1H-indol-3-yl)-propionic acid methyl ester (**19**, 1mmol) dissolved in 5 mL tetrahydrofuran, BEMP (1.1mmol), and 4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl chloride (**20**, 1.05 mmol) were combined and mixed at room temperature for 2 hours. The crude mixture was taken on to the next step.

*Step 5: Preparation of 3-{5-phenyl-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0082**)*

[0248] Into a flask, the crude mixture from Step 4 was dissolved in 1M NaOH solution, and stirred for 4 hours at ambient temperature. The hydrolysis was monitored via LC-MS. Upon full transformation, the basic solution was neutralized with acetic acid, followed by removal of the solvent under reduced pressure to yield a crude solid. The crude material was then taken up in dimethylsulfoxide and purified via reverse phase HPLC with a 20-100% acetonitrile gradient (12 minute gradient). The purified material was then analyzed via HPLC to identify the pure fractions. The fractions were then combined and concentrated down to afford the desired compound as a solid. Calculated molecular weight of 565.57, MS(ESI) $[M+H^+]^+ = 566.4$.

[0249] Additional compounds were prepared following the protocol of Scheme 4, optionally replacing phenyl boronic acid **18** with pyridine-3-boronic acid or thiophene-3-boronic acid in Step 3, and/or optionally replacing 4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl chloride **20** with an appropriate sulfonyl chloride in Step 4. The following compounds were prepared by this method, with the calculated molecular weight and measured mass (MS(ESI)) provided after the compound:

3-[1-(5-Isoxazol-3-yl-thiophene-2-sulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid (**P-0076**), calculated MW 478.55, $[M+H^+]^+$ = N/A,

3-{1-[5-(2-Methyl-thiazol-4-yl)-thiophene-2-sulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0077**), calculated MW 508.64, $[M+H^+]^+ = 509.1$,

3-{5-Phenyl-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0078**), calculated MW 498.56, $[M+H^+]^+ = 499.1$,

3-{1-[4-(4-Methoxy-phenoxy)-benzenesulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0079**), calculated MW 527.60, $[M+H^+]^+ = 528.3$,

3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0080**), calculated MW 566.46, $[M-H^+]^- = 566.4$

3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0081**), calculated MW 566.46, $[M-H^+]^- = 566.4$,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0083**), calculated MW 601.01, $[M+H^+]^+ = 601.2$,

3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0084**), calculated MW 566.46, $[M+H^+]^+ = 566.8$,

3-[1-(4'-Methoxy-biphenyl-4-sulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid (**P-0085**), calculated MW 511.60, $[M+H^+]^+$ = 512.3,
3-[1-(6-Morpholin-4-yl-pyridine-3-sulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid (**P-0086**), calculated MW 491.57, $[M+H^+]^+$ = 492.3,
3-[1-(6-Phenoxy-pyridine-3-sulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid (**P-0087**), calculated MW 498.56, $[M+H^+]^+$ = 499.1,
3-[5-Phenyl-1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0088**), calculated MW 488.59, $[M+H^+]^+$ = 489.1,
3-(1-{4-[(Morpholine-4-carbonyl)-amino]-benzenesulfonyl}-5-phenyl-1H-indol-3-yl)-propionic acid (**P-0089**), calculated MW 533.61, $[M+H^+]^+$ = 534.3,
3-{1-[5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid (**P-0091**), calculated MW 559.59, $[M+H^+]^+$ = 560.4,
3-{1-[5-(2-Methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0095**), calculated MW 536.65, $[M+H^+]^+$ = 537.1,
3-{5-Pyridin-3-yl-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0097**), calculated MW 499.55, $[M+H^+]^+$ = 500.3,
3-{1-[4-(4-Methoxy-phenoxy)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0098**), calculated MW 528.59, $[M+H^+]^+$ = 529.1,
3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0099**), calculated MW 567.45, $[M-H^+]^-$ = 567.2,
3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0100**), calculated MW 567.45, $[M-H^+]^-$ = 567.2,
3-{5-Pyridin-3-yl-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0101**), calculated MW 566.56, $[M+H^+]^+$ = 567.2,
3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0102**), calculated MW 601.99, $[M+H^+]^+$ = 602.4,
3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0103**), calculated MW 567.45, $[M-H^+]^-$ = 567.2,
3-[1-(4'-Methoxy-biphenyl-4-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0104**), calculated MW 512.59, $[M+H^+]^+$ = 513.5,
3-[1-(6-Phenoxy-pyridine-3-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0105**), calculated MW 499.55, $[M+H^+]^+$ = 500.3,
3-[5-Pyridin-3-yl-1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic

acid (**P-0106**), calculated MW 489.58, $[M+H^+]^+ = 490.3$,

3-{1-[5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0107**), calculated MW 560.58, $[M+H^+]^+ = 561.2$,

3-[1-(5-Methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0113**), calculated MW 486.55, $[M+H^+]^+ = 487.1$,

3-[1-(6-Morpholin-4-yl-pyridine-3-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0114**), calculated MW 492.56, $[M+H^+]^+ = 493.5$,

3-(1-{4-[(Morpholine-4-carbonyl)-amino]-benzenesulfonyl}-5-pyridin-3-yl-1H-indol-3-yl)-propionic acid (**P-0115**), calculated MW 534.60, $[M+H^+]^+ = 535.1$,

3-{5-Pyridin-3-yl-1-[4-(pyridin-4-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0118**), calculated MW 499.55, $[M+H^+]^+ = 500.3$,

3-{1-[3-(2-Methyl-pyrimidin-4-yl)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0120**), calculated MW 498.56, $[M+H^+]^+ = 499.1$,

3-[1-(Biphenyl-2-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0125**), calculated MW 482.56, $[M+H^+]^+ = 483.1$,

3-[1-(2-Phenoxy-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0128**), calculated MW 498.56, $[M+H^+]^+ = 499.1$,

3-{1-[3-(Pyridine-2-carbonyl)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid (**P-0131**), calculated MW 511.56, $[M+H^+]^+ = 512.3$,

3-[1-(4-Pyrazol-1-yl-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid (**P-0137**), calculated MW 472.53, $[M+H^+]^+ = 473.1$,

3-{1-[5-(2-Methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0573**), calculated MW 541.70,

3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0574**), calculated MW 572.49,

3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0575**), calculated MW 572.49,

3-{1-[4-(Pyridin-2-yloxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0581**), calculated MW 504.58,

3-{1-[4-(Pyridin-4-yloxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0582**), calculated MW 504.58,

3-{1-[4-(4-Methoxy-phenoxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0583**), calculated MW 533.62,

3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0584**), calculated MW 572.49,

3-{5-Thiophen-3-yl-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0585**), calculated MW 571.59,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0586**), calculated MW 607.03,

3-[1-(4'-Methoxy-biphenyl-4-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid (**P-0587**), calculated MW 517.62,

3-[1-(6-Morpholin-4-yl-pyridine-3-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid (**P-0588**), calculated MW 497.59,

3-[1-(6-Phenoxy-pyridine-3-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid (**P-0589**), calculated MW 504.58,

3-[1-(5-Pyridin-2-yl-thiophene-2-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid (**P-0590**), calculated MW 494.61,

3-{1-[5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0592**), calculated MW 565.62,

3-[1-(5-Methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid (**P-0599**), calculated MW 491.59,

3-{1-[3-(2-Methyl-pyrimidin-4-yl)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0601**), calculated MW 503.60,

3-{1-[3-(Pyridine-2-carbonyl)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid (**P-0607**), calculated MW 516.60,

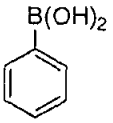
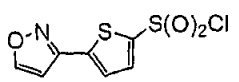
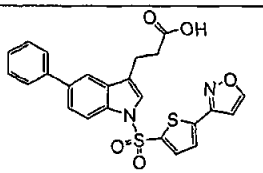
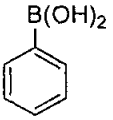
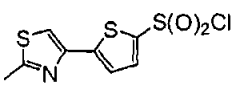
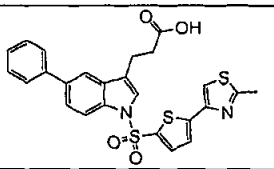
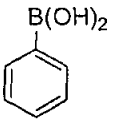
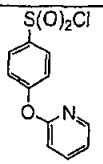
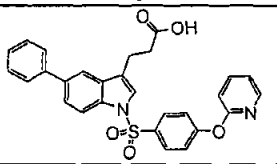
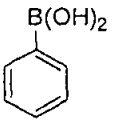
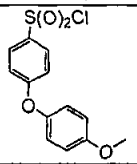
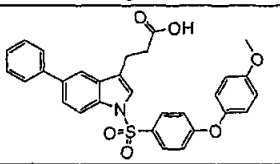
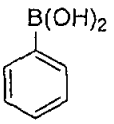
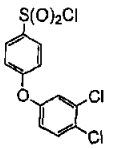
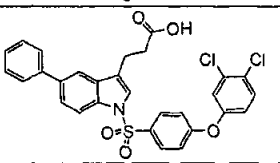
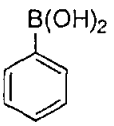
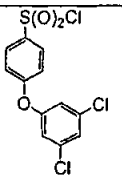
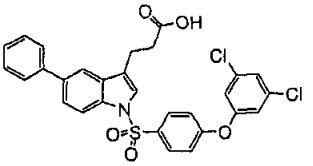
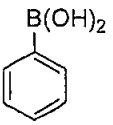
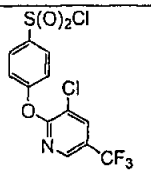
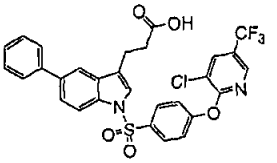
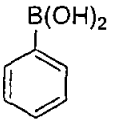
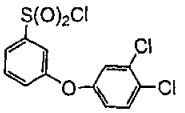
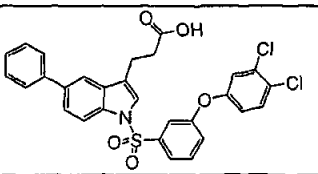
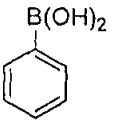
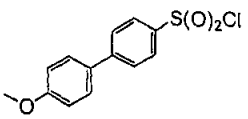
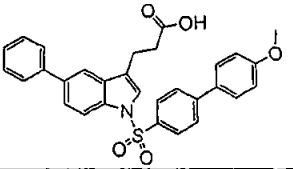
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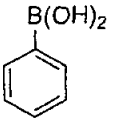
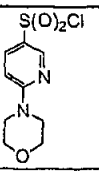
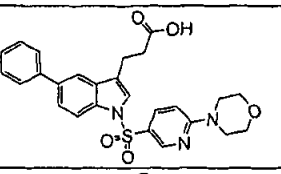
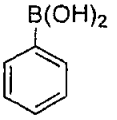
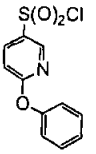
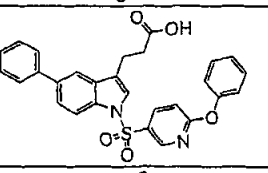
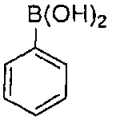
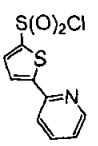
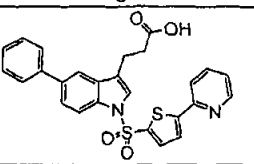
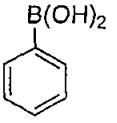
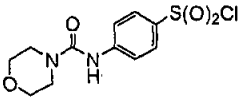
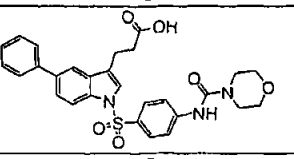
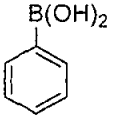
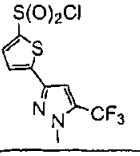
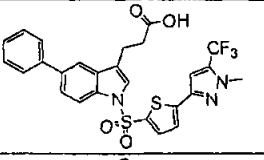
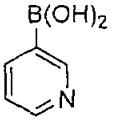
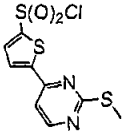
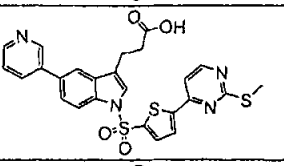
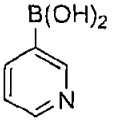
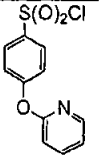
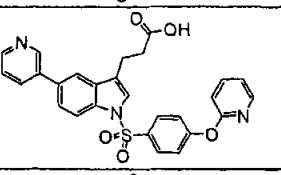
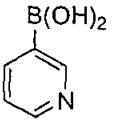
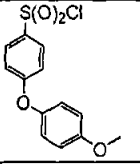
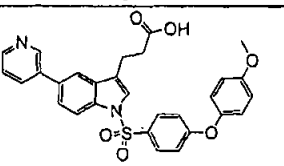
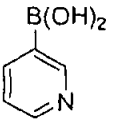
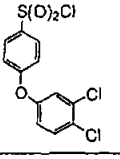
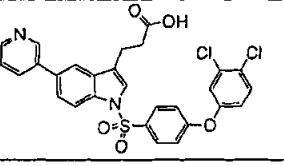
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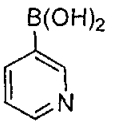
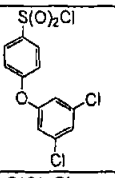
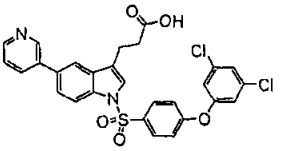
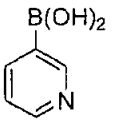
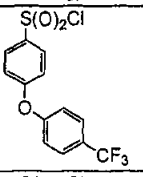
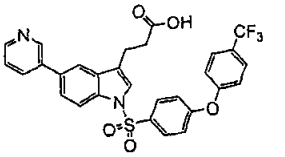
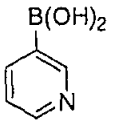
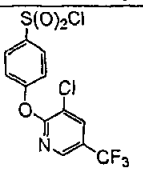
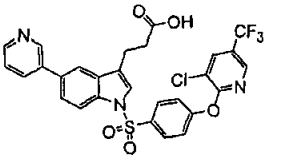
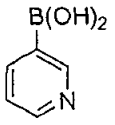
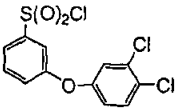
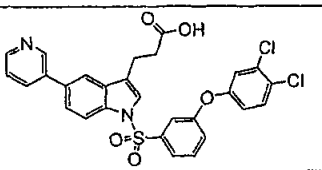
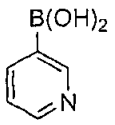
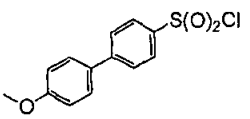
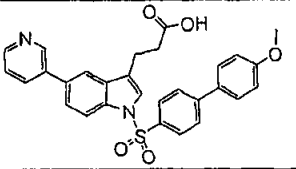
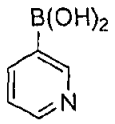
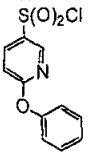
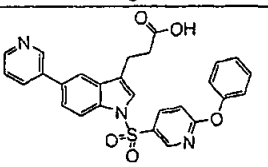
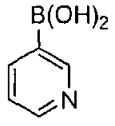
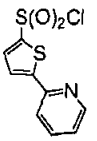
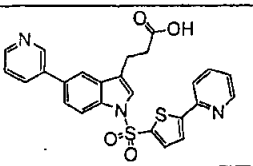
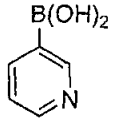
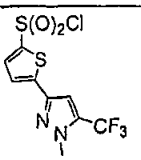
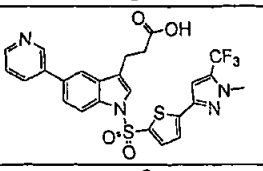
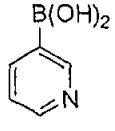
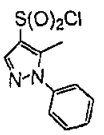
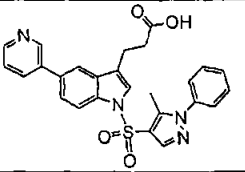
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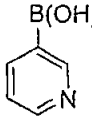
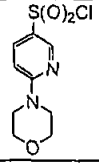
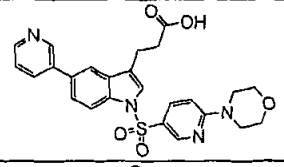
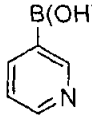
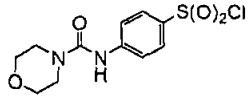
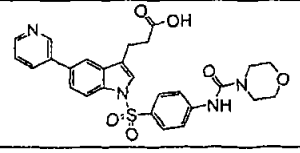
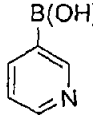
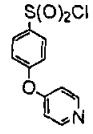
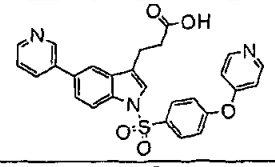
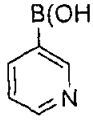
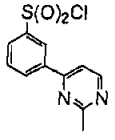
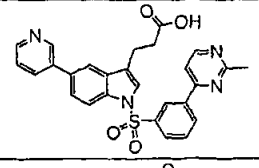
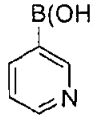
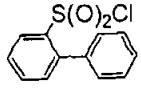
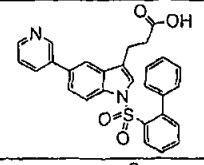
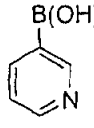
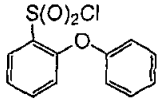
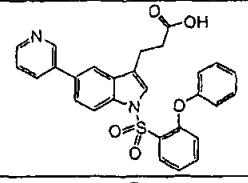
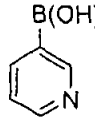
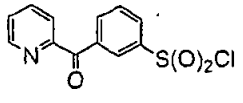
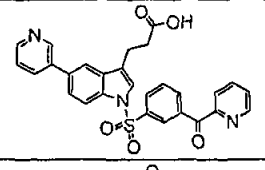
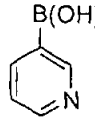
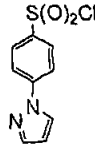
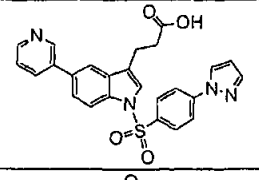
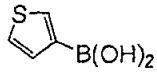
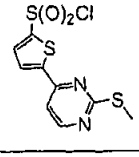
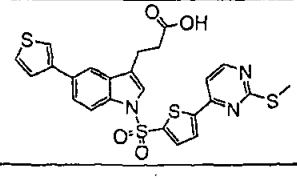
These compounds are shown in the following Table 5, indicating the boronic acid used in Step 3 (Column 2), and the sulfonyl chloride used in the Step 4 (Column 3), with the compound structure provided in Column 4 and the compound number provided in Column 1.

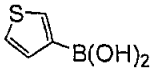
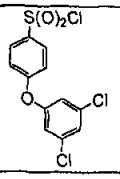
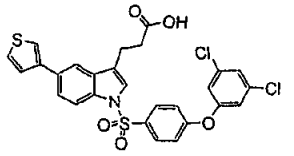
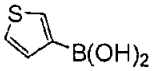
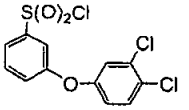
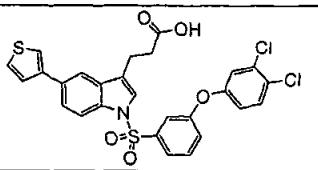
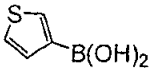
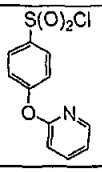
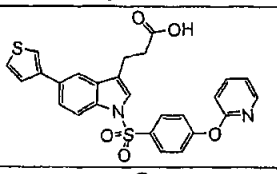
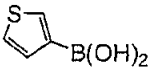
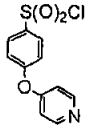
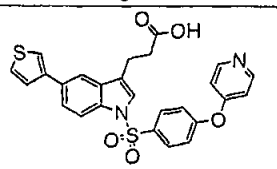
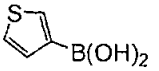
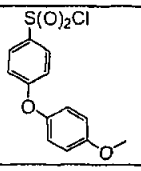
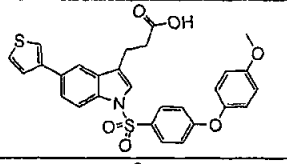
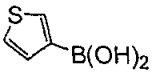
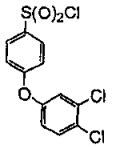
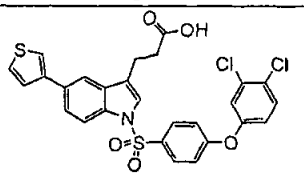
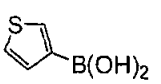
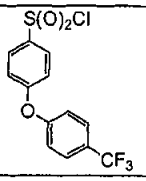
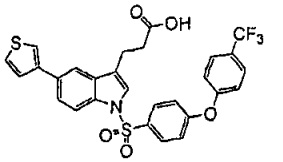
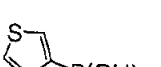
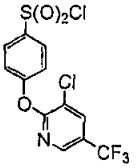
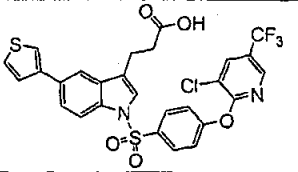
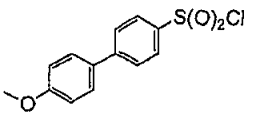
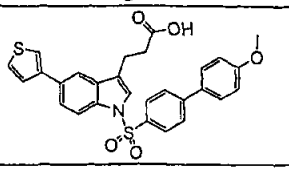
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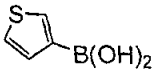
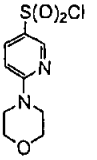
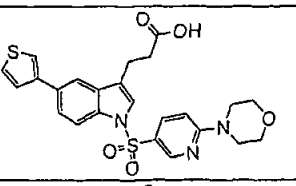
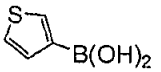
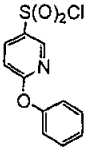
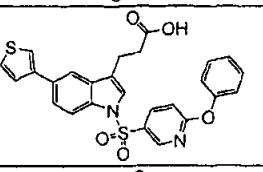
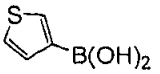
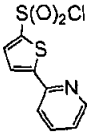
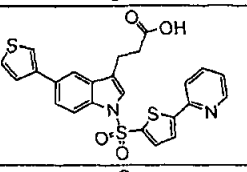
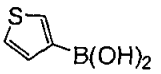
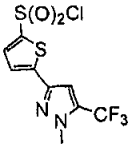
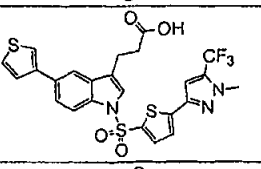
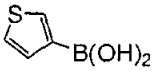
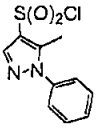
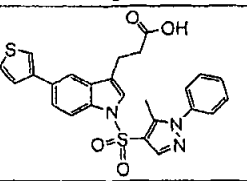
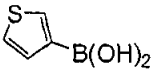
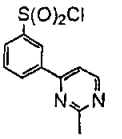
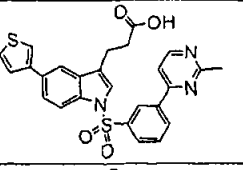
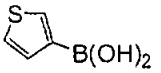
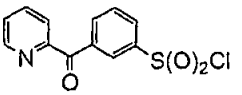
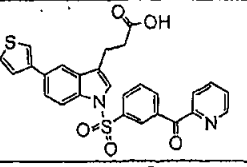
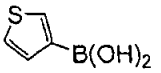
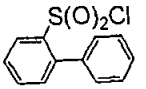
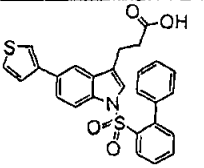
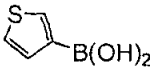
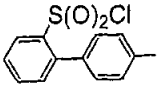
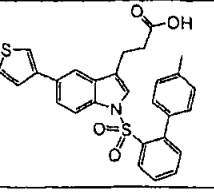
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P-0077			
P-0078			
P-0079			
P-0080			
P-0081			
P-0083			
P-0084			
P-0085			

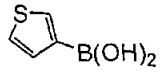
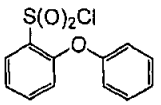
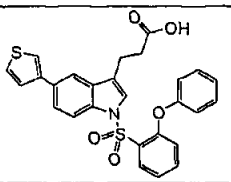
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P-0087			
P-0088			
P-0089			
P-0091			
P-0095			
P-0097			
P-0098			
P-0099			

Cmpd. number	Boronic acid	Sulfonyl chloride	Compound structure
P-0100			
P-0101			
P-0102			
P-0103			
P-0104			
P-0105			
P-0106			
P-0107			
P-0113			

Cmpd. number	Boronic acid	Sulfonyl chloride	Compound structure
P-0114			
P-0115			
P-0118			
P-0120			
P-0125			
P-0128			
P-0131			
P-0137			
P-0573			

Cmpd. number	Boronic acid	Sulfonyl chloride	Compound structure
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P-0575			
P-0581			
P-0582			
P-0583			
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P-0587			

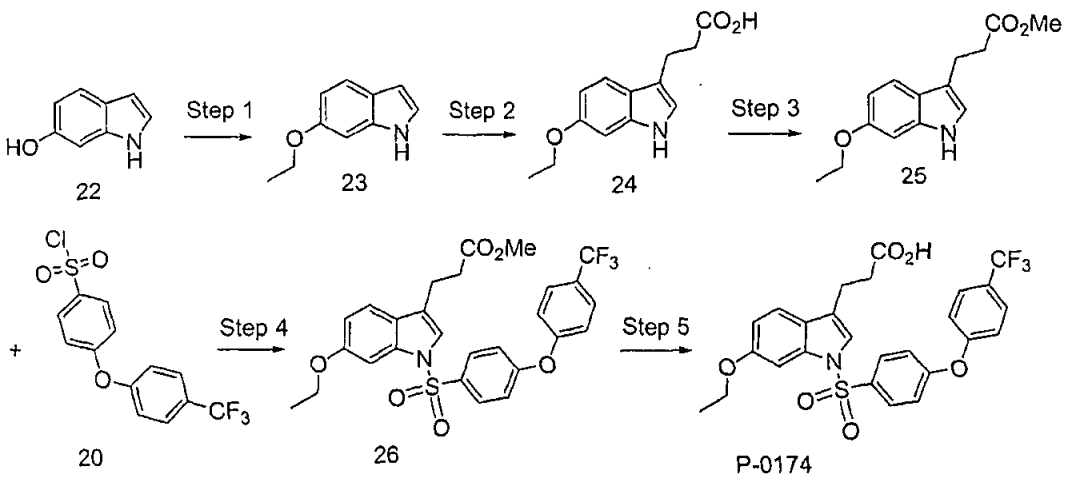
Cmpd. number	Boronic acid	Sulfonyl chloride	Compound structure
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P-0589			
P-0590			
P-0592			
P-0599			
P-0601			
P-0607			
P-0608			
P-0617			

Cmpd. number	Boronic acid	Sulfonyl chloride	Compound structure
P-0618			

Example 5: Synthesis of 3-{6-Ethoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (P-0174).

[0250] Compound **P-0174** was synthesized in five Steps as shown in Scheme 5.

Scheme 5



Step 1: preparation of 6-ethoxyindole (23)

[0251] Into a round bottom flask 6-hydroxyindole (**22**, 2 g, 0.02 mol), potassium carbonate (4 g, 0.03 mol), acetonitrile (20 g, 0.5 mol), and iodoethane (4 g, 0.02 mol) were combined and stirred at ambient temperature for 3-4 days. The reaction was filtered and washed with dichloromethane. The organic layer was then washed with water twice, brine once, and dried over sodium sulfate. The evaporation of the solvent yielded an oil. The oil was then absorbed onto silica and purified via 80% hexane, 20% ethyl acetate to yield a yellow solid. ^{1}H NMR is consistent with the compound structure set forth above.

Step 2: Preparation of the 6-ethoxy-indole-3-propionic acid (24)

[0252] Into a microwave vessel, 6-ethoxy indole (**23**, 1 equivalent), paraformaldehyde (1.1 equivalent), 2,2-dimethyl-1,3-dioxane-4,6-dione (1.1 equivalent), and triethylamine (1.1 equivalent) were dissolved in acetonitrile (2 mL/mmol). The reaction was heated at 150 °C for 3 minutes in a microwave reactor. The reaction was then diluted with acidified water to pH ~ 5 with acetic acid and the aqueous layer was extracted with ethyl acetate. The organic layer was then washed with water 2X, brine 1X, and dried over magnesium sulfate. Evaporation of solvent afforded a solid. The crude solid was then purified via flash chromatography with step gradient of 2 to 4 to 6% methanol in chloroform on silica to obtain the desired compound as an oil.

Step 3: Preparation of 6-ethoxy-indole-3-propionic acid methyl ester (25)

[0253] In a flask, the 6-ethoxy-indole-3-propionic acid **24** was treated with methanol (4 mol equiv), N,N'-Diisopropylcarbodiimide (2 mol equiv), a catalytic amount of dimethylaminopyridine in dichloromethane and stirred for 15 to 20 minutes at ambient conditions. The solvent was removed under reduced pressure and the mixture purified via flash chromatography on silica (chloroform) to obtain the desired compound as an off-white solid.

Step 4: Preparation of 3-{6-ethoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid methyl ester (26)

[0254] Into a flask containing 6-ethoxy-indole-3-propionic acid methyl ester (**25**, 1mmol) dissolved in 5 mL tetrahydrofuran, BEMP (1.1mmol), and 4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl chloride (**20**, 1.05 mmol) were combined and mixed at room temperature for 2 hours. The crude mixture was taken on to the next step.

*Step 5: Preparation of 3-{6-ethoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0174**)*

[0255] Into a flask, the crude mixture from Step 4 was dissolved in 1M NaOH solution, and stirred for 4 hours at ambient temperature. The hydrolysis was monitored via LC-MS. Upon full transformation, the basic solution was neutralized with acetic acid, followed by removal of the solvent under reduced pressure to yield a crude solid. The crude material was then taken up in dimethylsulfoxide and purified via reverse phase HPLC with a 20-100% acetonitrile gradient (12 minute gradient). The purified material was then analyzed via HPLC to identify the pure fractions. The fractions were then combined and

concentrated down to afford the desired compound as a solid. Calculated molecular weight of 533.53, MS (ESI) $[M+H^+]^+ = 534.3$.

[0256] Additional compounds were prepared following the protocol of Scheme 5, optionally replacing iodoethane with 2-iodopropane in Step 1, and/or optionally replacing 4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl chloride **20** with an appropriate sulfonyl chloride in Step 4. The following compounds were prepared by this method, with the calculated molecular weight and measured mass (MS(ESI)) provided after the compound:

3-{6-Ethoxy-1-[4-(pyridin-3-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0173**), calculated MW 466.52, $[M+H^+]^+ = 467.1$,

3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-6-ethoxy-1H-indol-3-yl}-propionic acid (**P-0175**), calculated MW 534.42, $[M-H^+]^- = 533.9$,

3-[6-Ethoxy-1-(6-morpholin-4-yl-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0176**), calculated MW 459.53, $[M+H^+]^+ = 460.3$,

3-[6-Ethoxy-1-(6-phenoxy-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0177**), calculated MW 466.52, $[M+H^+]^+ = 467.1$,

3-{6-Ethoxy-1-[3-(pyridine-2-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0182**), calculated MW 478.53, $[M+H^+]^+ = 479.1$,

3-{6-Ethoxy-1-[3-(pyridine-4-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0183**), calculated MW 478.53, $[M+H^+]^+ = 479.1$,

3-[1-(Biphenyl-2-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid (**P-0185**), calculated MW 449.53, $[M+H^+]^+ = 449.9$,

3-[6-Ethoxy-1-(2-phenoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid (**P-0191**), calculated MW 465.53, $[M+H^+]^+ = 466.3$,

3-{6-Ethoxy-1-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0195**), calculated MW 495.56, $[M+H^+]^+ = 496.3$,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-6-ethoxy-1H-indol-3-yl}-propionic acid (**P-0196**), calculated MW 568.96, $[M+H^+]^+ = 569.2$,

3-[6-Ethoxy-1-(4'-methyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0201**), calculated MW 463.56, $[M+H^+]^+ = 464.3$,

3-{6-Isopropoxy-1-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0206**), calculated MW 509.58, $[M+H^+]^+ = 510.3$,

3-{6-Isopropoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0207**), calculated MW 547.55, $[M+H^+]^+ = 548.3$,

3-{6-Isopropoxy-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0208**), calculated MW 541.57, $[M+H^+]^+$ = 543.1,

3-[6-Isopropoxy-1-(5-methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0232**), calculated MW 467.55, $[M+H^+]^+$ = 468.3,

3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-6-isopropoxy-1H-indol-3-yl}-propionic acid (**P-0233**), calculated MW 548.45, $[M+H^+]^+$ = 550.3,

3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-6-isopropoxy-1H-indol-3-yl}-propionic acid (**P-0234**), calculated MW 548.45, $[M-H^+]^-$ = 547.9,

3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-6-isopropoxy-1H-indol-3-yl}-propionic acid (**P-0235**), calculated MW 582.99, $[M+H^+]^+$ = 583.2,

3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-6-isopropoxy-1H-indol-3-yl}-propionic acid (**P-0236**), calculated MW 548.45, $[M-H^+]^-$ = 548.3,

3-[6-Isopropoxy-1-(4'-methoxy-biphenyl-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0237**), calculated MW 493.58, $[M+H^+]^+$ = 494.3,

3-[6-Ethoxy-1-(5-methyl-1-phenyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0346**), calculated MW 453.52, $[M+H^+]^+$ = 454.3,

3-{6-Ethoxy-1-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0347**), calculated MW 503.62, $[M+H^+]^+$ = 504.3,

3-{6-Ethoxy-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid (**P-0350**), calculated MW 466.52, $[M+H^+]^+$ = 467.1,

3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-6-ethoxy-1H-indol-3-yl}-propionic acid (**P-0351**), calculated MW 534.42, $[M-H^+]^-$ = 533.9,

3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-6-ethoxy-1H-indol-3-yl}-propionic acid (**P-0352**), calculated MW 534.42, $[M-H^+]^-$ = 533.9,

3-[6-Ethoxy-1-(4'methoxy-biphenyl-4-sulfonyl)-1H-indol-3-yl]-propionic acid (**P-0353**), calculated MW 479.56, $[M+H^+]^+$ = 479.9,

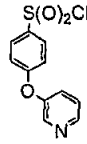
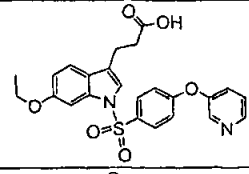
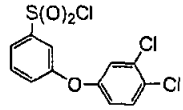
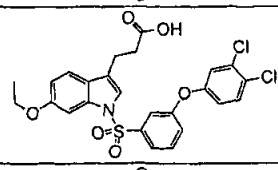
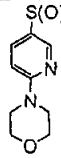
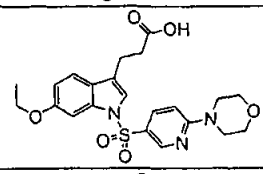
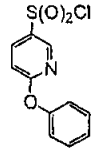
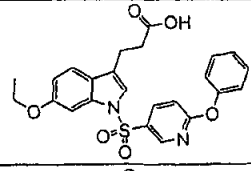
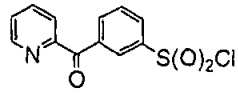
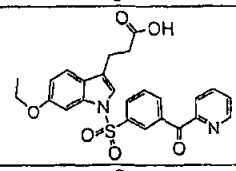
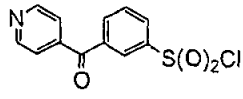
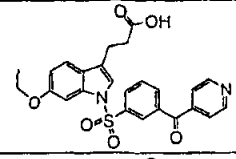
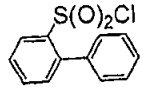
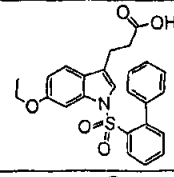
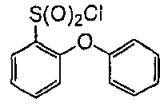
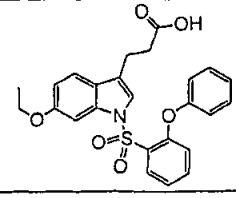
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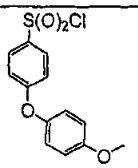
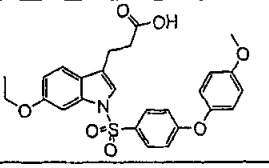
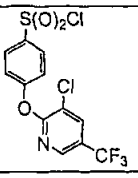
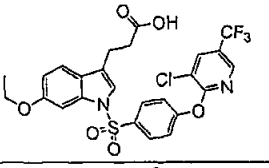
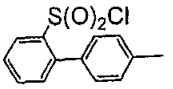
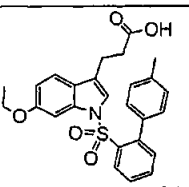
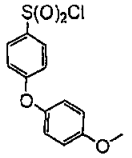
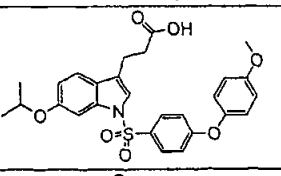
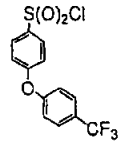
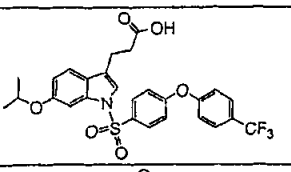
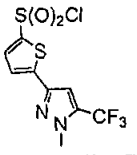
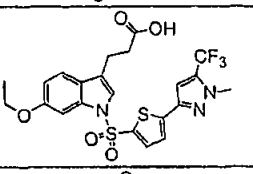
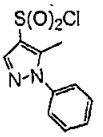
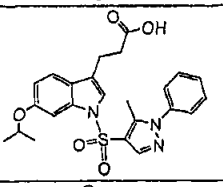
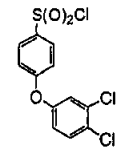
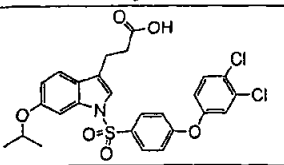
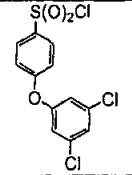
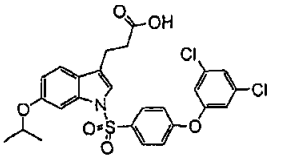
3-(6-Ethoxy-1-{4-[(morpholine-4-carbonyl)-amino]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid (**P-0355**), calculated MW 501.56, $[M+H^+]^+$ = 502.3, and

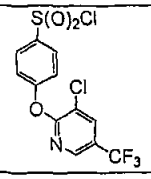
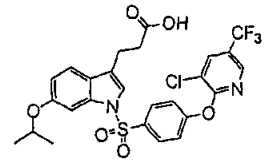
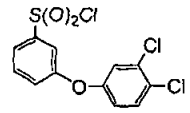
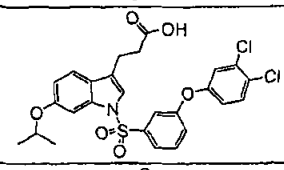
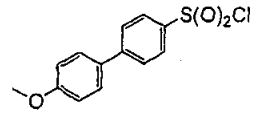
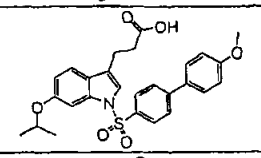
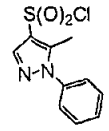
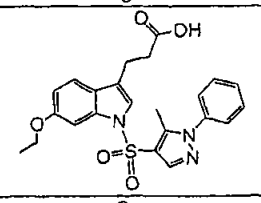
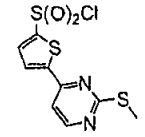
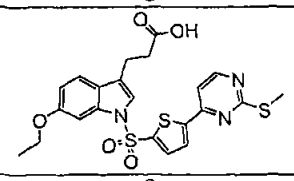
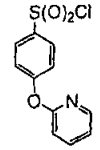
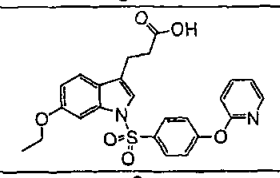
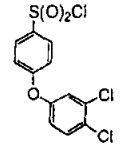
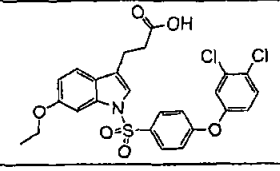
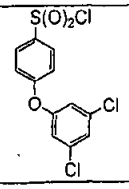
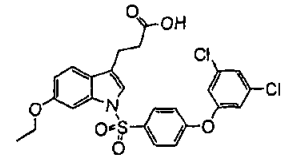
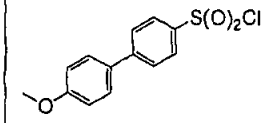
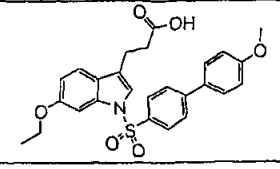
3-{6-Ethoxy-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid (**P-0356**), calculated MW 527.55, $[M+H^+]^+$ = 527.9

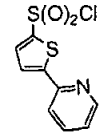
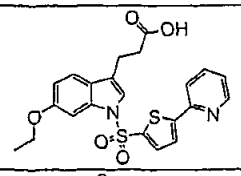
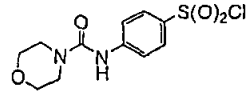
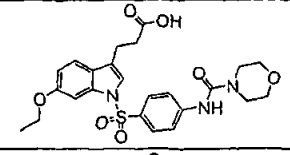
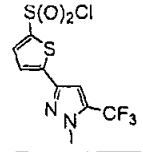
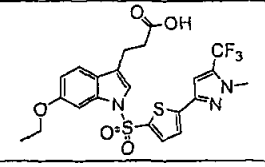
These compounds are shown in the following Table 6, indicating the iodoalkyl compound used in Step 1 (Column 2), and the sulfonyl chloride used in the Step 4 (Column 3), with the compound structure provided in Column 4 and the compound number provided in Column 1.

Table 6.

Cmpd. number	Iodo-alkyl	Sulfonyl chloride	Compound structure
P-0173			
P-0175			
P-0176			
P-0177			
P-0182			
P-0183			
P-0185			
P-0191			

Cmpd. number	Iodo-alkyl	Sulfonyl chloride	Compound structure
P-0195			
P-0196			
P-0201			
P-0206			
P-0207			
P-0208			
P-0232			
P-0233			
P-0234			

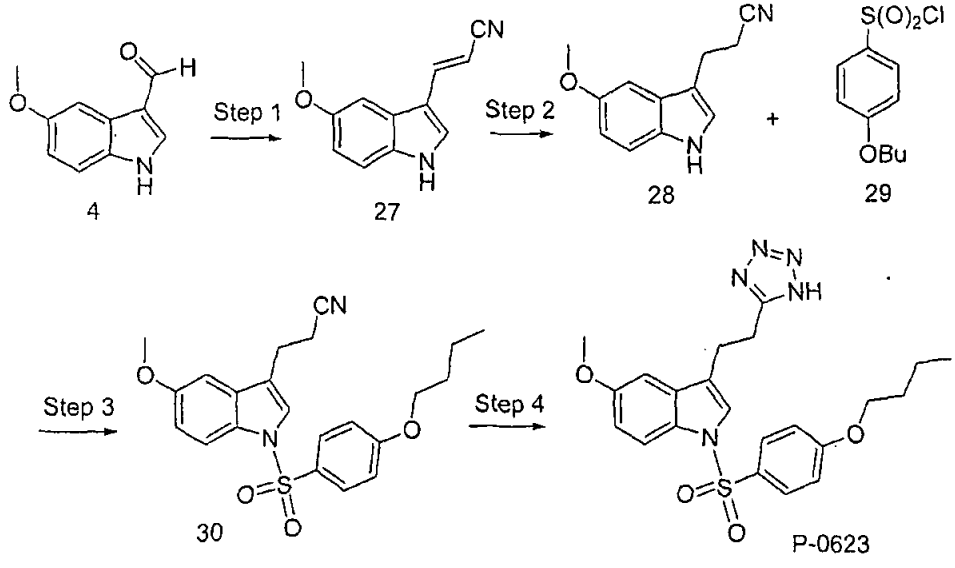
Cmpd. number	Iodo-alkyl	Sulfonyl chloride	Compound structure
P-0235			
P-0236			
P-0237			
P-0346			
P-0347			
P-0350			
P-0351			
P-0352			
P-0353			

Cmpd. number	Iodo-alkyl	Sulfonyl chloride	Compound structure
P-0354			
P-0355			
P-0356			

Example 6: Synthesis of 1-(4-butoxy-benzenesulfonyl)-5-methoxy-3-[2-(1H-tetrazol-5-yl)-ethyl]-1H-indole (P-0623).

[0257] Compound **P-0623** was synthesized in four Steps as shown in Scheme 6.

Scheme 6



Step 1: Preparation of (E)-3-(5-methoxy-1H-indol-3-yl)-acrylonitrile (27)

[0258] Into a 1-neck round-bottom flask, 5-methoxyindole-3-carboxaldehyde (**4**, 0.500

g, 0.00280 mol) was dissolved in tetrahydrofuran (18 mL, 0.23 mol). In a separate flask, diethyl cyanomethylphosphonate (0.909 mL, 0.00559 mol) was dissolved in 10 mL of tetrahydrofuran. The flask was cooled down and sodium hydride (224 mg, 0.00559 mol) was added to the flask under an atmosphere of argon. After the hydrogen gas evolution ceased, the solution was transferred into a syringe. The sodium phosphonoacetate tetrahydrofuran solution was added dropwise to the flask containing 5-methoxyindole-3-carboxyaldehyde at room temperature for 15 minutes. After the slow addition of the phosphonoacetate solution, the flask was heated at 55 °C overnight under an atmosphere of argon. The mixture was concentrated, then diluted with dichloromethane and washed with water (100 mL) three times. The combined organic layers were washed with brine one time, and dried over sodium sulfate. The dry organic layer was then filtered and the solvent removed by rotovap to afford a brown oil. The oil was purified with flash chromatography using 10-20% ethyl acetate in hexane. ^{1}H NMR is consistent with the compound structure set forth above.

Step 2: Preparation of 3-(5-methoxy-1H-indol-3-yl)-propionitrile (28)

[0259] Into a flask, (E)-3-(5-methoxy-1H-indol-3-yl)-acrylonitrile (**27**, 190 mg, 0.00096 mol) was dissolved in tetrahydrofuran (30 mL, 0.4 mol). 5% Pd/C (5:95, palladium:carbon, 2.0E2 mg) was added and this mixture stirred overnight at ambient conditions under an atmosphere of hydrogen. The catalyst was filtered through celite, and the solvent was evaporated to afford a lightly colored oil. ^{1}H NMR is consistent with lthe compound structure set forth above.

Step 3: Preparation of 3-[1-(4-butoxy-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionitrile (30)

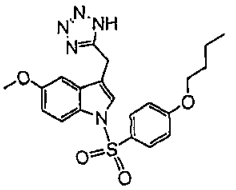
[0260] Into a round bottom flask, 3-(5-methoxy-1H-indol-3-yl)-propionitrile (**28**, 158 mg, 0.000789 mol) was suspended in toluene (2 mL, 0.02 mol). Potassium hydroxide (1 mL, 0.02 mol) and tetrabutylammonium hydrogen sulfate (7.5 mg, 0.000022 mol) were added. To this, 4-butoxy-benzenesulfonyl chloride (**29**, 156 μL, 0.000968 mol) was added and the reaction was stirred at ambient temperature for 5 hours. The reaction was diluted with ethyl acetate and water, the layers separated, and the aqueous layer extracted once with ethyl acetate. The combined organic layers were washed with water (3X), saturated sodium bicarbonate solution (1X), and brine (1X). The organic portion was dried over sodium sulfate and evaporated to dryness under reduced pressure. The product was

purified using chromatography, eluting with ethyl acetate in hexanes. ^{1}H NMR is consistent with the compound structure set forth above.

*Step 4: Preparation of 1-(4-butoxy-benzenesulfonyl)-5-methoxy-3-[2-(1H-tetrazol-5-yl)-ethyl]-1H-indole (**P-0623**)*

[0261] To a solution of 3-[1-(4-butoxy-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionitrile (**30**, 100 mg, 0.0002 mol) and azidotrimethylsilane (64.4 uL, 0.000485 mol) in toluene (1 mL, 0.009 mol) was added dibutyloxostannane (6.0 mg, 0.000024 mol) and the mixture was heated at 110 °C overnight. The reaction mixture was concentrated in vacuo. The residue was dissolved in methanol and re-concentrated. The residue was partitioned between ethyl acetate and water. The organic phase was dried over sodium sulfate. The product was isolated with two successive prep TLC plate purification with 100% ethyl acetate with some acetic acid as solvent for the first run, followed by another TLC plate with 30% hexane 70% ethyl acetate with some formic acid. ^{1}H NMR is consistent with the compound structure set forth above. Calculated molecular weight 455.54, MS (ESI) $[M-H^+]^-$ = 454.2.

[0262] 1-(4-Butoxy-benzenesulfonyl)-5-methoxy-3-(1H-tetrazol-5-ylmethyl)-1H-indole **P-0624**,

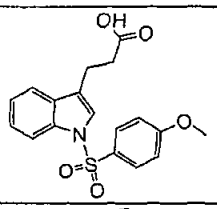
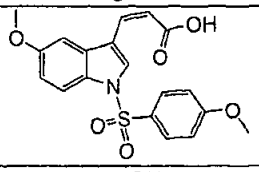
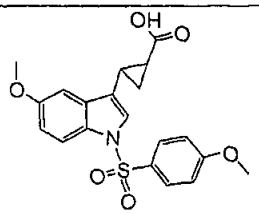
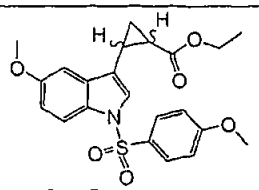
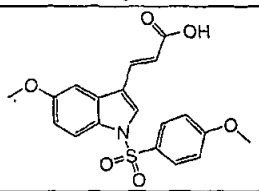
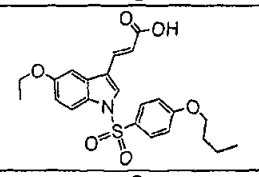
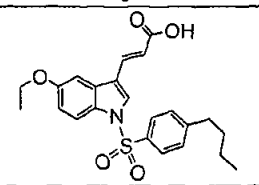
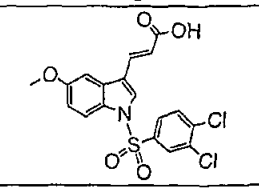


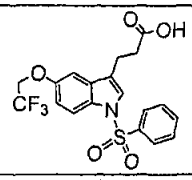
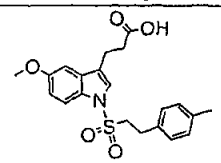
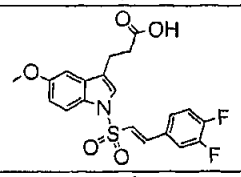
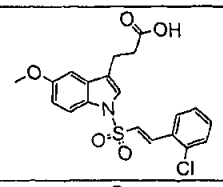
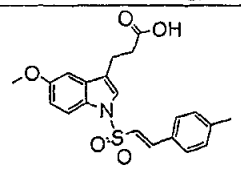
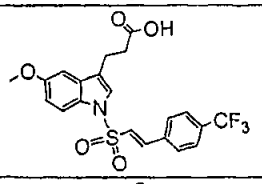
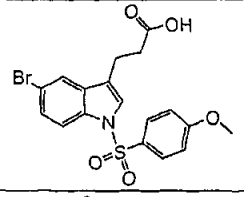
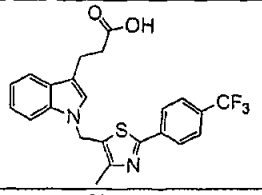
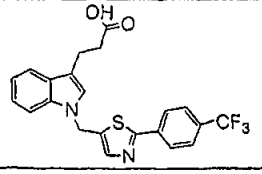
was prepared following Steps 3 and 4 of Scheme 6, replacing 3-(5-methoxy-1H-indol-3-yl)-propionitrile **28** with (5-methoxy-1H-indol-3-yl)-acetonitrile.

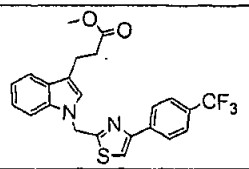
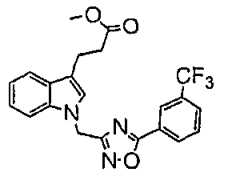
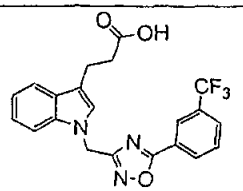
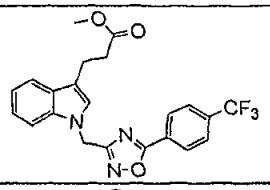
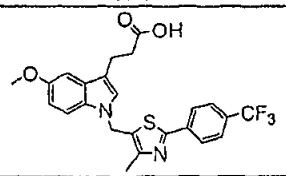
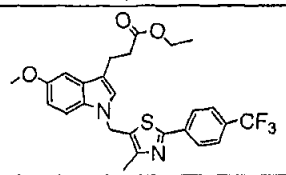
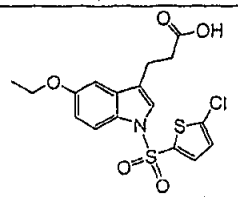
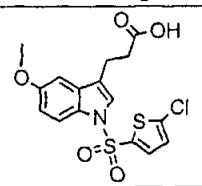
Example 7: Additional compounds

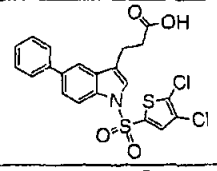
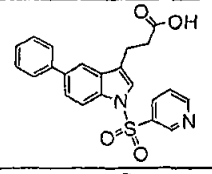
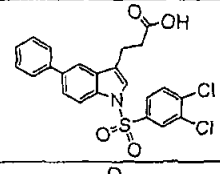
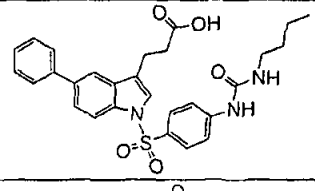
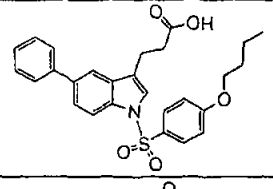
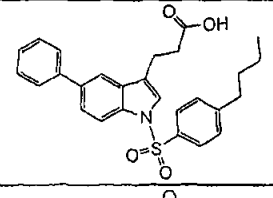
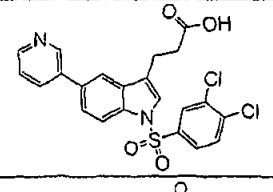
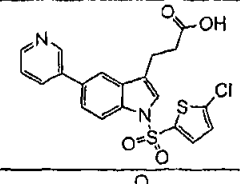
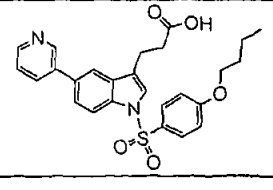
[0263] Additional compounds of the invention were synthesized following the methods of the Examples above, or similar methods known to those of skill in the art, and are shown in the following Table 7, with the compound number in Column 1, compound structure in Column 2, compound name in Column 3, and calculated molecular weight and experimental mass spectrometry result in Columns 4 and 5.

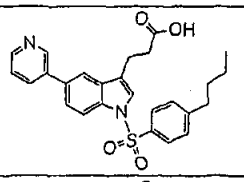
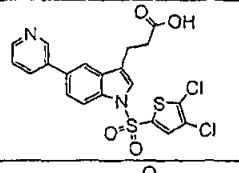
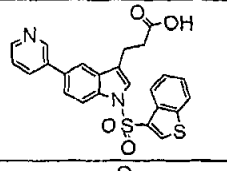
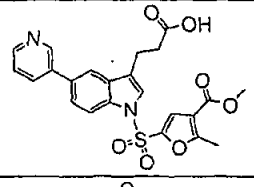
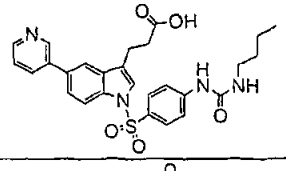
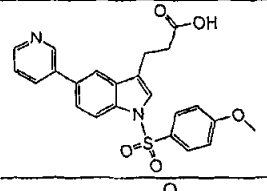
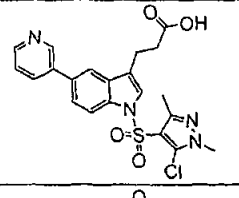
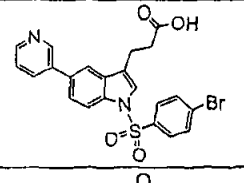
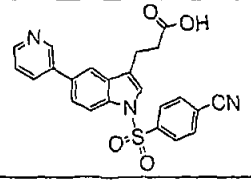
Table 7.

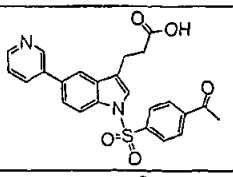
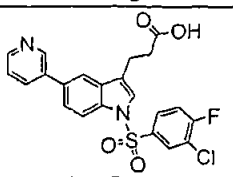
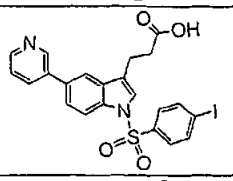
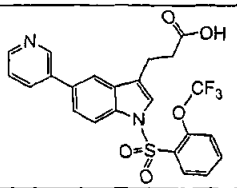
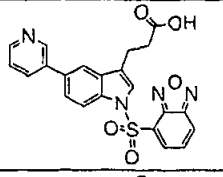
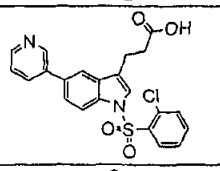
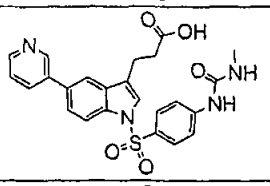
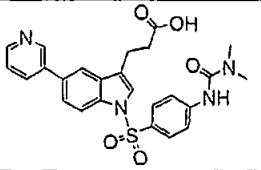
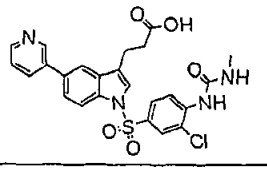
Comp. number	Structure	Name	Molecular weight Calc.	Molecular weight Measured MS(ESI)
P-0005		3-[1-(4-Methoxy-benzenesulfonyl)-1H -indol-3-yl]-propionic acid	359.40	$[M - H^+]^-$ = 358.2
P-0010		(Z)-3-[5-Methoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-acrylic acid	387.41	$[M - H^+]^-$ = 386.1
P-0011		2-[5-Methoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-cyclopropane carboxylic acid	401.43	$[M - H^+]^-$ = 400.2
P-0013		2-[5-Methoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-cyclopropane carboxylic acid ethyl ester	429.49	$[M+H^+]^+$ = 430.4
P-0021		(E)-3-[5-Methoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-acrylic acid	387.41	$[M+ H^+]^+$ = 389.04
P-0022		(E)-3-[1-(4-Butoxy-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-acrylic acid	443.52	$[M - H^+]^-$ = 441.90
P-0023		(E)-3-[1-(4-Butyl-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-acrylic acid	427.52	$[M - H^+]^-$ = 425.90
P-0024		(E)-3-[1-(3,4-Dichloro-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-acrylic acid	373.42	$[M+H^+]^+$ = 374.2

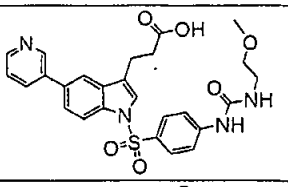
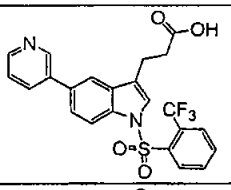
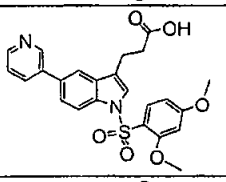
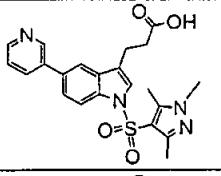
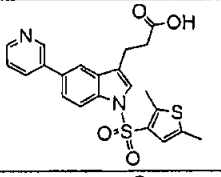
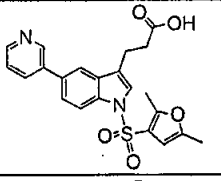
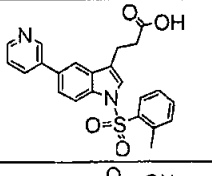
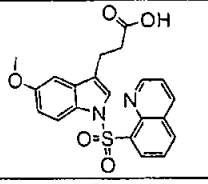
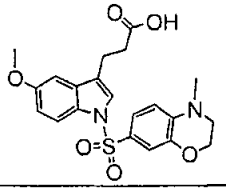
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0025		3-[1-Benzenesulfonyl-5-(2,2,2-trifluoro-ethoxy)-1H-indol-3-yl]-propionic acid	444.47	$[M+H^+]^+$ = 445.3
P-0027		3-[5-Methoxy-1-(2-p-tolyl-ethanesulfonyl)-1H-indol-3-yl]-propionic acid	401.48	$[M - H^+]^-$ = 400.1
P-0028		3-{1-[(E)-2-(3,4-Difluoro-phenyl)-ethenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid	421.42	$[M - H^+]^-$ = 420.0
P-0029		3-{1-[(E)-2-(2-Chloro-phenyl)-ethenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid	419.88	$[M - H^+]^-$ = 418.0
P-0030		3-[5-Methoxy-1-((E)-2-p-tolyl-ethenesulfonyl)-1H-indol-3-yl]-propionic acid	399.46	$[M - H^+]^-$ = 398.1
P-0031		3-{5-Methoxy-1-[(E)-2-(4-trifluoromethyl-phenyl)-ethenesulfonyl]-1H-indol-3-yl}-propionic acid	453.43	$[M - H^+]^-$ = 452.0
P-0032		3-[5-Bromo-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	436.99	$[M - H^+]^-$ = 436.11
P-0039		3-{1-[4-Methyl-2-(4-trifluoromethyl -phenyl)-thiazol-5-ylmethyl]-1H-indol-3-yl}-propionic acid	444.48	$[M+H^+]^+$ = 445.3
P-0040		3-{1-[2-(4-Trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-indol-3-yl}-propionic acid	430.45	$[M+H^+]^+$ = 431.3

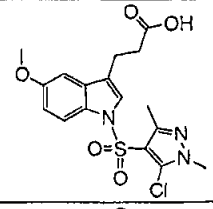
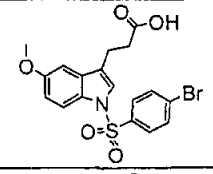
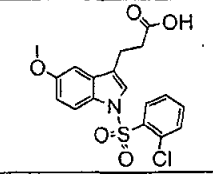
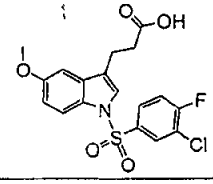
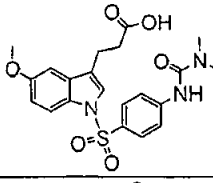
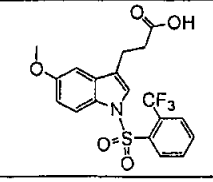
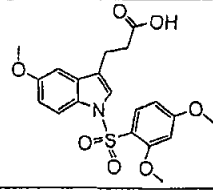
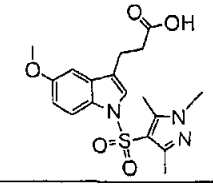
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0041		3-{1-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-ylmethyl]-1H-indol-3-yl}-propionic acid methyl ester	444.48	$[M+H^+]^+$ = 445.3
P-0042		3-{1-[5-(3-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-1H-indol-3-yl}-propionic acid methyl ester	429.40	$[M+H^+]^+$ = 430.4
P-0043		3-{1-[5-(3-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-1H-indol-3-yl}-propionic acid	415.37	$[M+H^+]^+$ = 416.4
P-0044		3-{1-[5-(4-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-1H-indol-3-yl}-propionic acid methyl ester	429.40	$[M+H^+]^+$ = 430.3
P-0045		3-{5-Methoxy-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-indol-3-yl}-propionic acid	474.50	$[M+H^+]^+$ = 475.2
P-0046		3-{5-Methoxy-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-indol-3-yl}-propionic acid ethyl ester	502.56	$[M+H^+]^+$ = 503.3
P-0054		3-[1-(5-Chloro-thiophene-2-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	413.90	$[M+H^+]^+$ = 466.3
P-0070		3-[1-(5-Chloro-thiophene-2-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	399.87	$[M+H^+]^+$ = 400.3

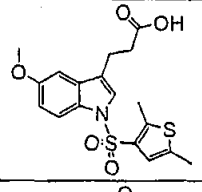
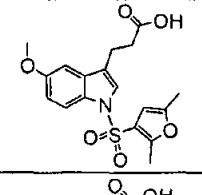
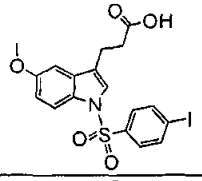
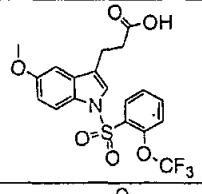
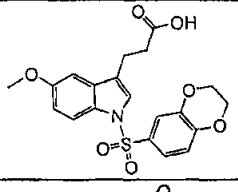
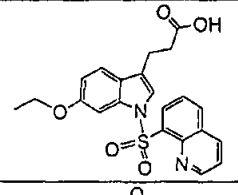
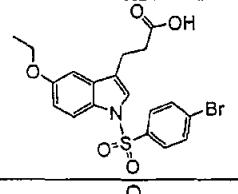
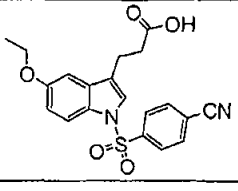
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0073		3-[1-(4,5-Dichloro-thiophene-2-sulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid	480.39	$[M+H^+]^+$ = 481.1
P-0074		3-[5-Phenyl-1-(pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	406.46	$[M+H^+]^+$ = 407.1
P-0075		3-[1-(3,4-Dichloro-benzenesulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid	474.37	
P-0090		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5-phenyl-1H-indol-3-yl}-propionic acid	519.62	$[M+H^+]^+$ = 520.3
P-0092		3-[1-(4-Butoxy-benzenesulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid	477.58	$[M-H^+]^-$ = 478.3
P-0093		3-[1-(4-Butyl-benzenesulfonyl)-5-phenyl-1H-indol-3-yl]-propionic acid	461.58	$[M+H^+]^+$ = 462.3
P-0094		3-[1-(3,4-Dichloro-benzenesulfonyl) -5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	475.35	$[M-H^+]^-$ = 471.5
P-0096		3-[1-(5-Chloro-thiophene-2-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	446.93	$[M+H^+]^+$ = 447.1
P-0108		3-[1-(4-Butoxy-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	478.57	$[M+H^+]^+$ = 479.1

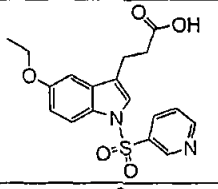
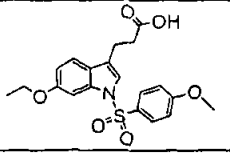
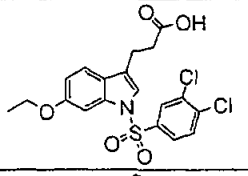
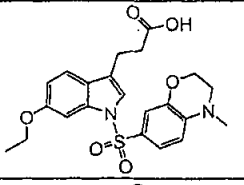
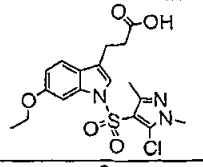
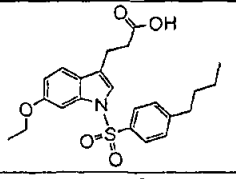
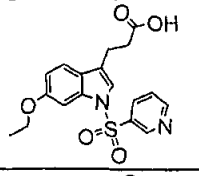
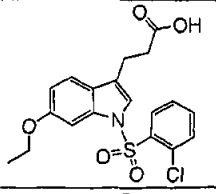
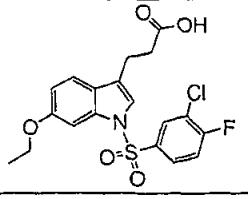
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0109		3-[1-(4-Butyl-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	462.57	$[M+H^+]^+$ = 463.1
P-0110		3-[1-(4,5-Dichloro-thiophene-2-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	481.38	$[M-H^+]^-$ = 481.1
P-0111		3-[1-(Benzo[b]thiophene-3-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	462.55	$[M+H^+]^+$ = 463.1
P-0112		5-[3-(2-Carboxy-ethyl)-5-pyridin-3-yl-indole-1-sulfonyl]-2-methyl-furan-3-carboxylic acid methyl ester	468.49	$[M+H^+]^+$ = 469.1
P-0116		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid	520.61	$[M+H^+]^+$ = 521.1
P-0117		3-[1-(4-Methoxy-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	436.39	$[M+H^+]^+$ = 437.1
P-0119		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	458.93	$[M+H^+]^+$ = 459.1
P-0121		3-[1-(4-Bromo-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	485.36	$[M+H^+]^+$ = 487.1
P-0122		3-[1-(4-Cyano-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	431.47	$[M+H^+]^+$ = 432.3

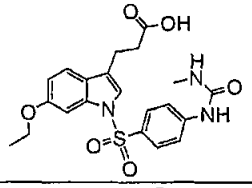
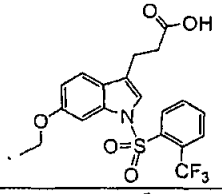
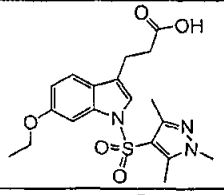
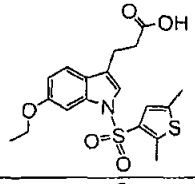
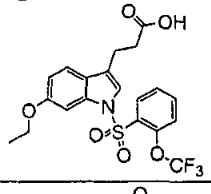
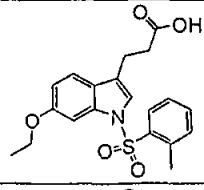
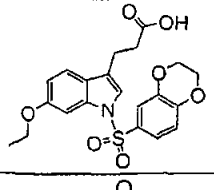
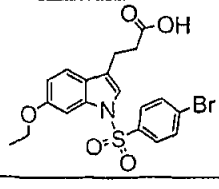
Comp. number	Structure	Name	Molecular weight Calc.	Measured MS(ESI)
P-0123		3-[1-(4-Acetyl-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	448.50	$[M+H^+]^+$ = 449.1
P-0124		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	458.90	$[M+H^+]^+$ = 459.1
P-0126		3-[1-(4-Iodo-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	532.36	$[M+H^+]^+$ = 533.1
P-0127		3-[5-Pyridin-3-yl-1-(2-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	490.46	$[M+H^+]^+$ = 491.1
P-0129		3-[1-(Benzo[1,2,5]oxadiazole-4-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl] -propionic acid	448.46	$[M+H^+]^+$ = 449.1
P-0130		3-[1-(2-Chloro-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	440.91	$[M+H^+]^+$ = 441.1
P-0132		3-{1-[4-(3-Methyl-ureido)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid	478.53	$[M+H^+]^+$ = 479.1
P-0133		3-{1-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid	492.56	$[M+H^+]^+$ = 493.1
P-0134		3-{1-[3-Chloro-4-(3-methyl-ureido)-benzenesulfonyl]-5-pyridin-3-yl-1H-indol-3-yl}-propionic acid	512.98	$[M+H^+]^+$ = 513.1

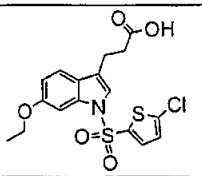
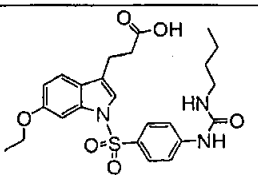
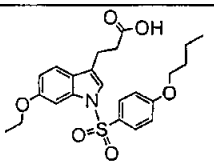
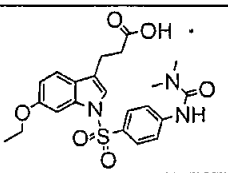
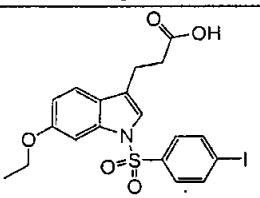
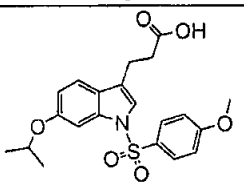
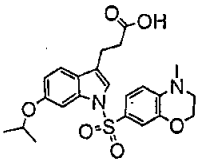
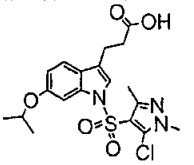
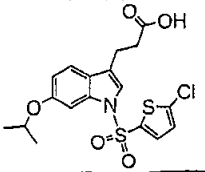
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0135		3-(1-{4-[3-(2-Methoxy-ethyl)-ureido]-benzenesulfonyl}-5-pyridin-3-yl-1H-indol-3-yl)-propionic acid	522.98	$[M+H^+]^+$ = 523.5
P-0136		3-[5-Pyridin-3-yl-1-(2-trifluoromethyl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	474.46	$[M+H^+]^+$ = 475.1
P-0138		3-[1-(2,4-Dimethoxy-benzenesulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	466.52	$[M+H^+]^+$ = 467.1
P-0139		3-[5-Pyridin-3-yl-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	438.51	$[M+H^+]^+$ = 439.5
P-0140		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	440.54	$[M+H^+]^+$ = 441.1
P-0141		3-[1-(2,5-Dimethyl-furan-3-sulfonyl)-5-pyridin-3-yl-1H-indol-3-yl]-propionic acid	424.48	$[M+H^+]^+$ = 425.1
P-0142		3-[5-Pyridin-3-yl-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	420.49	$[M+H^+]^+$ = 521.1
P-0143		3-[5-Methoxy-1-(quinoline-8-sulfonyl)-1H-indol-3-yl]-propionic acid	410.45	$[M+H^+]^+$ = 411.1
P-0144		3-[5-Methoxy-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-1H-indol-3-yl]-propionic acid	430.48	$[M+H^+]^+$ = 431.5

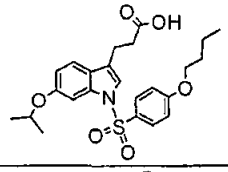
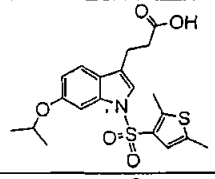
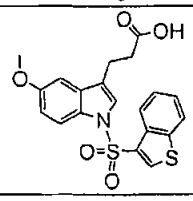
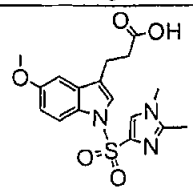
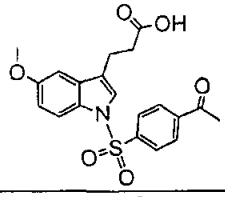
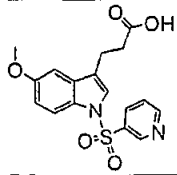
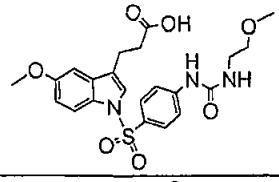
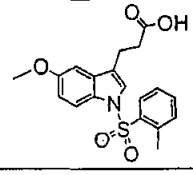
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0145		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	411.87	$[M+H^+]^+$ = 412.3
P-0147		3-[1-(4-Bromo-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	438.30	$[M+H^+]^+$ = 437.9
P-0148		3-[1-(2-Chloro-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	393.85	$[M+H^+]^+$ = 394.3
P-0149		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	411.84	$[M+H^+]^+$ = 411.9
P-0153		3-{1-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid	445.50	$[M+H^+]^+$ = 446.3
P-0154		3-[5-Methoxy-1-(2-trifluoromethyl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	427.40	$[M+H^+]^+$ = 427.9
P-0156		3-[1-(2,4-Dimethoxy-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	419.46	$[M+H^+]^+$ = 429.9
P-0157		3-[5-Methoxy-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	391.45	$[M+H^+]^+$ = 392.3

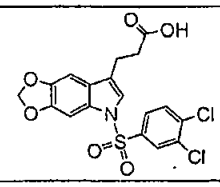
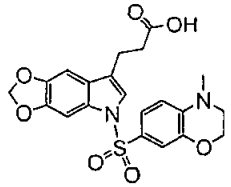
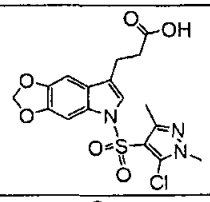
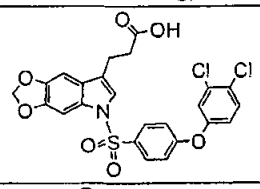
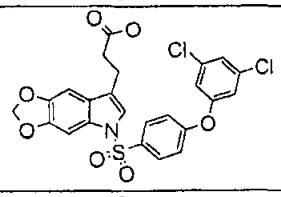
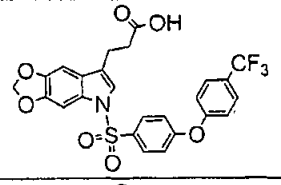
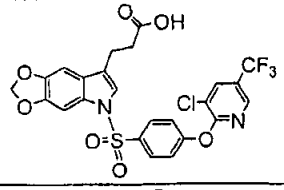
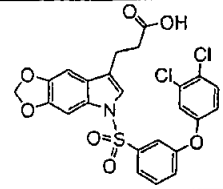
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0158		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	393.48	$[M+H^+]^+$ = 394.3
P-0159		3-[1-(2,5-Dimethyl-furan-3-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	377.42	$[M+H^+]^+$ = 378.3
P-0160		3-[1-(4-Iodo-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	485.30	$[M+H^+]^+$ = 486.3
P-0161		3-[5-Methoxy-1-(2-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	443.40	$[M+H^+]^+$ = 444.3
P-0163		3-[1-(2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	417.44	$[M+H^+]^+$ = 418.3
P-0164		3-[6-Ethoxy-1-(quinoline-8-sulfonyl)-1H-indol-3-yl]-propionic acid	424.48	$[M+H^+]^+$ = 425.1
P-0165		3-[1-(4-Bromo-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	452.33	$[M-H^+]^-$ = 451.9
P-0166		3-[1-(4-Cyano-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	398.44	$[M+H^+]^+$ = 399.1

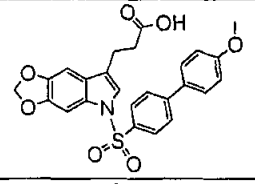
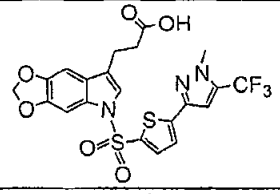
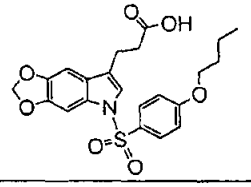
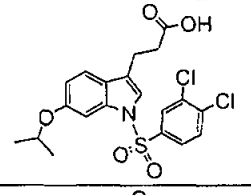
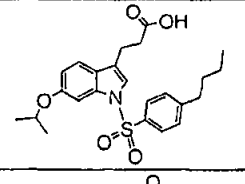
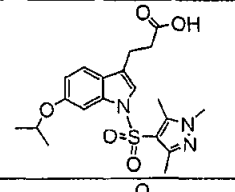
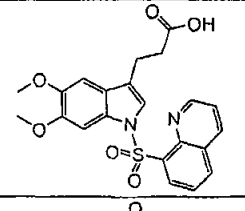
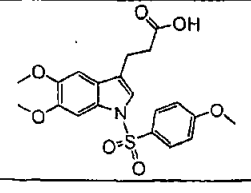
Comp. number	Structure	Name	Molecular weight Calc.	Measured MS(ESI)
P-0167		3-[5-Ethoxy-1-(pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	374.42	$[M+H^+]^+$ = 375.1
P-0169		3-[6-Ethoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	403.46	$[M+H^+]^+$ = 404.3
P-0170		3-[1-(3,4-Dichloro-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	442.32	$[M-H^+]^-$ = 442.3
P-0171		3-[6-Ethoxy-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-1H-indol-3-yl]-propionic acid	444.51	$[M+H^+]^+$ = 445.1
P-0172		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	425.89	$[M+H^+]^+$ = 425.9
P-0178		3-[1-(4-Butyl-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	429.54	$[M+H^+]^+$ = 430.3
P-0179		3-[6-Ethoxy-1-(pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	374.42	$[M+H^+]^+$ = 375.1
P-0180		3-[1-(2-Chloro-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	407.88	$[M+H^+]^+$ = 408.3
P-0181		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	425.87	$[M+H^+]^+$ = 426.3

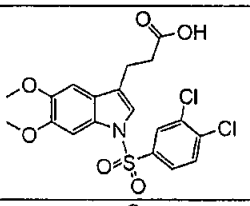
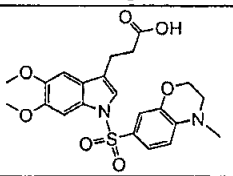
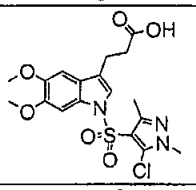
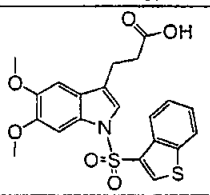
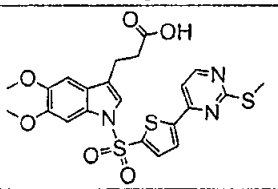
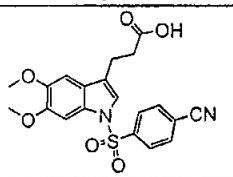
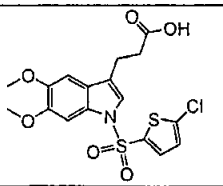
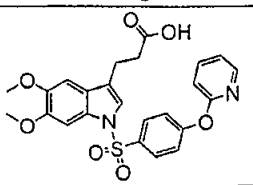
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0184		3-{6-Ethoxy-1-[4-(3-methyl-ureido)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	445.50	$[M+H^+]^+$ = 446.3
P-0186		3-[6-Ethoxy-1-(2-trifluoromethyl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	441.43	$[M+H^+]^+$ = 442.3
P-0187		3-[6-Ethoxy-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	405.48	$[M+H^+]^+$ = 406.3
P-0188		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	407.51	$[M+H^+]^+$ = 408.3
P-0189		3-[6-Ethoxy-1-(2-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	457.43	$[M+H^+]^+$ = 458.3
P-0190		3-[6-Ethoxy-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	387.46	$[M+H^+]^+$ = 388.3
P-0192		3-[1-(2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	431.67	$[M+H^+]^+$ = 432.3
P-0193		3-[1-(4-Bromo-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	452.33	$[M-H^+]^-$ = 451.9

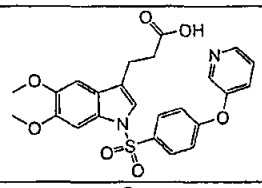
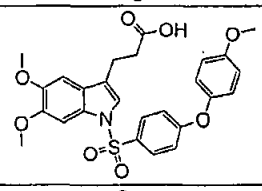
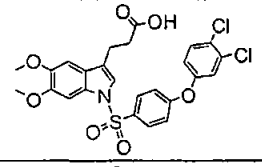
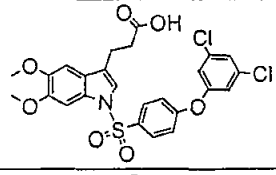
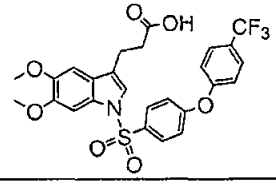
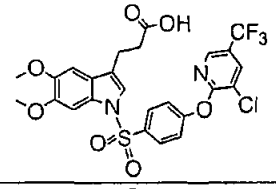
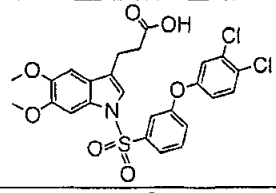
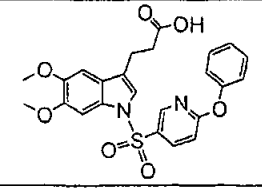
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0194		3-[1-(5-Chloro-thiophene-2-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	413.90	$[M-H^+]^-$ = 413.9
P-0197		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-6-ethoxy-1H-indol-3-yl}-propionic acid	487.58	$[M+H^+]^+$ = 488.3
P-0198		3-[1-(4-Butoxy-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	445.54	$[M+H^+]^+$ = 446.3
P-0199		3-{1-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-6-ethoxy-1H-indol-3-yl}-propionic acid	459.53	$[M+H^+]^+$ = 460.3
P-0200		3-[6-Ethoxy-1-(4-iodo-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	499.33	$[M+H^+]^+$ = 499.9
P-0202		3-[6-Isopropoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	417.48	$[M+H^+]^+$ = 418.3
P-0203		3-[6-Isopropoxy-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-1H-indol-3-yl]-propionic acid	458.54	$[M+H^+]^+$ = 459.1
P-0204		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-isopropoxy-1H-indol-3-yl]-propionic acid	439.92	$[M+H^+]^+$ = 440.3
P-0205		3-[1-(5-Chloro-thiophene-2-sulfonyl)-6-isopropoxy-1H-indol-3-yl]-propionic acid	427.93	$[M+H^+]^+$ = 428.3

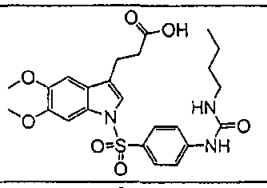
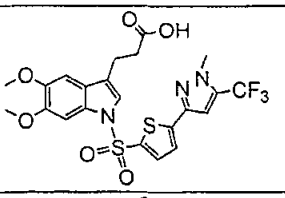
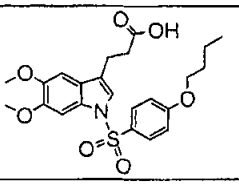
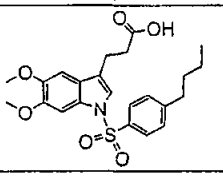
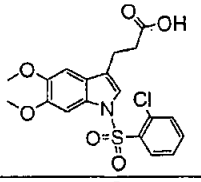
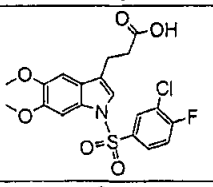
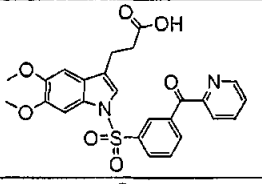
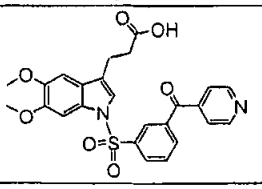
Comp. number	Structure	Name	Molecular weight Calc.	Measured MS(ESI)
P-0209		3-[1-(4-Butoxy-benzenesulfonyl)-6-isopropoxy-1H-indol-3-yl]-propionic acid	459.57	$[M+H^+]^+$ = 460.3
P-0210		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-6-isopropoxy-1H-indol-3-yl]-propionic acid	421.54	$[M+H^+]^+$ = 421.9
P-0211		3-[1-(Benzo[b]thiophene-3-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	415.59	$[M-H^+]^-$ = 415.1
P-0212		3-[1-(1,2-Dimethyl-1H-imidazole-4-sulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	377.42	$[M+H^+]^+$ = 378.3
P-0213		3-[1-(4-Acetyl-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	401.44	$[M+H^+]^+$ = 401.9
P-0217		3-[5-Methoxy-1-(pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	360.39	$[M+H^+]^+$ = 361.1
P-0218		3-(5-Methoxy-1-{4-[3-(2-methoxy-ethyl)-ureido]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid	475.52	$[M+H^+]^+$ = 475.9
P-0219		3-[5-Methoxy-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	373.43	$[M+H^+]^+$ = 374.3

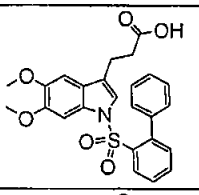
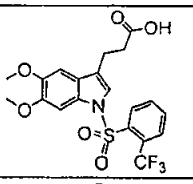
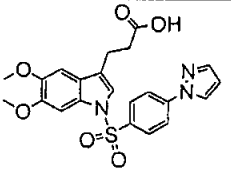
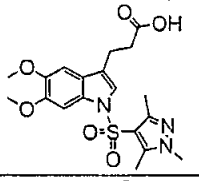
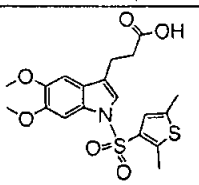
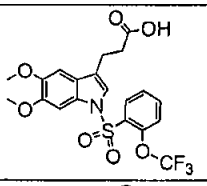
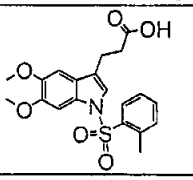
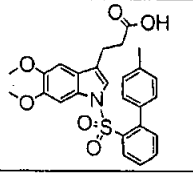
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0220		3-[5-(3,4-Dichloro-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	442.48	$[M-H^+]^-$ = 442.3
P-0221		3-[5-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	444.47	$[M+H^+]^+$ = 445.1
P-0222		3-[5-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	425.85	$[M+H^+]^+$ = 425.9
P-0223		3-{5-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f] indol-7-yl}-propionic acid	534.38	$[M-H^+]^-$ = 533.9
P-0224		3-{5-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f] indol-7-yl}-propionic acid	534.38	$[M-H^+]^-$ = 533.9
P-0225		3-{5-[4-(4-Trifluoromethyl-phenoxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	533.48	$[M+H^+]^+$ = 533.9
P-0226		3-{5-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5f]indol-7-yl}-propionic acid	568.92	$[M+H^+]^+$ = 569.2
P-0227		3-{5-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f] indol-7-yl}-propionic acid	534.38	$[M-H^+]^-$ = 533.9

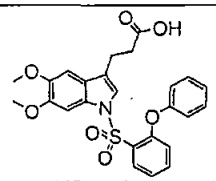
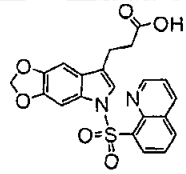
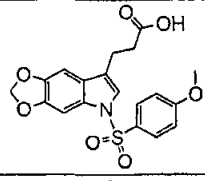
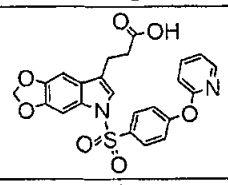
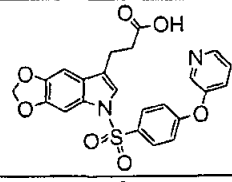
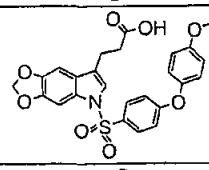
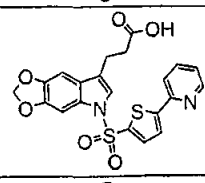
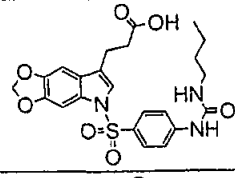
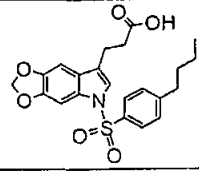
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0228		3-[5-(4'-Methoxy-biphenyl-4-sulfonyl)-5H-[1,3]dioxolo[4,5f]indol-7-yl]-propionic acid	479.51	$[M+H^+]^+$ = 479.9
P-0229		3-{5-[5-(1-Methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	527.50	$[M+H^+]^+$ = 527.9
P-0230		3-[5-(4-Butoxy-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	445.50	$[M+H^+]^+$ = 446.3
P-0231		3-[1-(3,4-Dichloro-benzenesulfonyl)-6-isopropoxy-1H-indol-3-yl]-propionic acid	456.35	$[M-H^+]^-$ = 456.3
P-0238		3-[1-(4-Butyl-benzenesulfonyl)-6-isopropoxy-1H-indol-3-yl]-propionic acid	443.57	$[M+H^+]^+$ = 444.3
P-0239		3-[6-Isopropoxy-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	419.50	$[M+H^+]^+$ = 420.3
P-0240		3-[5,6-Dimethoxy-1-(quinoline-8-sulfonyl)-1H-indol-3-yl]-propionic acid	440.48	$[M+H^+]^+$ = 441.1
P-0241		3-[5,6-Dimethoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	419.46	$[M+H^+]^+$ = 419.9

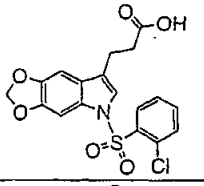
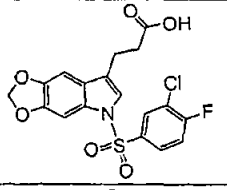
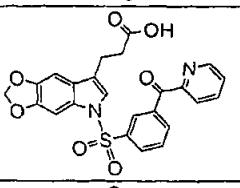
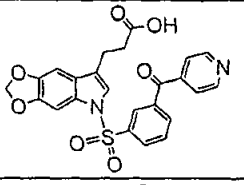
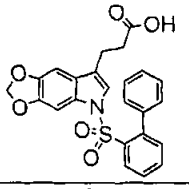
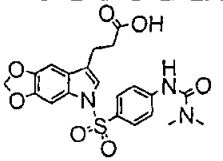
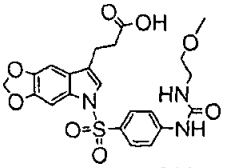
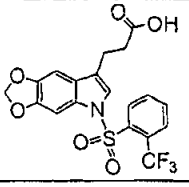
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0242		3-[1-(3,4-Dichloro-benzenesulfonyl) -5,6-dimethoxy-1H-indol-3-yl]-propionic acid	458.32	$[M-H^+]^-$ = 458.3
P-0243		3-[5,6-Dimethoxy-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-1H-indol-3-yl]-propionic acid	460.51	$[M+H^+]^+$ = 461.1
P-0244		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	441.89	$[M+H^+]^+$ = 442.3
P-0245		3-[1(Benzo[b]thiophene-3-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	445.52	$[M+H^+]^+$ = 446.3
P-0246		3-{5,6-Dimethoxy-1-[5-(2-methylsulfanyl-pyrimidin-4-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid	519.62	$[M+H^+]^+$ = 520.3
P-0247		3-[1-(4-Cyano-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	414.44	$[M+H^+]^+$ = 415.1
P-0248		3-[1-(5-Chloro-thiophene-2-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	429.90	$[M+H^+]^+$ = 430.3
P-0249		3-{5,6-Dimethoxy-1-[4-(pyridin-2-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	482.52	$[M+H^+]^+$ = 483.1

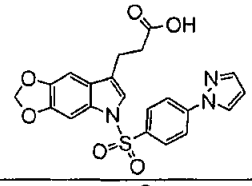
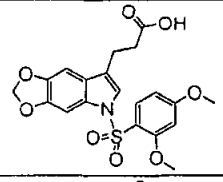
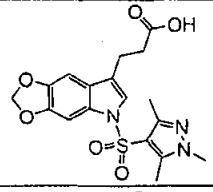
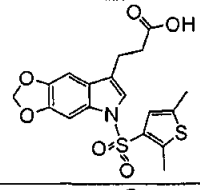
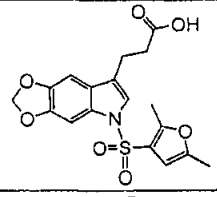
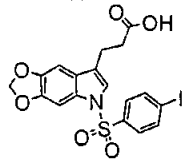
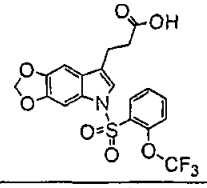
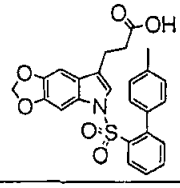
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0250		3-{5,6-Dimethoxy-1-[4-(pyridin-3-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	482.52	$[M+H^+]^+$ = 483.1
P-0251		3-{5,6-Dimethoxy-1-[4-(4-methoxy-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	511.56	$[M+H^+]^+$ = 512.3
P-0252		3-{1-[4-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	550.42	$[M-H^+]^-$ = 550.3
P-0253		3-{1-[4-(3,5-Dichloro-phenoxy)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	550.42	$[M-H^+]^-$ = 550.3
P-0254		3-{5,6-Dimethoxy-1-[4-(4-trifluoromethyl-phenoxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	549.53	$[M+H^+]^+$ = 550.3
P-0255		3-{1-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yloxy)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	584.96	$[M+H^+]^+$ = 585.2
P-0256		3-{1-[3-(3,4-Dichloro-phenoxy)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	550.42	$[M-H^+]^-$ = 550.3
P-0257		3-[5,6-Dimethoxy-1-(6-phenoxy-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	482.52	$[M+H^+]^+$ = 483.1

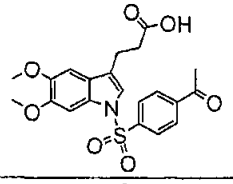
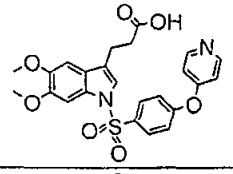
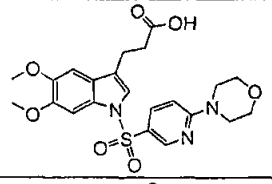
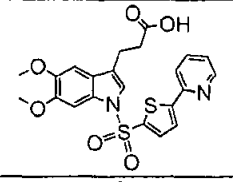
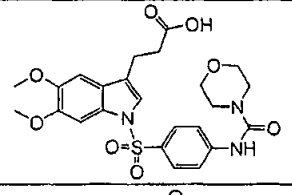
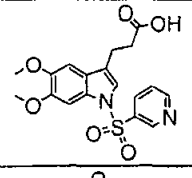
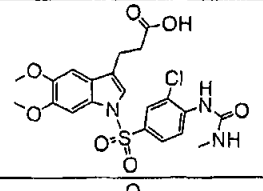
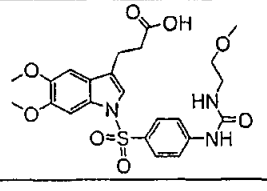
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0258		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	503.58	$[M+H^+]^+$ = 504.3
P-0259		3-{5,6-Dimethoxy-1-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid	543.54	$[M+H^+]^+$ = 544.3
P-0260		3-[1-(4-Butoxy-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	461.54	$[M+H^+]^+$ = 462.3
P-0261		3-[1-(4-Butyl-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	445.54	$[M+H^+]^+$ = 446.3
P-0262		3-[1-(2-Chloro-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	423.88	$[M+H^+]^+$ = 423.9
P-0263		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	441.87	$[M+H^+]^+$ = 442.3
P-0264		3-{5,6-Dimethoxy-1-[3-(pyridine-2-carbonyl)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	494.53	$[M+H^+]^+$ = 495.1
P-0265		3-{5,6-Dimethoxy-1-[3-(pyridine-4-carbonyl)benzenesulfonyl]-1H-indol-3-yl}-propionic acid	494.53	$[M+H^+]^+$ = 495.1

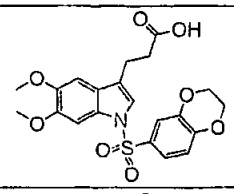
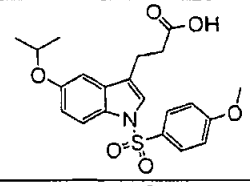
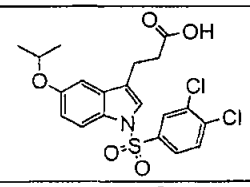
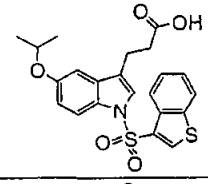
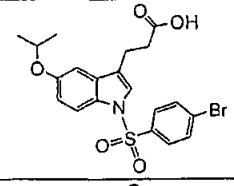
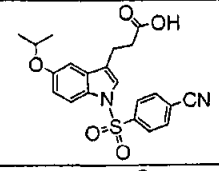
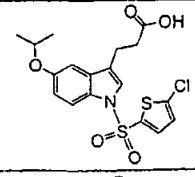
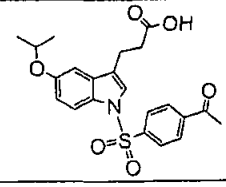
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0266		3-[1-(Biphenyl-2-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	465.53	$[M+H^+]^+$ = 466.3
P-0267		3-[5,6-Dimethoxy-1-(2-trifluoromethyl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	457.43	$[M+H^+]^+$ = 458.3
P-0268		3-[5,6-Dimethoxy-1-(4-pyrazol-1-yl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	455.49	$[M+H^+]^+$ = 456.3
P-0269		3-[5,6-Dimethoxy-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	421.48	$[M+H^+]^+$ = 421.9
P-0270		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	423.51	$[M+H^+]^+$ = 423.9
P-0271		3-[5,6-Dimethoxy-1-(2-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	473.43	$[M+H^+]^+$ = 473.9
P-0272		3-[5,6-Dimethoxy-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	403.46	$[M+H^+]^+$ = 404.3
P-0273		3-[5,6-Dimethoxy-1-(4'-methyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid	479.56	$[M+H^+]^+$ = 479.9

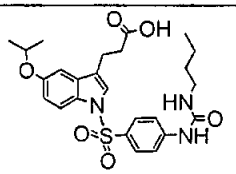
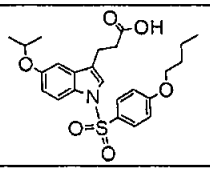
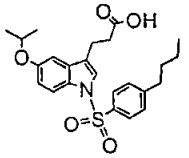
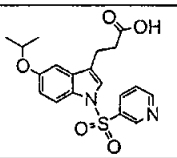
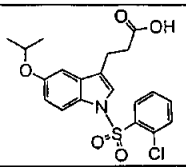
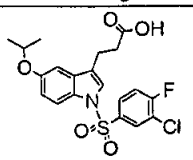
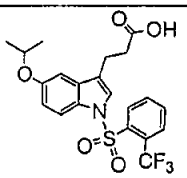
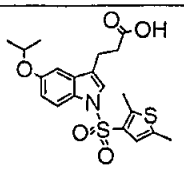
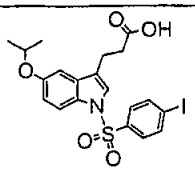
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0274		3-[5,6-Dimethoxy-1-(2-phenoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	481.53	$[M+H^+]^+$ = 482.3
P-0275		3-[5-(Quinoline-8-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	424.44	$[M+H^+]^+$ = 425.1
P-0276		3-[5-(4-Methoxy-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	403.41	$[M+H^+]^+$ = 404.3
P-0277		3-{5-[4-(Pyridin-2-yloxy)-benzenesulfonyl]-5H[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	466.47	$[M+H^+]^+$ = 467.1
P-0278		3-{5-[4-(Pyridin-3-yloxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	466.47	$[M+H^+]^+$ = 467.1
P-0279		3-{5-[4-(4-Methoxy-phenoxy)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	495.51	$[M+H^+]^+$ = 495.9
P-0280		3-[5-(5-Pyridin-2-yl-thiophene-2-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	456.50	$[M+H^+]^+$ = 457.1
P-0281		3-{5-[4-(3-Butyl-ureido)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	487.54	$[M+H^+]^+$ = 488.3
P-0282		3-[5-(4-Butyl-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	429.50	$[M+H^+]^+$ = 430.3

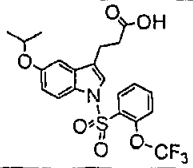
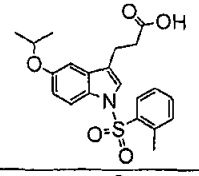
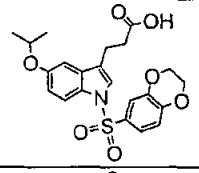
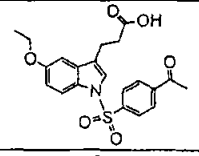
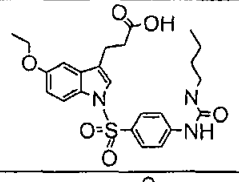
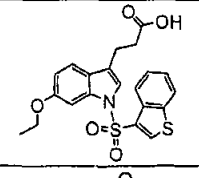
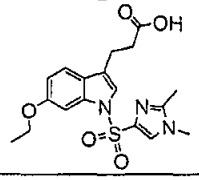
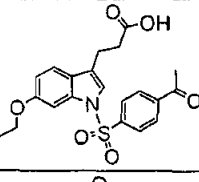
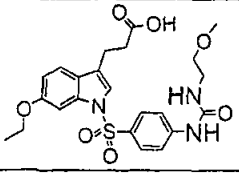
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0283		3-[5-(2-Chloro-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	407.83	$[M+H^+]^+$ = 408.3
P-0284		3-[5-(3-Chloro-4-fluoro-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	425.82	$[M+H^+]^+$ = 426.3
P-0285		3-{5-[3-(Pyridine-2-carbonyl)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	478.48	$[M+H^+]^+$ = 497.1
P-0286		3-{5-[3-(Pyridine-4-carbonyl)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	478.48	$[M+H^+]^+$ = 479.1
P-0287		3-[5-(Biphenyl-2-sulfonyl)-5H-[1,3] dioxolo[4,5-f]indol-7-yl]-propionic acid	449.49	$[M+H^+]^+$ = 450.3
P-0288		3-{5-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-5H-[1,3]dioxolo[4,5-f]indol-7-yl}-propionic acid	459.48	$[M+H^+]^+$ = 460.3
P-0289		3-(5-{4-[3-(2-Methoxy-ethyl)-ureido]-benzenesulfonyl}-5H-[1,3]dioxolo[4,5-f]indol-7-yl)-propionic acid	489.51	$[M+H^+]^+$ = 489.9
P-0290		3-[5-(2-Trifluoromethyl-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	441.39	$[M+H^+]^+$ = 442.3

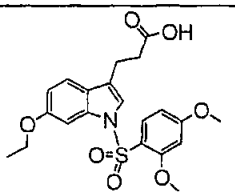
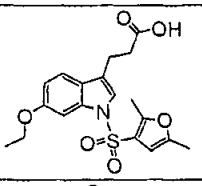
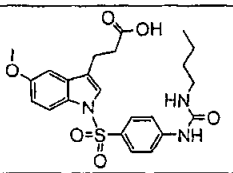
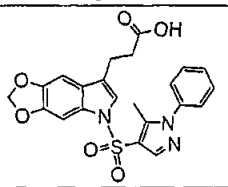
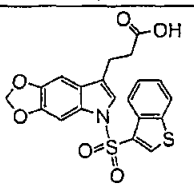
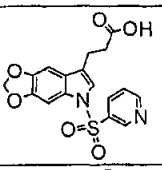
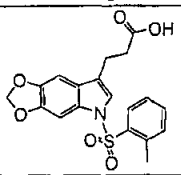
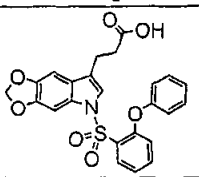
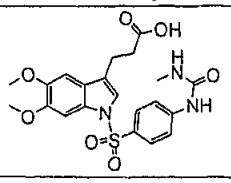
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0291		3-[5-(4-Pyrazol-1-yl-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	439.45	$[M+H^+]^+$ = 440.3
P-0292		3-[5-(2,4-Dimethoxy-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	433.44	$[M+H^+]^+$ = 434.3
P-0293		3-[5-(1,3,5-Trimethyl-1H-pyrazole-4-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	405.43	$[M+H^+]^+$ = 406.3
P-0294		3-[5-(2,5-Dimethyl-thiophene-3-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	407.47	$[M+H^+]^+$ = 407.9
P-0295		3-[5-(2,5-Dimethyl-furan-3-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	391.40	$[M+H^+]^+$ = 391.9
P-0296		3-[5-(4-Iodo-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	499.28	$[M+H^+]^+$ = 499.9
P-0297		3-[5-(2-Trifluoromethoxy-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	457.39	$[M+H^+]^+$ = 458.3
P-0298		3-[5-(4'-Methyl-biphenyl-2-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	463.51	$[M+H^+]^+$ = 463.9

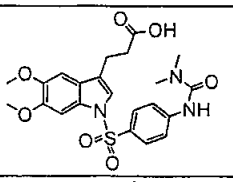
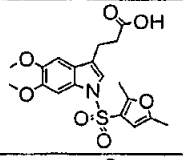
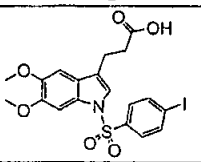
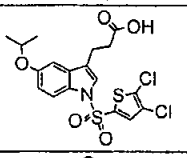
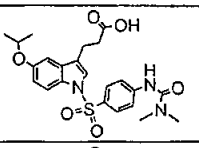
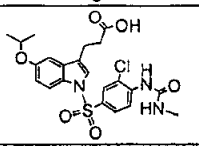
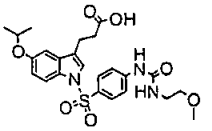
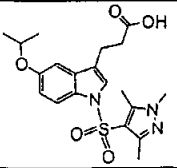
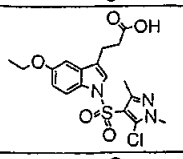
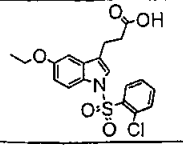
Comp. number	Structure	Name	Molecular weight Calc.	Measured MS(ESI)
P-0299		3-[1-(4-Acetyl-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	431.47	$[M+H^+]^+$ = 432.3
P-0300		3-{5,6-Dimethoxy-1-[4-(pyridin-4-yloxy)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	482.52	$[M+H^+]^+$ = 483.1
P-0301		3-[5,6-Dimethoxy-1-(6-morpholin-4-yl-pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	475.52	
P-0302		3-[5,6-Dimethoxy-1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	472.54	$[M+H^+]^+$ = 473.1
P-0303		3-(5,6-Dimethoxy-1-{4-[(morpholine-4-carbonyl)-amino]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid	517.56	$[M+H^+]^+$ = 518.3
P-0304		3-[5,6-Dimethoxy-1-(pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	390.42	$[M+H^+]^+$ = 391.1
P-0305		3-{1-[3-Chloro-4-(3-methyl-ureido)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	495.94	$[M+H^+]^+$ = 496.3
P-0306		3-(5,6-Dimethoxy-1-{4-[3-(2-methoxy-ethyl)-ureido]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid	505.55	$[M+H^+]^+$ = 505.9

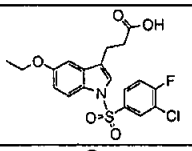
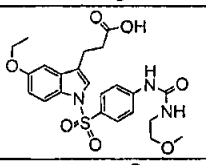
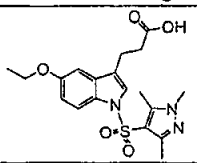
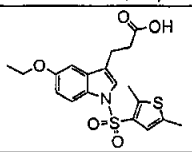
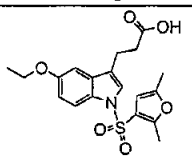
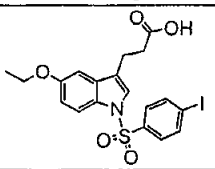
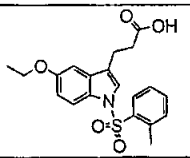
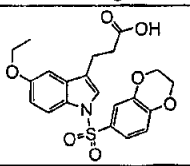
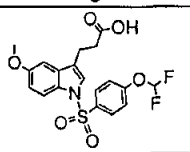
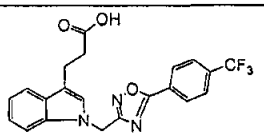
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0307		3-[1-(2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	447.47	$[M+H^+]^+$ = 447.9
P-0308		3-[5-Isopropoxy-1-(4-methoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	417.48	$[M+H^+]^+$ = 418.3
P-0309		3-[1-(3,4-Dichloro-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	456.35	$[M+H^+]^+$ = 456.3
P-0310		3-[1-(Benzo[b]thiophene-3-sulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	443.54	$[M+H^+]^+$ = 444.3
P-0312		3-[1-(4-Bromo-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	466.35	$[M+H^+]^+$ = 468.3
P-0313		3-[1-(4-Cyano-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	412.47	$[M+H^+]^+$ = 413.1
P-0314		3-[1-(5-Chloro-thiophene-2-sulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	427.93	$[M-H^+]^-$ = 427.9
P-0315		3-[1-(4-Acetyl-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	429.50	$[M+H^+]^+$ = 430.3

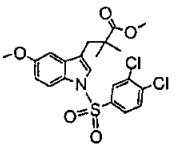
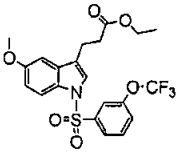
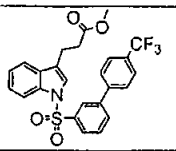
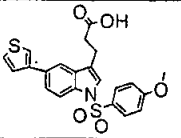
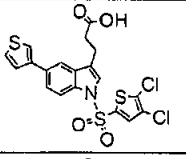
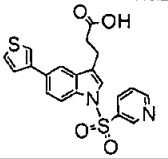
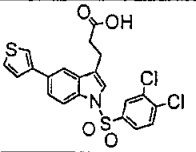
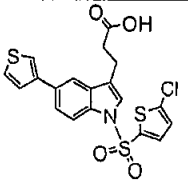
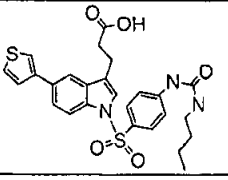
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0325		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5-isopropoxy-1H-indol-3-yl}-propionic acid	501.61	$[M+H^+]^+$ = 502.3
P-0327		3-[1-(4-Butoxy-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	459.57	$[M+H^+]^+$ = 460.3
P-0328		3-[1-(4-Butyl-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	443.57	$[M+H^+]^+$ = 444.3
P-0329		3-[5-Isopropoxy-1-(pyridine-3-sulfonyl)-1H-indol-3-yl]-propionic acid	388.45	$[M+H^+]^+$ = 389.1
P-0330		3-[1-(2-Chloro-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	421.90	$[M+H^+]^+$ = 421.9
P-0331		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	439.59	$[M+H^+]^+$ = 440.3
P-0333		3-[5-Isopropoxy-1-(2-trifluoromethyl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	455.46	$[M+H^+]^+$ = 456.3
P-0334		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	421.54	$[M+H^+]^+$ = 421.9
P-0335		3-[1-(4-Iodo-benzenesulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	513.35	$[M+H^+]^+$ = 514.3

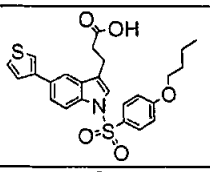
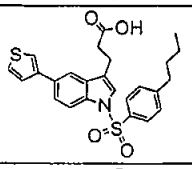
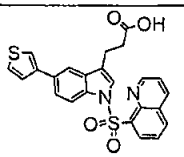
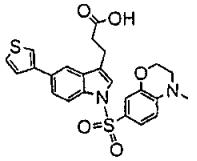
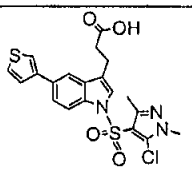
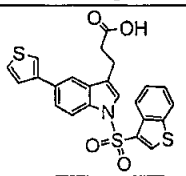
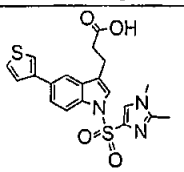
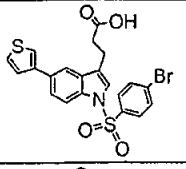
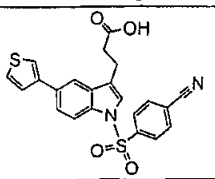
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0336		3-[5-Isopropoxy-1-(2-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	471.46	$[M+H^+]^+$ = 472.3
P-0337		3-[5-Isopropoxy-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	401.49	$[M+H^+]^+$ = 402.3
P-0340		3-[1-(2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	445.50	$[M+H^+]^+$ = 446.3
P-0341		3-[1-(4-Acetyl-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	415.47	$[M+H^+]^+$ = 416.3
P-0343		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid	487.58	$[M+H^+]^+$ = 488.3
P-0345		3-[1-(Benzo[b]thiophene-3-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	429.52	$[M+H^+]^+$ = 430.3
P-0348		3-[1-(1,2-Dimethyl-1H-imidazole-4-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	391.45	$[M+H^+]^+$ = 392.3
P-0349		3-[1-(4-Acetyl-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	415.47	$[M+H^+]^+$ = 416.3
P-0357		3-(6-Ethoxy-1-{4-[3-(2-methoxy-ethyl)-ureido]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid	489.55	$[M+H^+]^+$ = 490.3

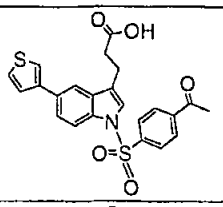
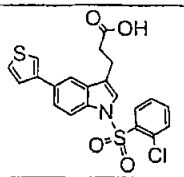
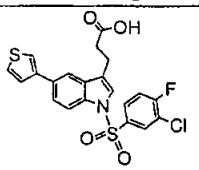
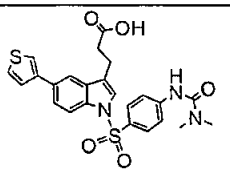
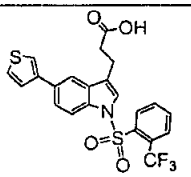
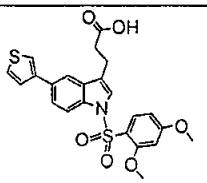
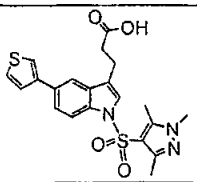
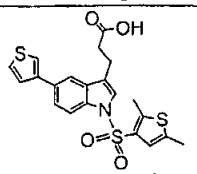
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0358		3-[1-(2,4-Dimethoxy-benzenesulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	433.48	$[M+H^+]^+$ = 434.3
P-0359		3-[1-(2,5-Dimethyl-furan-3-sulfonyl)-6-ethoxy-1H-indol-3-yl]-propionic acid	391.45	$[M+H^+]^+$ = 392.3
P-0360		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid	473.55	$[M+H^+]^+$ = 473.9
P-0361		3-[5-(5-Methyl-1-phenyl-1H-pyrazole 4-sulfonyl)-5H-[1,3]dioxolo[4,5-f] indol-7-yl]-propionic acid	453.48	$[M+H^+]^+$ = 453.9
P-0362		3-[5-(Benzo[b]thiophene-3-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	429.47	$[M+H^+]^+$ = 430.3
P-0363		3-[5-(Pyridine-3-sulfonyl)-5H-[1,3]-dioxolo[4,5-f]indol-7-yl]-propionic acid	374.37	$[M+H^+]^+$ = 375.1
P-0364		3-[5-(Toluene-2-sulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	387.41	$[M+H^+]^+$ = 387.9
P-0365		3-[5-(2-Phenoxy-benzenesulfonyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-propionic acid	465.49	$[M+H^+]^+$ = 466.3
P-0366		3-{5,6-Dimethoxy-1-[4-(3-methyl-ureido)-benzenesulfonyl]-1H-indol-3-yl}-propionic acid	461.50	$[M+H^+]^+$ = 462.3

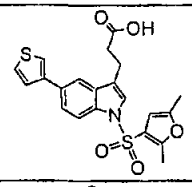
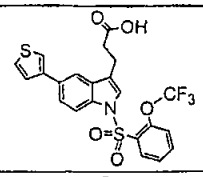
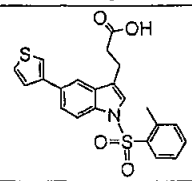
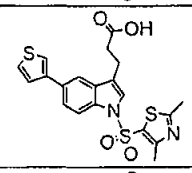
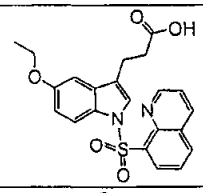
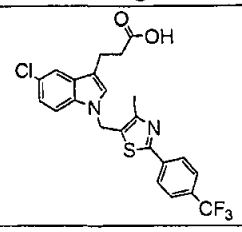
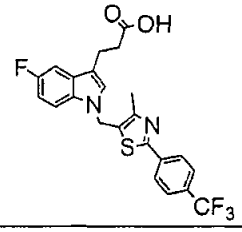
Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0367		3-{1-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-5,6-dimethoxy-1H-indol-3-yl}-propionic acid	475.52	$[M+H^+]^+$ = 475.9
P-0368		3-[1-(2,5-Dimethyl-furan-3-sulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	407.45	$[M+H^+]^+$ = 408.3
P-0369		3-[1-(4-Iodo-benzenesulfonyl)-5,6-dimethoxy-1H-indol-3-yl]-propionic acid	515.33	$[M+H^+]^+$ = 516.3
P-0370		3-[1-(4,5-Dichloro-thiophene-2-sulfonyl)-5-isopropoxy-1H-indol-3-yl]-propionic acid	462.37	$[M-H^+]^-$ = 461.9
P-0372		3-{1-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-5-isopropoxy-1H-indol-3-yl}-propionic acid	473.55	$[M+H^+]^+$ = 474.3
P-0373		3-{1-[3-Chloro-4-(3-methyl-ureido)-benzenesulfonyl]-5-isopropoxy-1H-indol-3-yl}-propionic acid	493.97	$[M+H^+]^+$ = 494.3
P-0374		3-(5-Isopropoxy-1-{4-[3-(2-methoxy-ethyl)-ureido]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid	503.58	$[M+H^+]^+$ = 504.3
P-0376		3-[5-Isopropoxy-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	419.50	$[M+H^+]^+$ = 420.3
P-0377		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	425.89	$[M+H^+]^+$ = 426.3
P-0378		3-[1-(2-Chloro-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	407.87	$[M+H^+]^+$ = 408.3

Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0379		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	425.86	$[M+H^+]^+$ = 425.9
P-0380		3-(5-Ethoxy-1-{4-[3-(2-methoxy-ethyl)-ureido]-benzenesulfonyl}-1H-indol-3-yl)-propionic acid	489.56	$[M+H^+]^+$ = 490.3
P-0381		3-[5-Ethoxy-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	405.47	$[M+H^+]^+$ = 406.3
P-0382		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	407.51	$[M+H^+]^+$ = 408.3
P-0383		3-[1-(2,5-Dimethyl-furan-3-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	391.44	$[M+H^+]^+$ = 392.3
P-0384		3-[5-Ethoxy-1-(4-iodo-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	499.32	$[M+H^+]^+$ = 500
P-0385		3-[5-Ethoxy-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	387.45	$[M+H^+]^+$ = 388.3
P-0387		3-[1-(2,3-Dihydro-benzo[1,4]dioxine-6-sulfonyl)-5-ethoxy-1H-indol-3-yl]-propionic acid	431.46	$[M+H^+]^+$ = 432.3
P-0389		3-[1-(4-Difluoromethoxy-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-propionic acid	425.1	$[M-H^+]^-$ = 442
P-0390		3-{1-[5-(4-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-1H-indol-3-yl}-propionic acid	415.37	$[M+H^+]^+$ = 416.4

Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0559		3-[1-(3,4-Dichloro-benzenesulfonyl)-5-methoxy-1H-indol-3-yl]-2,2-dimethyl-propionic acid methyl ester	470.37	$[M+H^+]^+$ = 470.1; 472.1
P-0569		3-[5-Methoxy-1-(3-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid ethyl ester	471.45	
P-0571		3-[1-(4'-Trifluoromethyl-biphenyl-3-sulfonyl)-1H-indol-3-yl]-propionic acid methyl ester	487.50	
P-0576		3-[1-(4-Methoxy-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	441.53	
P-0577		3-[1-(4,5-Dichloro-thiophene-2-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	486.42	
P-0578		3-[1-(Pyridine-3-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	412.49	
P-0579		3-[1-(3,4-Dichloro-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	480.39	
P-0580		3-[1-(5-Chloro-thiophene-2-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	451.97	
P-0591		3-{1-[4-(3-Butyl-ureido)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid	525.65	

Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0593		3-[1-(4-Butoxy-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	483.61	
P-0594		3-[1-(4-Butyl-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	467.61	
P-0595		3-[1-(Quinoline-8-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	462.55	
P-0596		3-[1-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	482.58	
P-0597		3-[1-(5-Chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	463.96	
P-0598		3-[1-(Benzo[b]thiophene-3-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	467.59	
P-0600		3-[1-(1,2-Dimethyl-1H-imidazole-4-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	429.52	
P-0602		3-[1-(4-Bromo-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	490.40	
P-0603		3-[1-(4-Cyano-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	436.51	

Comp. number	Structure	Name	Molecular weight Calc.	Measured MS(ESI)
P-0604		3-[1-(4-Acetyl-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	453.54	
P-0605		3-[1-(2-Chloro-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	445.95	
P-0606		3-[1-(3-Chloro-4-fluoro-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	463.94	
P-0609		3-{1-[4-(3,3-Dimethyl-ureido)-benzenesulfonyl]-5-thiophen-3-yl-1H-indol-3-yl}-propionic acid	497.59	
P-0610		3-[5-Thiophen-3-yl-1-(2-trifluoromethyl-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	479.50	
P-0611		3-[1-(2,4-Dimethoxy-benzenesulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	471.55	
P-0612		3-[5-Thiophen-3-yl-1-(1,3,5-trimethyl-1H-pyrazole-4-sulfonyl)-1H-indol-3-yl]-propionic acid	443.55	
P-0613		3-[1-(2,5-Dimethyl-thiophene-3-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	445.58	

Comp. number	Structure	Name	Molecular weight	
			Calc.	Measured MS(ESI)
P-0614		3-[1-(2,5-Dimethyl-furan-3-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	429.52	
P-0615		3-[5-Thiophen-3-yl-1-(2-trifluoromethoxy-benzenesulfonyl)-1H-indol-3-yl]-propionic acid	495.50	
P-0616		3-[5-Thiophen-3-yl-1-(toluene-2-sulfonyl)-1H-indol-3-yl]-propionic acid	425.53	
P-0619		3-[1-(2,4-Dimethyl-thiazole-5-sulfonyl)-5-thiophen-3-yl-1H-indol-3-yl]-propionic acid	446.57	
P-0620		3-[5-Ethoxy-1-(quinoline-8-sulfonyl)-1H-indol-3-yl]-propionic acid	424.48	
P-0621		3-{5-Chloro-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-indol-3-yl}-propionic acid	478.92	
P-0622		3-{5-Fluoro-1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethyl]-1H-indol-3-yl}-propionic acid	462.47	

Example 8: Expression and purification of PPARs for use in biochemical and cell assays.

Genetic engineering:

[0264] Plasmids encoding the Ligand-binding domains (LBDs) of PPARα, PPARγ, and PPARδ were engineered using common polymerase chain reaction (PCR) methods (pGal4-PPARα-LBD, pGal4-PPARγ-LBD, pGal4-PPARδ-LBD). The relevant DNA sequences and encoded protein sequences used in the assay are shown for each (see below). Complementary DNA cloned from various human tissues were purchased from Invitrogen, and these were used as substrates in the PCR reactions. Specific custom synthetic oligonucleotide primers (Invitrogen, see below) were designed to initiate the PCR product, and also to provide the appropriate restriction enzyme cleavage sites for ligation with the plasmids.

[0265] The plasmids used for ligation with the receptor-encoding inserts were either pET28 (Novagen) or a derivative of pET28, pET-BAM6, for expression using *E. coli.* In each of these cases the receptor LBD was engineered to include a Histidine tag for purification using metal affinity chromatography.

Protein Expression and Purification of PPAR's:

[0266] For protein expression, plasmids containing genes of interest were transformed into *E.coli* strain BL21(DE3)RIL (Invitrogen) and transformants selected for growth on LB agar plates containing appropriate antibiotics. Single colonies were grown for 4hrs at 37°C in 200ml LB media. For PPARα and PPARγ all protein expression was performed by large scale fermentation using a 30L bioreactor. 400ml of starter culture was added to 30L TB culture and allowed to grow at 37°C until an OD600nm of 2-5 was obtained. The culture was cooled to 20°C and 0.5mM IPTG added, the culture was allowed to grow for a further 18hrs.

[0267] For PPARδ protein expression, single colonies were grown for 4hrs at 37°C in 200ml LB media. 16x1L of fresh TB media in 2.8L flasks were inoculated with 10ml of starter culture and grown with constant shaking at 37°C. Once cultures reached an absorbance of 1.0 at 600nm, an additive to improve the solubility of the PPARδ was added to the culture and 30min later, 0.5mM IPTG was added and cultures allowed to grow for a

further 12 to 18hrs at 20°C. Cells were harvested by centrifugation and pellets frozen at -80°C until ready for lysis/purification.

[0268] For protein purification; all operations were carried out at 4°C. Frozen *E.coli* cell pellets were resuspended in lysis buffer and lysed using standard mechanical methods. Soluble proteins were purified via poly-Histidine tags using immobilized metal affinity purification (IMAC). For each of the PPAR's described all have been purified using a 3 step purification process utilizing IMAC, size exclusion chromatography and ion exchange chromatography. For PPARα the poly-Histidine tag was optionally removed using Thrombin (Calbiochem). In the case of PPARδ, during protein purification the solubility improving additive was present in order to maintain protein stability. During the final step of purification solubility improving additives were desalted away before concentration.

Plasmid sequence and PCR primer information:

PPARα: (Nucleic acid SEQ ID NO:___) (Protein SEQ ID NO:___)

P332. pET28 PPARA E199-Y468-X

```
                                        taatacgactcactatagggaattgt
gagcggataacaattcccctctagaaataattttgtttaactttaagaaggagatatacc
atgggcagcagccatcatcatcatcacagcagcggcctggtgccgcgcggcagccat
 M  G  S  S  H  H  H  H  H  H  S  S  G  L  V  P  R  G  S  H
atggaaactgcagatctcaaatctctggccaagagaatctacgaggcctacttgaagaac
 M  E  T  A  D  L  K  S  L  A  K  R  I  Y  E  A  Y  L  K  N
ttcaacatgaacaaggtcaaagcccgggtcatcctctcaggaaaggccagtaacaatcca
 F  N  M  N  K  V  K  A  R  V  I  L  S  G  K  A  S  N  N  P
ccttttgtcatacatgatatggagacactgtgtatggctgagaagacgctggtggccaag
 P  F  V  I  H  D  M  E  T  L  C  M  A  E  K  T  L  V  A  K
ctggtggccaatggcatccagaacaaggaggcggaggtccgcatctttcactgctgccag
 L  V  A  N  G  I  Q  N  K  E  A  E  V  R  I  F  H  C  C  Q
tgcacgtcagtggagaccgtcacggagctcacggaattcgccaaggccatcccaggcttc
 C  T  S  V  E  T  V  T  E  L  T  E  F  A  K  A  I  P  G  F
gcaaacttggacctgaacgatcaagtgacattgctaaaatacggagtttatgaggccata
 A  N  L  D  L  N  D  Q  V  T  L  L  K  Y  G  V  Y  E  A  I
ttcgccatgctgtcttctgtgatgaacaaagacgggatgctggtagcgtatggaaatggg
 F  A  M  L  S  S  V  M  N  K  D  G  M  L  V  A  Y  G  N  G
tttataactcgtgaattcctaaaaagcctaaggaaaccgttctgtgatatcatggaaccc
 F  I  T  R  E  F  L  K  S  L  R  K  P  F  C  D  I  M  E  P
aagtttgattttgccatgaagttcaatgcactggaactggatgacagtgatatctccctt
 K  F  D  F  A  M  K  F  N  A  L  E  L  D  D  S  D  I  S  L
tttgtggctgctatcatttgctgtggagatcgtcctggccttctaaacgtaggacacatt
 F  V  A  A  I  I  C  C  G  D  R  P  G  L  L  N  V  G  H  I
gaaaaaatgcaggagggtattgtacatgtgctcagactccacctgcagagcaaccacccg
 E  K  M  Q  E  G  I  V  H  V  L  R  L  H  L  Q  S  N  H  P
gacgatatctttctcttcccaaaacttcttcaaaaaatggcagacctccggcagctggtg
 D  D  I  F  L  F  P  K  L  L  Q  K  M  A  D  L  R  Q  L  V
acggagcatgcgcagctggtgcagatcatcaagaagacggagtcggatgctgcgctgcac
 T  E  H  A  Q  L  V  Q  I  I  K  K  T  E  S  D  A  A  L  H
ccgctactgcaggagatctacagggacatgtactgagtcgacaagcttgcggccgcactc
 P  L  L  Q  E  I  Y  R  D  M  Y  -
gagcaccaccaccaccaccactgagat
```

PCR primers:

PPARA	PPARA-S	GCTGACACATATGGAAACTGCAGATCTCAAATC	(SEQ ID NO:___)
	PPARA-A	GTGACTGTCGACTCAGTACATGTCCCTGTAGA	(SEQ ID NO:___)

PPARγ: (Nucleic acid SEQ ID NO:___) (Protein SEQ ID NO:___)

P333. pET28 PPARG E205-Y475-X

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                                                taatacgactcactatagggaattgt
gagcggataacaattcccctctagaaataattttgtttaactttaagaaggagatatacc
atgggcagcagccatcatcatcatcatcacagcagcggcctggtgccgcgcggcagccat
 M  G  S  S  H  H  H  H  H  H  S  S  G  L  V  P  R  G  S  H
atggagtccgctgacctccgggccctggcaaaacatttgtatgactcatacataaagtcc
 M  E  S  A  D  L  R  A  L  A  K  H  L  Y  D  S  Y  I  K  S
ttcccgctgaccaaagcaaaggcgagggcgatcttgacaggaaagacaacagacaaatca
 F  P  L  T  K  A  K  A  R  A  I  L  T  G  K  T  T  D  K  S
ccattcgttatctatgacatgaattccttaatgatgggagaagataaaatcaagttcaaa
 P  F  V  I  Y  D  M  N  S  L  M  M  G  E  D  K  I  K  F  K
cacatcaccccctgcaggagcagagcaaagaggtggccatccgcatctttcagggctgc
 H  I  T  P  L  Q  E  Q  S  K  E  V  A  I  R  I  F  Q  G  C
cagtttcgctccgtggaggctgtgcaggagatcacagagtatgccaaaagcattcctggt
 Q  F  R  S  V  E  A  V  Q  E  I  T  E  Y  A  K  S  I  P  G
tttgtaaatcttgacttgaacgaccaagtaactctcctcaaatatggagtccacgagatc
 F  V  N  L  D  L  N  D  Q  V  T  L  L  K  Y  G  V  H  E  I
atttacacaatgctggcctccttgatgaataaagatggggttctcatatccgagggccaa
 I  Y  T  M  L  A  S  L  M  N  K  D  G  V  L  I  S  E  G  Q
ggcttcatgacaagggagtttctaaagagcctgcgaaagccttttggtgactttatggag
 G  F  M  T  R  E  F  L  K  S  L  R  K  P  F  G  D  F  M  E
cccaagtttgagtttgctgtgaagttcaatgcactggaattagatgacagcgacttggca
 P  K  F  E  F  A  V  K  F  N  A  L  E  L  D  D  S  D  L  A
atatttattgctgtcattattctcagtggagaccgcccaggtttgctgaatgtgaagccc
 I  F  I  A  V  I  I  L  S  G  D  R  P  G  L  L  N  V  K  P
attgaagacattcaagacaacctgctacaagccctggagctccagctgaagctgaaccac
 I  E  D  I  Q  D  N  L  L  Q  A  L  E  L  Q  L  K  L  N  H
cctgagtcctcacagctgtttgccaagctgctccagaaaatgacagacctcagacagatt
 P  E  S  S  Q  L  F  A  K  L  L  Q  K  M  T  D  L  R  Q  I
gtcacggaacatgtgcagctactgcaggtgatcaagaagacggagacagacatgagtctt
 V  T  E  H  V  Q  L  L  Q  V  I  K  K  T  E  T  D  M  S  L
cacccgctcctgcaggagatctacaaggacttgtactaggtcgacaagcttgcggccgca
 H  P  L  L  Q  E  I  Y  K  D  L  Y  -
ctcgagcaccaccaccaccaccactgagat
```

PCR Primers:

PPARG	PPARG-S	GCTCAGACATATGGAGTCCGCTGACCTCCGGGC	(SEQ ID NO:___)
	PPARG-A	GTGACTGTCGACCTAGTACAAGTCCTTGTAGA	(SEQ ID NO:___)

PPARδ: (Nucleic acid SEQ ID NO:___) (Protein SEQ ID NO:___)

P1057. pET BAM6 PPARD G165-Y441-X

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                                                taatacgactcactatagggaattgt
gagcggataacaattcccctctagaaataattttgtttaactttaagaaggagatatacc
atgaaaaaaggtcaccaccatcaccatcacggatcccagtacaacccacaggtggccgac
 M  K  K  G  H  H  H  H  H  H  G  S  Q  Y  N  P  Q  V  A  D
ctgaaggccttctccaagcacatctacaatgcctacctgaaaaacttcaacatgaccaaa
 L  K  A  F  S  K  H  I  Y  N  A  Y  L  K  N  F  N  M  T  K
aagaaggcccgcagcatcctcaccggcaaagccagccacacggcgccctttgtgatccac
 K  K  A  R  S  I  L  T  G  K  A  S  H  T  A  P  F  V  I  H
gacatcgagacattgtggcaggcagagaaggggctggtgtggaagcagttggtgaatggc
 D  I  E  T  L  W  Q  A  E  K  G  L  V  W  K  Q  L  V  N  G
ctgcctccctacaaggagatcagcgtgcacgtcttctaccgctgccagtgcaccacagtg
```

```
 L  P  P  Y  K  E  I  S  V  H  V  F  Y  R  C  Q  C  T  T  V
gagaccgtgcgggagctcactgagttcgccaagagcatccccagcttcagcagcctcttc
 E  T  V  R  E  L  T  E  F  A  K  S  I  P  S  F  S  S  L  F
ctcaacgaccaggttacccttctcaagtatggcgtgcacgaggccatcttcgccatgctg
 L  N  D  Q  V  T  L  L  K  Y  G  V  H  E  A  I  F  A  M  L
gcctctatcgtcaacaaggacgggctgctggtagccaacggcagtggctttgtcacccgt
 A  S  I  V  N  K  D  G  L  L  V  A  N  G  S  G  F  V  T  R
gagttcctgcgcagcctccgcaaacccttcagtgatatcattgagcctaagtttgaattt
 E  F  L  R  S  L  R  K  P  F  S  D  I  I  E  P  K  F  E  F
gctgtcaagttcaacgccctggaacttgatgacagtgacctggccctattcattgcggcc
 A  V  K  F  N  A  L  E  L  D  D  S  D  L  A  L  F  I  A  A
atcattctgtgtggagaccggccaggcctcatgaacgttccacgggtggaggctatccag
 I  I  L  C  G  D  R  P  G  L  M  N  V  P  R  V  E  A  I  Q
gacaccatcctgcgtgccctcgaattccacctgcaggccaaccaccctgatgcccagtac
 D  T  I  L  R  A  L  E  F  H  L  Q  A  N  H  P  D  A  Q  Y
ctcttccccaagctgctgcagaagatggctgacctgcggcaactggtcaccgagcacgcc
 L  F  P  K  L  L  Q  K  M  A  D  L  R  Q  L  V  T  E  H  A
cagatgatgcagcggatcaagaagaccgaaaccgagacctcgctgcaccctctgctccag
 Q  M  M  Q  R  I  K  K  T  E  T  E  T  S  L  H  P  L  L  Q
gagatctacaaggacatgtactaagtcgaccaccaccaccaccaccactgagatccggct
 E  I  Y  K  D  M  Y  -
ggccctactggccgaaaggaattcgaggccagcagggccaccgctgagcaataactagca
taacccctttggggcctctaaacgggtcttgaggggttttttg
```

PCR Primers:

PPARD	PPARD-G165	GTTGGATCCCAGTACAACCCACAGGTGGC	(SEQ ID NO:___)
	PPARD-A	GTGACTGTCGACTTAGTACATGTCCTTGTAGA	(SEQ ID NO:___)

Example 9: Bio-chemical Screening

[0269] The homogenous Alpha screen assay was used in the agonist mode to determine the ligand dependent interaction of the PPARs (α,δ,γ) with the coactivator Biotin-PGC-1 peptide (biotin-AHX-DGTPPPQEAEEPSLLKKLLLAPANT-$CONH_2$ (SEQ ID NO:___), supplied by Wyeth). All compounds tested were serially diluted 1:3 into DMSO for a total of 8 concentration points. Samples were prepared with His-tagged PPAR-LBD prepared per Example 8. Ni-chelate acceptor beads were added that bind to the his-tagged PPAR-LBD and streptavidin donor beads were added that bind to the biotin of the coactivator (Perkin-Elmer #6760619M) such that agonist activity correlates to signal from the donor and acceptor beads in close proximity. Each sample was prepared by mixing 1 μl of compound and 15 μl of 1.33x receptor/peptide mix, incubating for 15 minutes at room temperature, then adding 4 μl of 4x beads in assay buffer. The assay buffer was 50 mM HEPES, pH 7.5, 50 mM KCl, 1 mM DTT and 0.8% BSA. Final concentrations for each sample were 25 nM biotin-PGC-1 peptide, 20 nM PPARγ or 10 nM PPARα or δ, and each bead at 5 μg/ml, with compound added to the desired concentration resulting in final

DMSO of 5%. WY-14643(PPARα), farglitazar (PPARγ) and bezafibrate (PPARδ) were assayed as control samples. The samples were incubated for 1 hour in the dark at room temperature before taking the reading in the Fusion alpha or Alpha Quest reader. The signal vs. compound concentration was used to determine the EC_{50}. The data was expressed in μMol/L. The data points from the Fusion alpha instrument were transferred to Assay Explorer® (MDL) to generate a curve and calculate the inflection point of the curve as EC_{50}.

Example 10: Co-transfection assay

[0270] This assay serves to confirm the observed biochemical activity (Example 9) on the modulation of intended target molecule(s) at the cellular level. 293T cells (ATCC) were seeded at 1-2 x 10^6 cells per well of a 6 well plate (Corning 3516) in 3 ml of growth medium (Dulbecco's eagle medium, Mediatech, with 10% FBS). These were incubated to 80-90% confluent and the medium was removed by aspirating. These cells were transfected with PPAR LBD and luciferase such that agonist results in activation of the luciferase. Measurement of luciferase activity of transfected cells treated with compounds directly correlates with agonist activity. To 100 μl of serum free growth medium was added 1 μg of pFR-Luc (Stratagene catalog number 219050), 6 μl Metafectene (Biontex, Inc.) and 1 mg of the pGal4-PPAR-LBD(α, γ or δ from Example 8). This was mixed by inverting, then incubated for 15-20 minutes at room temperature, and diluted with 900 μl of serum free growth medium. This was overlayed onto the 293T cells and incubated for 4-5 hours at 37°C in CO_2 incubator. The transfection medium was removed by aspirating and growth medium was added and the cells incubated for 24 hours. The cells were then suspended in 5 ml of growth medium and diluted with an additional 15 ml of growth medium. For each test sample, 95 μl of the transfected cells were transferred per well of a 96 well culture plate. Compounds tested were diluted in DMSO to 200x the desired final concentration. This was diluted 10x with growth medium and 5 μl was added to the 95 μl of transfected cells. The plate was incubated for 24 hours 37°C in CO_2 incubator. Luciferase reaction mixture was prepared by mixing 1 ml of lysis buffer, 1 ml of substrate in lysis buffer, and 3 ml of reaction buffer (Roche Diagnostics Luciferase assay kit #1814036). For each sample well, the growth medium was replaced with 50 ml of reaction mixture and the plate shaken for 15-20 minutes, and the luminescence was

measured on a Victor2 V plate reader (Perkin Elmer). The signal vs. compound concentration was used to determine the EC_{50}.

[0271] This assay serves to confirm the observed biochemical activity (Example 9) on the modulation of intended target molecule(s) at the cellular level. Compounds having EC_{50} of less than or equal to 1 μM in either of the biochemical assay of Example 9 or this cell based assay for at least one of the PPARs are shown in Table 8. Additional compounds disclosed in PCT publication WO 2005/009958 demonstrated EC_{50} of less than or equal to 1 μM for at least one of PPARs. These were compounds 1, 22, 29, 41, 43, 45, 47, 51, 53, 55, 59, 63, 65, 67, 69, 77, 79, 82, 83, 90, 92, 94, 101, 102, 107, 108, 109, 110, 111, 112, 113, 115, and 116 from Table 1 beginning on page 184 of the published application and compound 119 (Example 81), compound 121 (Example 99) and Compound 126 (Example 103) from the application.

Table 8. Compounds having EC_{50} of less than or equal to 1 μM in at least one of PPARα, PPARγ and PPARδ activity assays.

P-0001, P-0002, P-0003, P-0004, P-0007, P-0008, P-0010, P-0015, P-0016, P-0017, P-0018, P-0019, P-0020, P-0022, P-0026, P-0031, P-0032, P-0033, P-0034, P-0035, P-0037, P-0039, P-0046, P-0048, P-0049, P-0050, P-0051, P-0052, P-0053, P-0054, P-0055, P-0056, P-0057, P-0058, P-0060, P-0063, P-0064, P-0066, P-0067, P-0068, P-0069, P-0070, P-0071, P-0072, P-0080, P-0082, P-0092, P-0099, P-0100, P-0108, P-0144, P-0147, P-0149, P-0150, P-0151, P-0155, P-0158, P-0159, P-0160, P-0163, P-0165, P-0166, P-0167, P-0174, P-0175, P-0188, P-0203, P-0207, P-0208, P-0209, P-0210, P-0214, P-0215, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0236, P-0270, P-0276, P-0277, P-0278, P-0279, P-0280, P-0282, P-0283, P-0284, P-0285, P-0286, P-0289, P-0290, P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0308, P-0309, P-0310, P-0311, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0322, P-0323, P-0324, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0334, P-0335, P-0337, P-0340, P-0341, P-0343, P-0344, P-0347, P-0351, P-0356, P-0359, P-0360, P-0361, P-0362, P-0363, P-0364, P-0371, P-0373, P-0376, P-0377, P-0378, P-0379, P-0380, P-0381, P-0382, P-0383, P-0384, P-0385, P-0386, P-0387, P-0388, P-0389, P-0395, P-0396, P-0398, P-0399, P-0400, P-0401, P-0402, P-0404, P-0405, P-0408, P-0409, P-0411, P-0412,

P-0413, P-0415, P-0419, P-0420, P-0422, P-0423, P-0424, P-0427, P-0430, P-0431, P-0434, P-0435, P-0436, P-0437, P-0438, P-0439, P-0440, P-0446, P-0447, P-0448, P-0449, P-0450, P-0451, P-0452, P-0454, P-0455, P-0456, P-0458, P-0462, P-0463, P-0464, P-0465, P-0466, P-0467, P-0468, P-0470, P-0471, P-0472, P-0473, P-0474, P-0475, P-0476, P-0477, P-0478, P-0479, P-0481, P-0482, P-0483, P-0484, P-0485, P-0486, P-0487, P-0488, P-0489, P-0490, P-0491, P-0492, P-0493, P-0494, P-0495, P-0496, P-0497, P-0498, P-0499, P-0501, P-0502, P-0503, P-0504, P-0505, P-0506, P-0508, P-0509, P-0510, P-0511, P-0512, P-0513, P-0514, P-0515, P-0516, P-0517, P-0518, P-0519, P-0520, P-0521, P-0523, P-0524, P-0529, P-0530, P-0533, P-0535, P-0537, P-0538, P-0539, P-0540, P-0541, P-0549, P-0552, P-0553, P-0555, P-0560, P-0561, P-0564, P-0566, P-0567, P-0568, P-0570, P-0572

[0272] All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0273] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[0274] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, variations can be made to exemplary compounds of I, Ia, Ib, II, or III to provide additional active compounds. Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0275] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms

"comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0276] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

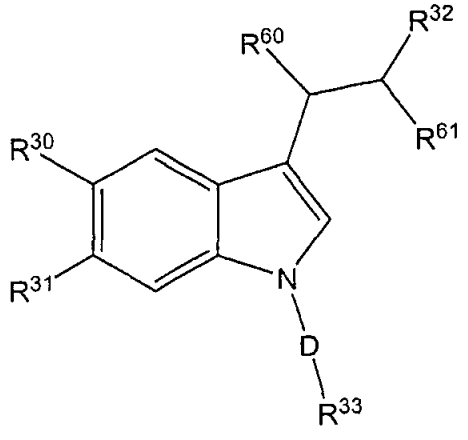
[0277] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0278] Thus, additional embodiments are within the scope of the invention and within the following claims.

CLAIMS

What is claimed is:

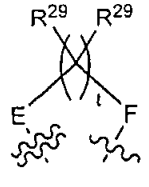
1. A compound having the chemical structure



all salts, prodrugs, tautomers and isomers thereof,

wherein:

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$; or

R^{30} and R^{31} combine to form a fused ring, wherein the combined R^{30} and R^{31} are of the formula 

, wherein  indicates the point of attachment of R^{30} to the indole ring and  indicates the point of attachment of R^{31} to the indole ring;

E and F are independently selected from the group consisting of $CR^{29}R^{29}$, O, $S(O)_2$ and NR^{44};

R^{29} at each occurrence is independently selected from the group consisting of hydrogen, fluoro, optionally fluoro substituted lower alkyl, optionally fluoro substituted lower alkoxy, and optionally fluoro substituted lower alkylthio;

R^{44} is hydrogen or lower alkyl;

t is 1 or 2;

R^{32} is selected from the group consisting of $-C(O)OR^{26}$, $-C(O)NR^{27}R^{28}$, and a carboxylic acid isostere;

R^{33} is $L-R^{42}$ or heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -OH, $-NO_2$, -CN, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

L is $-(CR^{51}R^{52})_m-$ or $-CR^{55}=CR^{56}-$;

D is $-CR^{51}R^{52}-$ or $-S(O)_2-$;

R^{34} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{34} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the O of $-OR^{34}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{34} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the O of $-OR^{34}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, and $-C(Z)NR^{38}R^{39}$;

R^{35} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{35} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the S of $-SR^{35}$ or the O of $-OR^{35}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{35} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the S of $-SR^{35}$ or the O of $-OR^{35}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{36} and R^{37} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{36} and/or R^{37} are optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{36}R^{37}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{36} and/or R^{37} are optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{36}R^{37}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally

substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$, and $-S(O)_2NR^{38}R^{39}$;

R^{38} and R^{39} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{38} and/or R^{39} are optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $NR^{38}R^{39}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{38} and/or R^{39} are optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $NR^{38}R^{39}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{40} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{40} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to -C(Z)-, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{40} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to -C(Z)-, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, and $-OR^{35}$;

R^{41} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{41} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to $-S(O)_n-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{41} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to $-S(O)_n-$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally optionally substituted aryl, and optionally substituted heteroaryl;

R^{42} is aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -OH, $-NO_2$, -CN, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

R^{51} and R^{52} are independently selected from the group consisting of hydrogen, fluoro, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally

substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

or any two of R^{51} and R^{52} on the same carbon or on adjacent carbons may be combined to form an optionally substituted 3-7 membered monocyclic cycloalkyl or optionally substituted 5-7 membered monocyclic heterocycloalkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{55} and R^{56} combine to form an optionally substituted 5-7 membered monocyclic cycloalkyl or optionally substituted 5-7 membered monocyclic heterocycloalkyl;

R^{60} and R^{61} are each hydrogen, or R^{60} and R^{61} combine to form optionally substituted 3-7 membered monocyclic cycloalkyl;

R^{26} is selected from the group consisting of hydrogen, lower alkyl, phenyl, 5-7 membered monocyclic heteroaryl, 3-7 membered monocyclic cycloalkyl, and 5-7 membered monocylic heterocycloalkyl, wherein phenyl, monocyclic heteroaryl, monocyclic cycloalkyl and monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio, and wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, $-NH_2$, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio and fluoro substituted lower alkylthio, provided, however, that when R^{26} is lower alkyl, any substitution on the lower alkyl carbon bound to the O of OR^{26} is fluoro;

R^{27} and R^{28} are independently selected from the group consisting of hydrogen, lower alkyl, phenyl, 5-7 membered monocyclic heteroaryl, 3-7 membered monocyclic cycloalkyl, and 5-7 membered monocylic heterocycloalkyl, wherein phenyl, monocyclic heteroaryl, monocyclic cycloalkyl and monocyclic heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio, and wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, $-NH_2$,

lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio and fluoro substituted lower alkylthio, provided, however, that when R^{27} and/or R^{28} is lower alkyl, any substitution on the lower alkyl carbon bound to the N of $NR^{27}R^{28}$ is fluoro; or

R^{27} and R^{28} together with the nitrogen to which they are attached form a 5-7 membered monocyclic heterocycloalkyl or a 5 or 7 membered nitrogen containing monocyclic heteroaryl, wherein the monocyclic heterocycloalkyl or monocyclic nitrogen containing heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, $-NH_2$, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, and fluoro substituted lower alkylthio;

n is 1, or 2;

m is 1, 2, or 3; and

Z is O or S.

provided, however, that when D is $-S(O)_2-$, R^{30} is OCH_3, R^{31} is H, and R^{32} is COOH or $COOCH_3$, then R^{33} is not unsubstituted thiophenyl.

2. The compound according to claim **1**, wherein D is $-CR^{51}R^{52}-$.

3. The compound according to claim **1**, wherein D is $-S(O)_2-$.

4. The compound according to claim **1**, wherein R^{33} is substituted heteroaryl.

5. The compound according to claim **4**, wherein:

R^{33} is heteroaryl substituted with one or more substituents selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

wherein wherein one of R^{36} and R^{37} is selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted

heteroaryl, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$, and $-S(O)_2NR^{38}R^{39}$, and the other of R^{36} and R^{37} is hydrogen or lower alkyl;

wherein one of R^{38} and R^{39} is selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, and the other of R^{38} and R^{39} is hydrogen or lower alkyl; and

wherein R^{34}, R^{35}, R^{40}, and R^{41} are independently selected from the group consisting of lower alkyl, wherein lower alkyl is substituted with optionally substituted aryl or optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

6. The compound according to claim **5**,

wherein

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl and optionally substituted heteroaryl, or

R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen.

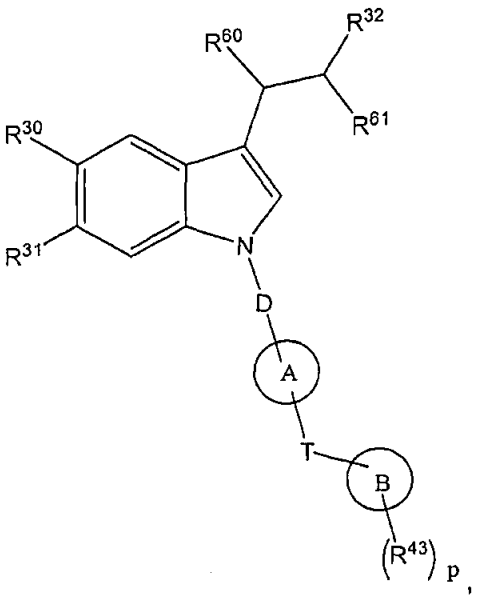
7. The compound according to claim **6**, wherein R^{31} is hydrogen.

8. The compound according to claim **6**, wherein R^{30} and R^{31} are independently optionally substituted lower alkoxy, or R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen.

9. The compound according to claim **6**, wherein D is $-S(O)_2-$.

10. The compound according to claim **6**, wherein D is $-CH_2-$.

11. A compound having the chemical structure

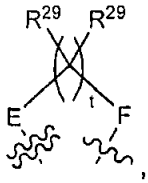


all salts, prodrugs, tautomers and isomers thereof,

wherein:

D is $-CR^{51}R^{52}-$ or $-S(O)_2-$;

R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$; or

R^{30} and R^{31} combine to form a fused ring, wherein the combined R^{30} and R^{31} are of the formula 

, wherein  indicates the point of attachment of R^{30} to the indole ring and  indicates the point of attachment of R^{31} to the indole ring;

E and F are independently selected from the group consisting of $CR^{29}R^{29}$, O, $S(O)_2$ and NR^{44};

R^{29} at each occurrence is independently selected from the group consisting of hydrogen, fluoro, optionally fluoro substituted lower alkyl, optionally fluoro substituted lower alkoxy, and optionally fluoro substituted lower alkylthio;

R^{44} is hydrogen or lower alkyl;

t is 1 or 2;

R^{32} is selected from the group consisting of $-C(O)OR^{26}$, $-C(O)NR^{27}R^{28}$, and a carboxylic acid isostere;

R^{60} and R^{61} are each hydrogen, or R^{60} and R^{61} combine to form optionally substituted 3-7 membered monocyclic cycloalkyl;

A is arylene or heteroarylene, wherein arylene or heteroarylene are optionally substituted with one or more substituents selected from the group consisting of halogen, -OH, lower alkyl, lower alkoxy, and lower alkylthio, wherein lower alkyl and the lower alkyl chains of lower alkoxy and lower alkylthio are optionally substituted with one or more substituents selected from the group consisting of fluoro, -OH, lower alkoxy, and lower alkylthio, provided, however, that any substitution of the carbon bound to the lower alkoxy O or lower alkylthio S is fluoro;

T is a covalent bond or is selected from the group consisting of $-(CR^{51}R^{52})_m-$, $-(CR^{51}R^{52})_qO(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{53}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(O)_n(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}S(O)_2(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(O)_2NR^{54}(CR^{51}R^{52})_r-$, and $-(CR^{51}R^{52})_qNR^{54}S(O)_2NR^{54}(CR^{51}R^{52})_r-$;

R^{51} and R^{52} are independently selected from the group consisting of hydrogen, fluoro, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

or any two of R^{51} and R^{52} on the same carbon or on adjacent carbons may be combined to form an optionally substituted 3-7 membered monocyclic cycloalkyl or optionally substituted 5-7 membered monocyclic heterocycloalkyl;

m is 1, 2, or 3;

q and r are independently 0, 1, or 2;

B is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R^{43} at each occurence is independently selected from the group consisting of halogen, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,-OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$;

R^{53} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{53} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{53}-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{53} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{53}-$, optionally substituted cycloalkyl, optionally substituted heterocyclyoalkyl, optionally substituted aryl, optionally substituted heteroaryl,$-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_2R^{41}$;

R^{54} at each occurrence is independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{54} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{54}-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{54} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{54}-$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

p is 0, 1, 2 or 3;

n is 1, or 2;

Z is O or S;

R^{34} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{34} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the O of $-OR^{34}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{34} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the O of $-OR^{34}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, and $-C(Z)NR^{38}R^{39}$;

R^{35} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{35} is optionally

substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the S of $-SR^{35}$ or the O of $-OR^{35}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{35} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the S of $-SR^{35}$ or the O of $-OR^{35}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

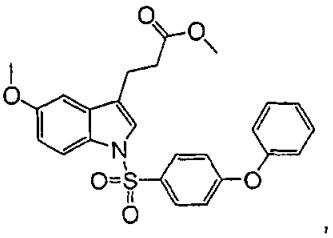
R^{36} and R^{37} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{36} and/or R^{37} are optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $-NR^{36}R^{37}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{36} and/or R^{37} are optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $-NR^{36}R^{37}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$, and $-S(O)_2NR^{38}R^{39}$;

R^{38} and R^{39} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{38} and/or R^{39} are optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to the N of $NR^{38}R^{39}$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{38} and/or R^{39} are optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to the N of $NR^{38}R^{39}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

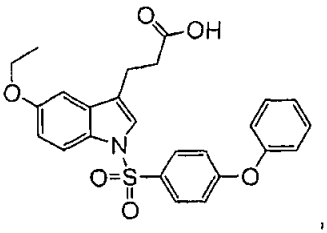
R^{40} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{40} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to -C(Z)-, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{40} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to -C(Z)-, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -OH, and $-OR^{35}$;

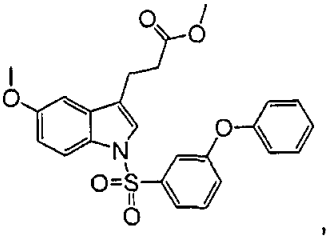
R^{41} is selected from the group consisting of optionally substituted lower alkyl, optionally substituted C_{3-6} alkenyl, provided, however, that when R^{41} is optionally substituted C_{3-6} alkenyl, no alkene carbon thereof is bound to $-S(O)_n-$, optionally substituted C_{3-6} alkynyl, provided, however, that when R^{41} is optionally substituted C_{3-6} alkynyl, no alkyne carbon thereof is bound to $-S(O)_n-$, optionally substituted

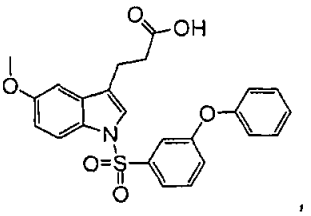
cycloalkyl, optionally substituted heterocycloalkyl, optionally optionally substituted aryl, and optionally substituted heteroaryl;

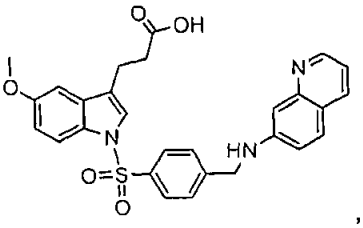


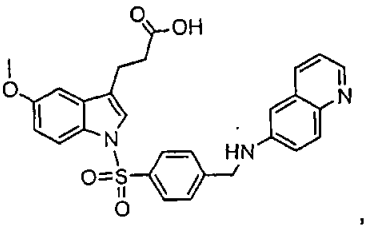
provided, however, said compound is not

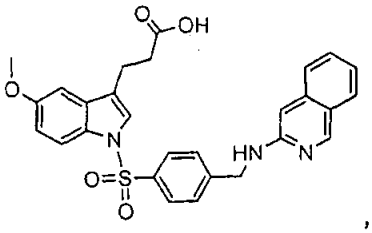


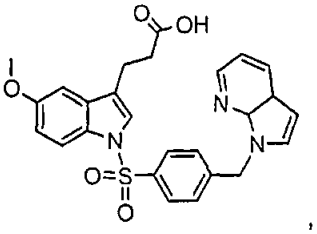


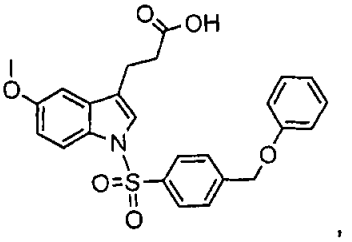


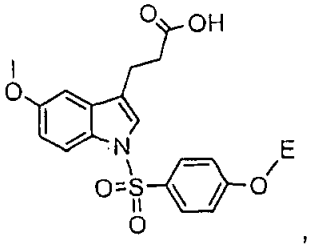




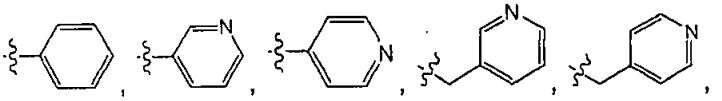


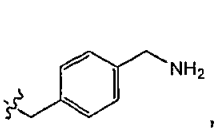


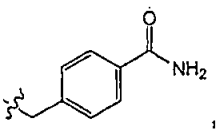




or

wherein E is 



, or 

, wherein indicates the point of attachment of E to O.

12. The compound according to claim **11**, wherein A is phenyl and T-B is ortho to D.

13. The compound according to claim **12**, wherein D is $-S(O)_2-$.

14. The compound according to claim **12**, wherein D is $-CR^{51}R^{52}-$.

15. The compound according to claim **11**, wherein R^{43} is selected from the group consisting of halogen, -OH, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, and $-S(O)_nR^{41}$, wherein R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} and R^{41} are other than a member selected from the group consisting of optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, or lower alkyl substituted with optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

16. The compound according to claim **15**, wherein R^{30} and R^{31} are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl, or R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen.

17. The compound according to claim **16**, wherein R^{31} is hydrogen.

18. The compound according to claim **16**, wherein R^{30} and R^{31} are independently optionally substituted lower alkoxy, or R^{30} and R^{31} combine to form a fused ring wherein E and F are O, t is 1 or 2, and each R^{29} is hydrogen.

19. The compound according to claim **11**, wherein D is $-S(O)_2-$.

20. The compound according to claim **11**, wherein D is $-CH_2-$.

21. The compound of claim 11, wherein the compound is selected from the group consisting of 3-{1-[5-(2,4-Dimethoxy-pyrimidin-5-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid,
3-{5-Chloro-1-[5-(2,4-dimethoxy-pyrimidin-5-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid,
3-{1-[5-(6-Benzyloxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid,
3-{1-[5-(2,6-Dimethoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid,
3-{1-[5-(4-Benzyloxy-phenyl)-thiophene-2-sulfonyl]-5-ethoxy-1H-indol-3-yl}-propionic acid,
3-{5-Ethoxy-1-[5-(6-methoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid,
3-{1-[5-(3-Chloro-4-fluoro-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid,
3-{1-[5-(3-Fluoro-4-methoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid,
3-{5-Methoxy-1-[5-(6-methoxy-pyridin-3-yl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid,
3-{5-Methoxy-1-[5-(4-trifluoromethoxy-phenyl)-thiophene-2-sulfonyl]-1H-indol-3-yl}-propionic acid,
3-{1-[5-(4-Ethoxy-phenyl)-thiophene-2-sulfonyl]-5-methoxy-1H-indol-3-yl}-propionic acid,
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3-[5-Ethoxy-1-(4'-propyl-biphenyl-2-sulfonyl)-1H-indol-3-yl]-propionic acid,
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3-[5-Ethoxy-1-(5-methyl-3-p-tolyl-thiophene-2-sulfonyl)-1H-indol-3-yl]-propionic acid,
3-[1-(4'-Trifluoromethyl-biphenyl-3-sulfonyl)-1H-indol-3-yl]-propionic acid, and
3-[5-Methoxy-1-(4'-trifluoromethyl-biphenyl-3-sulfonyl)-1H-indol-3-yl]-propionic acid.

22. A method for treating a subject suffering from or at risk of a disease or condition for which PPAR modulation provides a therapeutic benefit, comprising administering to said subject a therapeutically effective amount of a compound according to Claim 1.

23. A method for treating a subject suffering from or at risk of a disease or condition for which PPAR modulation provides a therapeutic benefit, comprising administering to said subject a therapeutically effective amount of a compound according to Claim 11.

24. The method according to claim 22 or 23, wherein said compound is approved for administration to a human.

25. The method according to claim 22 or 23, wherein said disease or condition is a PPAR-mediated disease or condition.

26. The method according to claim 22 or 23, wherein said disease or condition is selected from the group consisting of obesity, overweight condition, bulimia, anorexia nervosa, hyperlipidemia, dyslipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, low HDL, Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, a diabetic complication of neuropathy, nephropathy, retinopathy, diabetic foot ulcer or cataracts, hypertension, coronary heart disease, heart failure, congestive heart failure, atherosclerosis, arteriosclerosis, stroke, cerebrovascular disease, myocardial infarction, peripheral vascular disease, vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, eczema, psoriasis, dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome, thrombosis, infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular

degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic or inflammatory pain, infertility, and cancer.

27. A composition comprising:

a pharmaceutically acceptable carrier; and

a compound according to Claim **1**.

28. A composition comprising:

a pharmaceutically acceptable carrier; and

a compound according to Claim **11**.

29. A kit comprising a compound according to claim **1**.

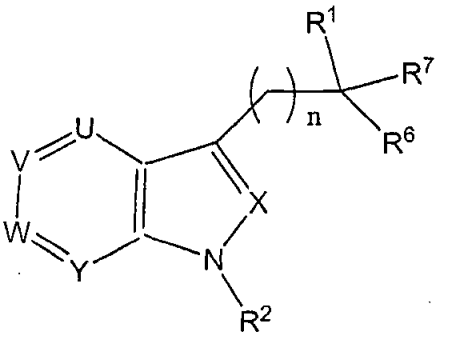
30. A kit comprising a compound according to claim **11**.

31. A kit comprising a composition according to claim **27**.

32. A kit comprising a composition according to claim **28**.

33. A method for treating a subject suffering from or at risk of a disease or condition for which PPAR modulation provides a therapeutic benefit, comprising:

administering to said subject a therapeutically effective amount of a PPAR modulator having the chemical structure of



all salts, prodrugs, tautomers and isomers thereof,xxxxx

wherein:

U, V, W, X, and Y are independently N or CR^8, wherein at most two of U, V, W, and Y are N;

R^1 is selected from the group consisting of $C(O)OR^{16}$ and a carboxylic acid isostere;

R^2 is selected from the group consisting of hydrogen, optionally substituted lower alkyl, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ and $-S(O)_2R^{21}$;

R^6 and R^7 are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

R^6 and R^7 combine to form a 3-7 membered monocyclic cycloalkyl or 5-7 membered monocyclic heterocycloalkyl;

R^8 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^9$, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{21}$;

R^9 is selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; or

R^{10} and R^{11} together with the nitrogen to which they are attached form a 5-7 membered monocyclic heterocycloalkyl or a 5 or 7 membered monocyclic nitrogen containing heteroaryl;

R^{16} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyoalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{20} is selected from the group consisting of $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{21} is selected from the group consisting of $-OR^{17}$, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C \equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{12}, R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{17} is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and $-C(O)R^{18}$;

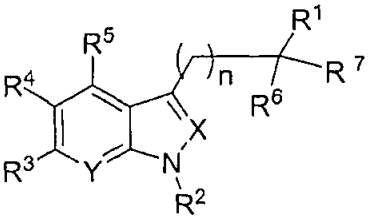
R^{18} is selected from the group consisting of hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyoalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

Z is O or S; and

n = 0, 1, or 2;

wherein said disease or condition is selected from the group consisting of vitiligo, uveitis, pemphigus foliaceus, inclusion body myositis, polymyositis, dermatomyositis, scleroderma, Grave's disease, Hashimoto's disease, chronic graft versus host disease, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, multiple sclerosis, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, and hepatitis), dermatitis, impaired wound healing, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, acute disseminated encephalomyelitis, Guillain-Barre syndrome, infarction of the large or small intestine, renal insufficiency, erectile dysfunction, urinary incontinence, neurogenic bladder, ophthalmic inflammation, macular degeneration, pathologic neovascularization, HCV infection, HIV infection, Helicobacter pylori infection, neuropathic pain, inflammatory pain, and infertility.

34. The method according to claim **33**, wherein said PPAR modulator has the chemical structure of



wherein:

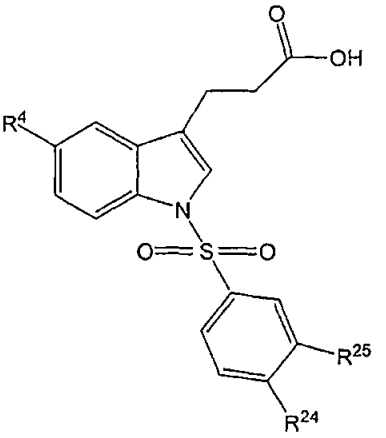
U is CR^8, wherein R^8 is R^5;

V is CR^8, wherein R^8 is R^4;

W is CR^8, wherein R^8 is R^3;

R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, $-CH_2-CR^{12}= CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^9$, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{21}$.

35. The method according to claim 33, wherein said PPAR modulator has the chemical structure of



wherein:

U is CR^8, wherein R^8 is H;

V is CR^8, wherein R^8 is R^4;

W is CR^8, wherein R^8 is H;

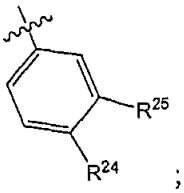
X is CR^8, wherein R^8 is H;

Y is CR^8, wherein R^8 is H;

n is 1;

R^1 is –COOH;

R^6 and R^7 are hydrogen;

R^2 is $-S(O)_2R^{21}$, wherein R^{21} is  ;

R^4 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^9$, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{21}$;

R^{24} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, $-OR^{19}$, and $-O(CH_2)_pO$-aryl;

p is 1, 2, 3, or 4;

R^{25} is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, and $-OR^{19}$; or

R^{24} and R^{25} combine to form cycloalkyl, heterocycloalkyl, aryl or heteroaryl fused with the phenyl ring; and

R^{19} is selected from the group consisting of optionally substituted lower alkyl and optionally substituted aryl.

36. The method according to claim **33**, **34**, or **35**, wherein the disease or condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

37. The method according to Claim **22** or **23**, wherein said disease or condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease, multiple sclerosis, infertility, asthma, chronic obstructive pulmonary disease, and macular degeneration.

SEQUENCE LISTING

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SEQ ID NO:2 (GenBank NP_005027)

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 241 ihdmetlcma ektlvaklva ngiqnkeaev rifhccqcts vetvteltef akaipgfanl
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 361 famkfnalel ddsdislfva aiiccgdrpg llnvghiekm qegivhvlrl hlqsnhpddi
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SEQ ID NO:3 (GenBank NM_015869)

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1861 aaa
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SEQ ID NO:4 (GenBank NP_056953)

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SEQ ID NO:6 (GenBank NP_006229)

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421 kktetetslh pllqeiykdm y
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DERIVADOS DE INDOL 1,3-DISUSTITUIDO PARA SU USO COMO MODULADORES DE PPAR

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con el campo de los moduladores para miembros de la familia de los receptores nucleares identificados como receptores activados por el proliferador del peroxisoma.

ANTECEDENTES DE LA INVENCIÓN

La siguiente descripción se proporciona solamente para ayudar al entendimiento del lector. Ninguna de las referencias citadas o información proporcionada se admite como técnica anterior a la presente invención. Cada una de las referencias citadas en la presente se incorpora para referencia en su totalidad, en el mismo grado como si cada referencia se indicara individualmente como incorporada para referencia en la presente en su totalidad.

Los receptores activados por el proliferador del peroxisoma (PPARs) forman una subfamilia en la superfamilia de receptores nucleares. Tres isoformas, codificadas por genes separados, se han identificado hasta ahora: PPARγ, PPARα y PPARδ.

Existen dos isoformas de PPARγ expresadas al nivel de proteína en ratón y humano, γ1 y γ2. Éstas difieren sólo en que la última tiene 30 aminoácidos adicionales en su extremo N debido al uso diferencial del promotor dentro del mismo gen y al procesamiento alternativo subsecuente del ARN. El PPARγ2 se expresa principalmente en el tejido adiposo, mientras que el PPARγ1 se expresa en una amplia variedad de tejidos.

El PPARα murino fue el primer miembro de esta subclase de receptores nucleares que se clonó; desde entonces se ha clonado a partir de humanos. El PPARα se expresa en numerosos tejidos metabólicamente activos, incluyendo hígado, riñón, corazón, músculo esquelético y grasa parda. También se presenta en monocitos, endotelio vascular y células del músculo liso vascular. La activación de PPARα induce la proliferación del peroxisoma hepático, hepatomegalia y hepatocarcinogénesis en roedores. Estos efectos tóxicos no se observan en humanos, aunque los mismos compuestos activan PPARα entre las especies.

El PPARδ humano se clonó al inicio de la década de 1990 y se clonó subsecuentemente a partir de roedores. El PPARδ se expresa en una amplia variedad de tejidos y células, con los niveles más altos de expresión encontrados en el tracto digestivo, corazón, riñón, hígado, tejido adiposo y cerebro.

Los PPARs son factores de transcripción dependientes de ligando que regulan la expresión del gen objetivo al unirse a elementos de respuesta al proliferador peroxisoma (PPREs) específicos en sitios potenciadores de genes regulados. Los PPARs poseen una estructura modular compuesta de dominios funcionales que incluyen un dominio de unión a ADN (DBN) y un dominio de unión a ligando (LBD). El DBD se une específicamente a los PPREs en la región reguladora de los genes sensibles a PPAR. El DBD, ubicado en la mitad C terminal del receptor, contiene el dominio de activación dependiente de ligando, AF-2. Cada receptor se une a su PPRE como un heterodímero con un receptor X retinoide (RXR). Con la unión de un agonista, la conformación de un PPAR se altera y estabiliza de modo que se crea una hendidura de unión, constituida en parte del dominio AF-2, y ocurre el reclutamiento de coactivadores transcripcionales. Los coactivadores aumentan la capacidad de los receptores nucleares de iniciar el proceso de transcripción. El resultado de la interacción PPAR-coactivador inducida por agonistas en el PPRE es un incremento en la transcripción génica. La subregulación de la expresión génica por los PPARs parece ocurrir a través de mecanismos indirectos. (Bergen & Wagner, 2002, *Diabetes Tech. & Ther.*, 4:163-174).

La primera clonación de un PPAR (PPARα) ocurrió en el transcurso de la búsqueda del objetivo molecular de los agentes de proliferación de peroxisoma hepático de roedores. Desde entonces, se ha demostrado que numerosos ácidos grasos y sus derivados, incluyendo una diversidad de eicosanoides y prostanglandinas, sirven como ligandos de los PPARs. De esta manera, estos receptores pueden jugar un papel central en la detección de niveles de nutrientes y en la modulación de su metabolismo. Además, los PPARs son los objetivos principales de clases seleccionadas de compuestos sintéticos que se han usado en el tratamiento exitoso de la diabetes y la dislipidemia. Como tal, un entendimiento de las características

moleculares y fisiológicas de estos receptores se ha vuelto extremadamente importante para el desarrollo y utilización de fármacos usados para tratar trastornos metabólicos.

Kota et al., 2005, *Pharmacological Research* 51: 85-94, proporciona una revisión de los mecanismos biológicos que involucran a los PPARs que incluye una discusión de la posibilidad de usar moduladores de PPAR para tratar una diversidad de padecimientos, incluyendo trastornos inflamatorios crónicos tales como ateroesclerosis, artritis y síndrome del intestino inflamado, trastornos retinianos asociados con angiogénesis, fertilidad incrementada y enfermedades neurodegenerativas.

Yousef et al, 2004, *Journal of Biomedicine and Biotechnology* 2004(3): 156-166, discute los efectos anti-inflamatorios de los agonistas de PPARα, PPARγ y PPARδ, sugiriendo que los agonistas de PPAR pueden tener un papel en el tratamiento de enfermedades neuronales tal como la enfermedad de Alzheimer, y enfermedades autoinmunes tales como enfermedad del intestino inflamado y esclerosis múltiple. Un papel potencial para los agonistas de PPAR en el tratamiento de la enfermedad de Alzheimer se ha descrito en Combs et al., 2000, *Journal of Neuroscience* 20(2): 558, y tal función para los agonistas de PPAR en la enfermedad de Parkinson se discute en Breidert et al. 2002, *Journal of Neurochemistry*, 82: 615. Una función relacionada potencial de los agonistas de PPAR en el tratamiento de la enfermedad de Alzheimer, aquella de la regulación de la enzima de procesamiento de APP, BACE, se ha discutido en Sastre et al. 2003, *Journal of Neuroscience* 23(30):9796. Estos estudios indican colectivamente que los agonistas de PPAR pueden proporcionar ventajas en el tratamiento de una diversidad de enfermedades neurodegenerativas al actuar a través de mecanismos complementarios.

La discusión de los efectos anti-inflamatorios de los agonistas de PPAR también se encuentra disponible en Feinstein, 2004, *Drug Discovery Today: Therapeutic Strategies* 1(1):29-34 en relación con esclerosis múltiple y enfermedad de Alzheimer; Patel et al., 2003, *The Journal of Immunology*, 170:2663-2669 en relación con enfermedad pulmonar obstructiva crónica (COPD) y asma; Lovett-Racke et al., 2004, *The Journal of Immunology*, 172:5790-5798 en relación con enfermedad autoinmune; Malhotra et al., 2005, *Expert Opinions in Pharmacotherapy*, 6(9): 1455-

1461 en relación con psoriasis; y Storer et al., 2005, *Journal of Neuroimmunology*, 161 :113-122 en relación con esclerosis múltiple.

Esta amplia variedad de funciones para los PPARs que se han descubierto, sugiere que PPARα, PPARγ y PPARδ pueden jugar un papel en una amplia variedad de eventos que involucran la vasculatura, incluyendo formación y estabilidad de placas ateroescleróticas, trombosis, tono vascular, angiogénesis, cáncer, embarazo, enfermedad pulmonar, enfermedad autoinmune y trastornos neurológicos.

Entre los ligandos sintéticos identificados para los PPARs se encuentran las tiazolidindionas (TZDs). Estos compuestos se desarrollaron originalmente sobre la base de sus efectos de sensibilización a la insulina en estudios farmacológicos en animales. Subsecuentemente, se encontró que las TZDs inducían diferenciación de adipocitos e incrementaban la expresión de genes de adipocitos, incluyendo la proteína de unión a ácidos grasos de adipocitos, aP2. En forma independiente, se descubrió que el PPARγ interactuaba con un elemento regulador del gen aP2 que controlaba su expresión específica en adipocitos. Sobre la base de estas observaciones fundamentales, se realizaron experimentos que determinaron que las TZDs eran ligandos y agonistas de PPARγ, y demostraron una correlación bien definida entre sus actividades de PPARγ *in vitro* y sus acciones de sensibilización a la insulina *in vivo*. (Bergen & Wagner, *supra*).

Varias TZDs, incluyendo troglitazona, rosiglitazona y pioglitazona, tienen actividad de sensibilización a la insulina y anti-diabética en humanos con diabetes tipo 2 e intolerancia a la glucosa. El farglitazar es un agonista selectivo de PPAR-γ, no TZD, muy potente, del cual se demostró recientemente que tiene eficacia anti-diabética, así como de alteración de lípidos en humanos. Además de estos potentes ligandos de PPARγ, un subconjunto de los fármacos anti-inflamatorios no esteroideos (NSAIDs), incluyendo indometacina, fenoprofeno e ibuprofeno, han mostrado actividades débiles de PPARγ y PPARα. (Bergen & Wagner, *supra*).

Los fibratos, ácidos carboxílicos anfipáticos que han probado ser útiles en el tratamiento de la hipertrigliceridemia, son ligandos de PPARα. El miembro prototípico de esta clase

de compuestos, clofibrato, se desarrolló antes de la identificación de los PPARs, usando ensayos *in vivo* en roedores para valorar la eficacia de disminución de lípidos. (Bergen & Wagner, *supra*).

Fu et al., *Nature*, 2003, 425:9093, demostraron que el compuesto de unión a PPARα, oleiletanolamida, produce saciedad y reduce la ganancia de peso corporal en ratones.

Se ha mostrado que el clofibrato y el fenofibrato activan a PPARα con una selectividad 10 veces por arriba de PPARγ. El bezafibrato actúa comc un pan-agonista que muestra una potencia similar sobre las tres isoformas de PPAR. Wy-14643, el análogo del ácido 2-ariltioacético del clofibrato, es un potente agonista de PPARα murino, asi como un débil agonista de PPARγ. En humanos, todos los fibratos deben usarse en dosis elevadas (200-1,200 mg/día) para conseguir una actividad eficaz de disminución de lípidos.

Se han identificado también TZDs y no TZDs que son agonistas duales de PPARγ/α. En virtud de de la actividad agonista de PPARα adicional, esta clase de compuestos tiene una potente eficacia de alteración de lípidos, además de actividad anti-hiperglicémica en modelos animales de diabetes y trastornos de lípidos. KRP-297 es un ejemplo de un agonista de PPARγ/α dual TZD (Fajas, 1997, *J. Biol. Chem.*, 272:18779-18789); adicionalmente, DRF-2725 y AZ-242 son agonistas de PPARγ/α duales, no TZD. (Lohray, et al., 2001, *J. Med. Chem.*, 44:2675-2678; Cronet, et al., 2001, Structure (Camb.) 9:699-706).

Con el fin de definir el papel fisiológico de PPARδ, se han hecho esfuerzos para desarrollar compuestos novedosos que activan este receptor de una manera selectiva. Entre los ácidos carboxílicos α-sustituidos previamente descritos, el potente ligando de PPARδ, L-165041, demostró selectividad de agonista de aproximadamente 30 veces para este receptor sobre PPARγ, y no fue activo sobre el PPARα murino (Liebowitz, et al., 2000, *FEBS Lett.*, **473**:333-336). Se encontró que este compuesto incrementa los niveles de lipoproteínas de alta densidad en roedores. Se reportó también que GW501516 era un potente agonista de PPARδ, altamente selectivo, que producía cambios benéficos en los parámetros de lípidos séricos en macacos obesos de la India resistentes a insulina. (Oliver et al., 2001, *Proc. Natl Acad. Sci.*, 98:5306-5311).

Además de los compuestos discutidos en lo anterior, se han descrito ciertos derivados de tiazol activos sobre los PPARs. (Cadilla et al., Solicitud Internacional

PCT/US01/149320, Publicación Internacional WO 02/062774, incorporadas en la presente para referencia en su totalidad.)

Se han descrito algunos ácidos tricíclic-α-alquiloxifenilpropiónicos como agonistas de PPARα/γ duales en Sauerberg et al., 2002, *J. Med. Chem.* 45:789-804.

Un grupo de compuestos que se estipula que tienen actividad igual sobre PPARα/γ/δ se describe en Morgensen et al., 2002, *Bioorg. & Med. Chem. Lett.* 13:257-260.

Oliver et al., describe un agonista de PPARδ selectivo que promueve el transporte inverso del colesterol. (Oliver, et al., *supra*)

Yamamoto et al., Patente Norteamericana No. 3,489,767 describe "derivados del ácido 1-(fenilsulfonil)-indolilalifático" que se estipula que tienen "acciones antiflogísticas, analgésicas y antipiréticas" (Col. 1, líneas 16-19.)

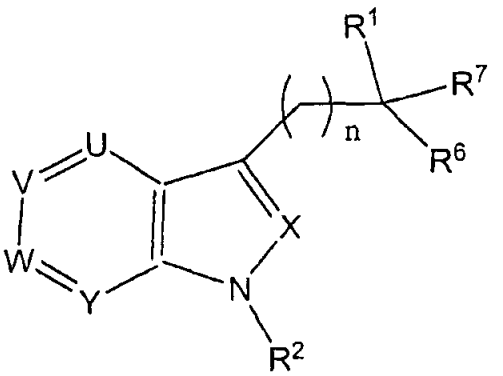
Kato, et al., Solicitud de Patente Europea 94101551.3, Publicación No. 0 610 793 A1, describe el uso de ácido 3-(5-metoxi-1-p-toluensulfonilindol-3-il)propiónico (página 6) y ácido 1-(2,3,6-triisopropilfenilsulfonil)-indol-3-propiónico (página 9) como intermediarios en la síntesis de derivados particulares de morfolina tetracíclica útiles como analgésicos.

Esta solicitud se relaciona con las siguientes solicitudes de patentes publicadas: WO 2005009958, US 20050038246, y US 20050288354, cada una de las cuales se incorpora por esto para referencia en la presente en sus totalidades, incluyendo todas las especificaciones, figuras, y tablas, y para todos los propósitos.

ARTE PREVIO

La presente invención se relaciona con compuestos activos sobre los PPARs, los cuales son útiles para una diversidad de aplicaciones, por ejemplo, métodos terapéuticos y/o profilácticos que involucran la modulación de por lo menos uno de PPARα, PPARδ, y PPARγ. Se incluyen compuestos que tienen pan-actividad significativa en toda la familia PPAR (PPARα, PPARδ, y PPARγ), así como compuestos que tienen especificidad significativa (por lo menos 5, 10, 20, 50, o 100 veces mayor actividad) sobre un solo PPAR, o sobre dos de los tres PPARs.

En una modalidad, la invención involucra el uso de compuestos de la Fórmula I como moduladores de uno o más de los PPARs, PPARα, PPARδ, y PPARγ, donde la Fórmula I es:



Fórmula I

todas las sales, profármacos, tautómeros e isómeros de los mismos, en donde:

U, V, W, X, y Y son independientemente N o CR^8, en donde, como máximo, dos de U, V, W, y Y son N;

R^1 se selecciona del grupo que consiste de $C(O)OR^{16}$ y un isóstero de ácido carboxílico;

R^2 se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$;

R^6 y R^7 se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido; o

R^6 y R^7 se combinan para formar un cicloalquilo monocíclico de 3-7 miembros o heterocicloalquilo monocíclico de 5-7 miembros;

R^8 se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^9, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$;

R^9 se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{10} y R^{11} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido; o

R^{10} y R^{11} junto con el nitrógeno al cual se unen, forman un heterocicloalquilo monocíclico de 5-7 miembros o un heteroarilo que contiene nitrógeno monocíclico de 5 ó 7 miembros;

R^{16} se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{20} se selecciona del grupo que consiste de $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{21} se selecciona del grupo que consiste de $-OR^{17}$, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{12}, R^{13}, R^{14} y R^{15} se seleccionan independientemente del grupo que consiste de alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

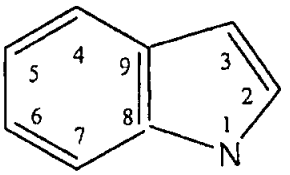
R^{17} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido y $-C(O)R^{18}$;

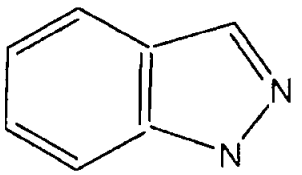
R^{18} se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

Z es O o S; y

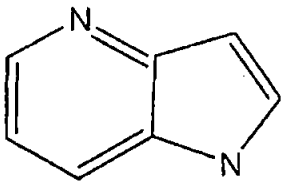
n = 0, 1 ó 2.

En algunas modalidades que involucran compuestos de la Fórmula I, el núcleo biciclico mostrado para la Fórmula I tiene una de las siguientes estructuras:

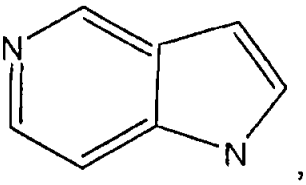




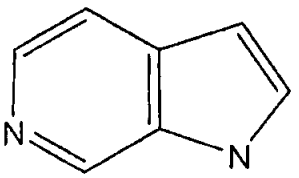
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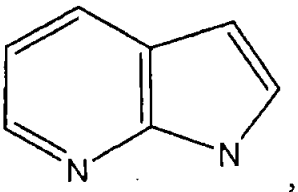
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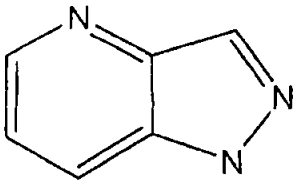
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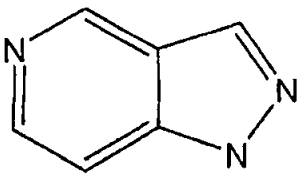
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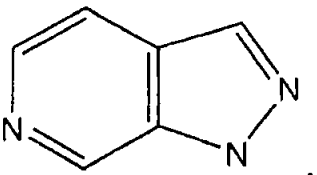
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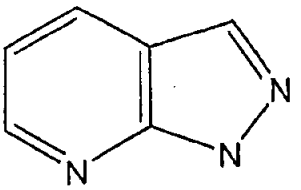
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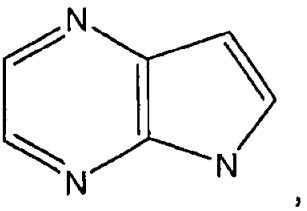
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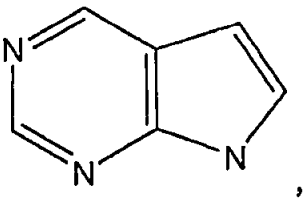
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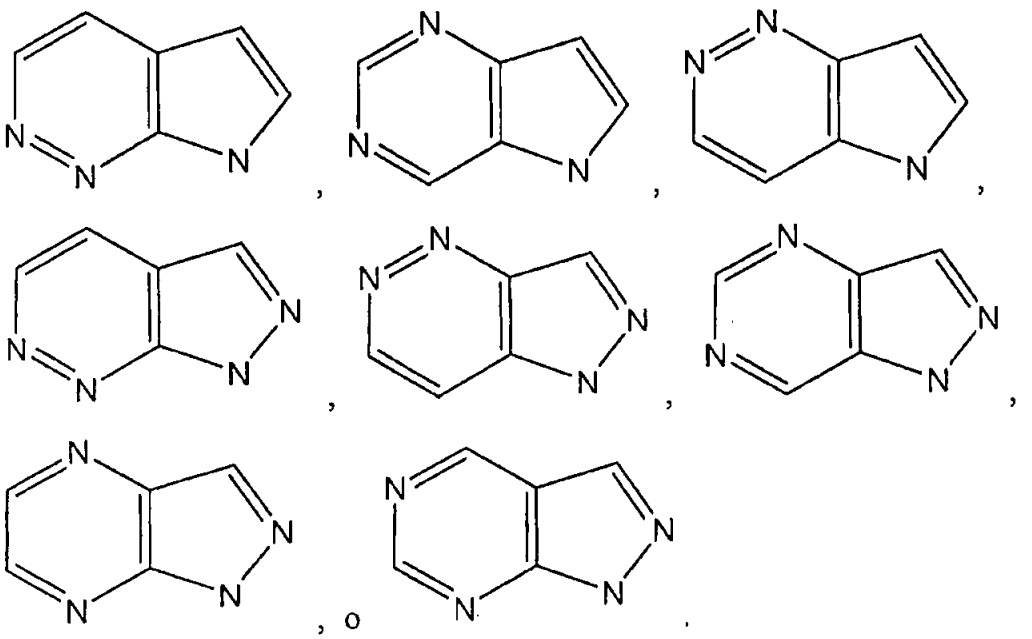
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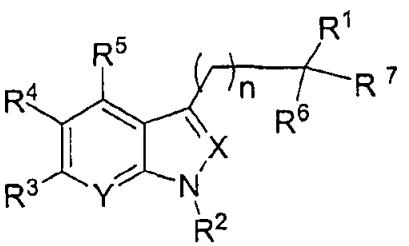
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la referencia a la numeración de posición de las estructuras bicíclicas proporcionadas en la presente, se basa en la numeración del indol como se muestra en lo anterior.

En algunas modalidades que involucran compuestos de la Fórmula I incluyendo un núcleo biciclico como se muestra en lo anterior, tales compuestos pueden incluir sustituyentes como se describe para la Fórmula I, con el entendimiento de que los nitrógenos del anillo, diferentes al nitrógeno que corresponde a la posición 1 de la estructura del indol, no son sustituidos. En algunas modalidades, los compuestos tienen uno de los núcleos bicíclicos mostrados en lo anterior y selecciones de sustitución como se muestra en la presente para los compuestos que tienen un núcleo indolilo; los compuestos tienen uno de los núcleos bicíclicos en lo anterior, y los sustituyentes mostrados en la posición 5 se unen en cambio en la posición 6.

En algunas modalidades que involucran compuestos de la Fórmula I, los compuestos tienen una estructura de la Fórmula Ia, es decir



Fórmula Ia

todas las sales, profármacos, tautómeros e isómeros de los mismos, en donde:

U es CR^8, en donde R^8 is R^5;

V es CR^8, en donde R^8 is R^4;

W es CR^8, en donde R^8 is R^3;

R^3, R^4 y R^5 se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^9, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$; y

n, X, Y, R^1, R^2, R^6, R^7, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{20} y R^{21} son como se define en la Fórmula I en lo anterior.

En algunas modalidades, tales compuestos son compuestos de la Fórmula I con Y=N; con $Y=CR^8$; con Y=CH; con todos los sustituyentes R diferentes a R^1, R^2 y R^4 como H (para cada uno de X como N, X como CH y X como CR^8); y con R^6 y R^7 como H (para cada uno de X como N, X como CH y X como CR^8).

En algunas modalidades, n=1; n=1 y X y/o Y es CH; n=1, X y/o Y es CH, y R^6 y R^7 son H; n=1 y X y/o $Y=CR^8$.

En algunas modalidades, n=1, R^2 es $-S(O)_2R^{21}$, con R^{21} siendo arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido. En algunas modalidades, en las cuales n=1, y R^2 es $-S(O)_2R^{21}$, con R^{21} siendo arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, el grupo arilo es un anillo de 5 ó 6 miembros; el grupo arilo es un anillo de 6 miembros; en modalidades adicionales en las cuales el grupo arilo es un anillo de 6 miembros, el anillo se sustituye con uno o dos grupos seleccionados independientemente del grupo que consiste de halógeno, alquilo inferior sustituido con arilo, alquilo inferior sustituido con heteroarilo, alcoxi inferior, alcoxi inferior sustituido con arilo, alcoxi inferior sustituido con heteroarilo, cicloalquilo, arilo, ariloxi, heteroarilo y heteroariloxi; en modalidades adicionales en las cuales un anillo de 6 miembros se sustituye con halógeno o alcoxi inferior, el anillo se sustituye en la posición 3 (meta), posición 4 (para) o posiciones 3 y 4 (meta y para); en modalidades adicionales en las cuales un

anillo de 6 miembros se sustituye en la posición 4 o posiciones 3 y 4, o el sustituyente de la posición 4 es alquilo inferior, o el sustituyente de la posición 4 no es alquilo inferior, o el sustituyente de la posición 4 es halógeno (por ejemplo, flúor o cloro), o los sustituyentes de la posición 3 y 4 son flúor, o los sustituyentes de la posición 3 y 4 son cloro, o uno de los sustituyentes de la posición 3 y 4 es flúor y el otro es cloro, o la posición 3 es halógeno (por ejemplo, flúor o cloro) y la posición 4 es alcoxi inferior (por ejemplo, metoxi o etoxi), o la posición 3 es alcoxi inferior (por ejemplo, metoxi o etoxi) y la posición 4 es halógeno (por ejemplo, flúor o cloro), o la posición 3 es cloro y la posición 4 es alcoxi inferior, o la posición 3 es alcoxi inferior y la posición 4 es cloro; o el anillo de 6 miembros se fusiona con un segundo anillo carbocíclico o heterocíclico, aromático o no aromático de 5 ó 6 miembros. En modalidades adicionales en las cuales el grupo arilo es un anillo de 5 miembros, el anillo se sustituye con uno o dos grupos ubicados en posiciones del anillo no adyacentes al átomo del anillo enlazado al grupo $-S(O)_2-$; o el anillo de 5 miembros se sustituye con uno o dos sustituyentes de anillo seleccionados del grupo que consiste de halógeno, alquilo inferior sustituido con arilo, alquilo inferior sustituido con heteroarilo, alcoxi inferior, alcoxi inferior sustituido con arilo, alcoxi inferior sustituido con heteroarilo, cicloalquilo, arilo, ariloxi, heteroarilo y heteroariloxi; el anillo se sustituye con cloro; el anillo se sustituye con alcoxi inferior; o el anillo se sustituye con alquilo inferior; o el anillo se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido; o el anillo se sustituye con ariloxi opcionalmente sustituido o heteroariloxi opcionalmente sustituido; o el anillo de 5 miembros se fusiona con un segundo anillo carbocíclico o heterocíclico, aromático o no aromático de 5 o 6 miembros.

En algunas modalidades en las cuales n=1 y R^2 es $-S(O)_2R^{21}$, con R^{21} siendo arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, R^4 no es H o alcoxi inferior, o R^4 no es H u OR^9.

En algunas modalidades, n=2; o n=2 y X y/o Y es CH; o n=2, X y/o Y es CH, y R^6 y R^7 son H; o n=2 y X y/o $Y=CR^8$; o n=2 y X y/o Y son N.

En algunas modalidades en las cuales n=2, R^4 no es H, halógeno, alquilo inferior, alcoxi inferior o alquiltio inferior; o R^4 no es H, halógeno, alquilo de 1 a 3 átomos de carbono, alcoxi

de 1 a 3 átomos de carbono o alquiltio de 1 a 3 átomos de carbono; R^4 no es alcoxi de 1 a 3 átomos de carbono; o R^4 no es metoxi.

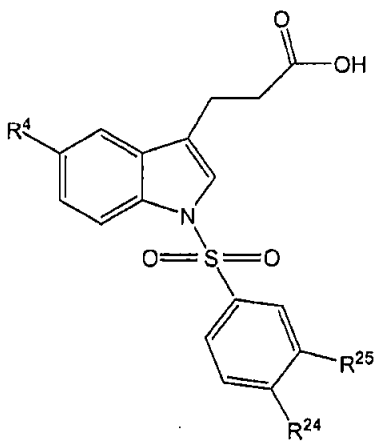
En algunas modalidades, n=2, R^2 es $-S(O)_2R^{21}$, con R^{21} siendo arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido. En algunas modalidades, en las cuales n=2, y R^2 es $-S(O)_2R^{21}$, con R^{21} siendo arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, el grupo arilo es un anillo de 5 ó 6 miembros; o el grupo arilo es un anillo de 6 miembros; en modalidades adicionales en las cuales el grupo arilo es un anillo de 6 miembros, el anillo se sustituye con uno o dos grupos seleccionados independientemente del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con arilo, alquilo inferior sustituido con heteroarilo, alcoxi inferior sustituido con arilo, alcoxi inferior sustituido con heteroarilo, cicloalquilo, arilo, ariloxi, heteroarilo y heteroariloxi; en modalidades adicionales en las cuales un anillo de 6 miembros se sustituye con halógeno o alcoxi inferior, el anillo se sustituye en la posición 3 (meta), posición 4 (para) o posiciones 3 y 4 (meta y para); en modalidades adicionales en las cuales un anillo de 6 miembros se sustituye en la posición 4 o posiciones 3 y 4, el sustituyente de la posición 4 es alquilo inferior inferior, o el sustituyente de la posición 4 no es alquilo inferior, o el sustituyente de la posición 4 es halógeno (por ejemplo, flúor o cloro), o los sustituyentes de la posición 3 y 4 son flúor, o los sustituyentes de la posición 3 y 4 son cloro, o uno de los sustituyentes de la posición 3 y 4 es flúor y el otro es cloro, o la posición 3 es halógeno (por ejemplo, flúor o cloro) y la posición 4 es alcoxi inferior (por ejemplo, metoxi o etoxi), o la posición 3 es alcoxi inferior (por ejemplo, metoxi o etoxi) y la posición 4 es halógeno (por ejemplo, flúor o cloro), o la posición 3 es cloro y la posición 4 es alcoxi inferior, o la posición 3 es alcoxi inferior y la posición 4 es cloro; o el anillo de 6 miembros se fusiona con un segundo anillo carbocíclico o heterocíclico, aromático o no aromático de 5 ó 6 miembros. En modalidades adicionales en las cuales el grupo arilo es un anillo de 5 miembros, el anillo se sustituye con uno o dos grupos ubicados en posiciones del anillo no adyacentes al átomo del anillo enlazado al grupo $-S(O)_2-$; o el anillo de 5 miembros se sustituye con uno o dos sustituyentes de anillo seleccionados del grupo que consiste de halógeno, alquilo inferior sustituido con arilo, alquilo inferior sustituido con heteroarilo, alcoxi inferior, alcoxi inferior sustituido con arilo, alcoxi inferior sustituido con heteroarilo, cicloalquilo, arilo, ariloxi, heteroarilo y

heteroariloxi; o el anillo se sustituye con cloro; o el anillo se sustituye con alcoxi inferior; o el anillo se sustituye con alquilo inferior; o el anillo se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido; o el anillo se sustituye con ariloxi opcionalmente sustituido o heteroariloxi opcionalmente sustituido; o el anillo de 5 miembros se fusiona con un segundo anillo carbocíclico o heterocíclico, aromático o no aromático de 5 o 6 miembros.

En algunas modalidades, en las cuales n=2 y R^2 es $-S(O)_2R^{21}$, con R^{21} siendo un grupo arilo de 6 miembros sustituido, la sustitución en el grupo arilo no es metoxi, o la sustitución en el grupo arilo no es alcoxi inferior; o R^4 y la sustitución en el grupo arilo no son alcoxi inferior; o R^4 y la sustitución en el grupo arilo no son metoxi; o R^4 no es alcoxi inferior; o R^4 no es metoxi.

Ciertas modalidades adicionales incluyen compuestos descritos para las modalidades correspondientes como se describe en lo anterior para n=1 y n=2.

En algunas modalidades, los compuestos de la Fórmula I tienen una estructura de la Fórmula Ib como se muestra en lo siguiente:



Fórmula Ib

todas las sales, profármacos, tautómeros e isómeros de los mismos, en donde:

U es CR^8, en donde R^8 is H;

V es CR^8, en donde R^8 is R^4;

W es CR^8, en donde R^8 is H;

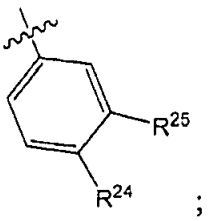
X es CR^8, en donde R^8 is H;

Y es CR^8, en donde R^8 is H;

n es 1;

R^1 es -COOH;

R^6 y R^7 son hidrógeno;



;

R^2 es $-S(O)_2R^{21}$, en donde R^{21} es

R^4 se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^9, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$;

R^{24} se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, $-OR^{19}$ y $-O(CH_2)_pO$-arilo;

p es 1, 2, 3 ó 4;

R^{25} se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido y $-OR^{19}$; o

R^{24} y R^{25} se combinan para formar cicloalquilo, heterocicloalquilo, arilo o heteroarilo fusionado con el anillo fenilo;

R^{19} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido y arilo opcionalmente sustituido; y

R^9, R^{10}, R^{11}, R^{20} y R^{21} son como se define en la Fórmula I en lo anterior.

En algunas modalidades, R^4 es alcoxi inferior opcionalmente sustituido (por ejemplo, metoxi, etoxi, propoxi, isopropoxi), ariloxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, alquilo inferior opcionalmente sustituido (por ejemplo, metilo o etilo), cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o halógeno.

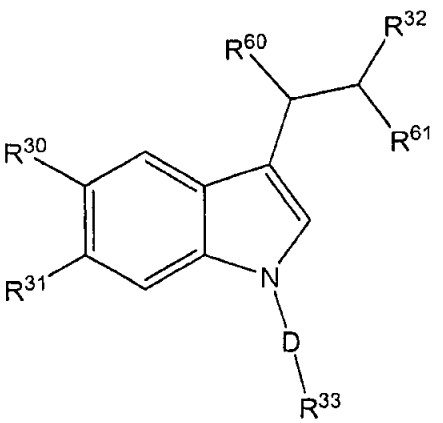
En algunas modalidades, R^4 es alcoxi inferior opcionalmente sustituido (por ejemplo, metoxi, etoxi, propoxi, isopropoxi), alquilo inferior opcionalmente sustituido (por ejemplo, metilo o etilo), arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o halógeno.

En algunas modalidades, los compuestos de la Fórmula I pueden ser como se especifica para la Fórmula Ib, pero con el anillo fenilo al cual se unen R^{24} y R^{25} como un anillo heteroarilo, en donde cuando el anillo heteroarilo es un anillo de 5 miembros, R^{24} y R^{25} no se unen a los átomos del anillo de 5 miembros que se encuentran adyacentes al átomo del anillo de 5 miembros unido al grupo sulfonilo mostrado en la Fórmula Ib.

En algunas modalidades de los compuestos de la Fórmula Ib, R^4 es alcoxi inferior y R^{24} y R^{25} son cloro; o R^4 es alcoxi inferior y R^{24} y R^{25} son flúor; o R^4 es alcoxi inferior y R^{24} es alcoxi inferior; o R^4 es alcoxi inferior y R^{24} es alquilo inferior; o R^4 es metoxi o etoxi y R^{24} y R^{25} son cloro; o R^4 es metoxi o etoxi y R^{24} es alcoxi inferior; o R^4 es metoxi o etoxi y R^{24} es alquilo inferior.

En algunas modalidades de los compuestos de la Fórmula Ib, R^{24} y R^{25} no son alquilo inferior; o R^{24} es H y R^{25} no es alquilo inferior; o R^{25} es H y R^{24} no es alquilo inferior.

En algunas modalidades, la invención involucra compuestos de la Fórmula II como sigue:



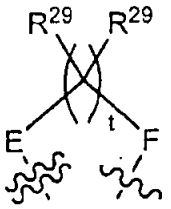
Fórmula II

todas las sales, profármacos, tautómeros e isómeros de los mismos,

en donde:

R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido,

alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, y $-S(O)_nR^{41}$; o

R30 y R31 se combinan para formar un anillo fusionado, en donde los R30 y R31 combinados son de la fórmula 

, en donde  indica el punto de unión de R30 al anillo indol y  indica el punto de unión de R31 al anillo indol;

E y F se seleccionan independientemente del grupo que consiste de $CR^{29}R^{29}$, O, $S(O)_2$ y NR^{44};

R^{29} en cada caso, se selecciona independientemente del grupo que consiste de hidrógeno, flúor, alquilo inferior opcionalmente sustituido con flúor, alcoxi inferior opcionalmente sustituido con flúor y alquiltio inferior opcionalmente sustituido con flúor;

R^{44} es hidrógeno o alquilo inferior;

t es 1 ó 2;

R^{32} se selecciona del grupo que consiste de $C(O)OR^{26}$, $-C(O)NR^{27}R^{28}$ y un isóstero de ácido carboxílico;

R^{33} es $L-R^{42}$ o heteroarilo opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-NO_2$, -CN $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

L es $-(CR^{51}R^{52})_m-$ o $-CR^{55}=CR^{56}-$;

D es $-CR^{51}R^{52}-$ o $-S(O)_2-$;

R^{34} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{34} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al O de $-OR^{34}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{34} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al O de $-OR^{34}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)R^{40}$ y $-C(Z)NR^{38}R^{39}$;

R^{35} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{35} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al S de $-SR^{35}$ o al O de $-OR^{35}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{35} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al S de $-SR^{35}$ o al O de $-OR^{35}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{36} y R^{37} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{36} y/o R^{37} son alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $-NR^{36}R^{37}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{36} y/o R^{37} son alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $-NR^{36}R^{37}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$ y $-S(O)_2NR^{38}R^{39}$;

R^{38} y R^{39} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente

sustituido, con la condición, sin embargo, de que cuando R^{38} y/o R^{39} son alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $NR^{38}R^{39}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{38} y/o R^{39} son alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $NR^{38}R^{39}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{40} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{40} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une a -C(Z)-, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{40} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une a -C(Z)-, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, y $-OR^{35}$;

R^{41} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{41} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une a $-S(O)_n-$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{41} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une a $-S(O)_n-$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{42} es arilo o heteroarilo, en donde arilo o heteroarilo se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido,

heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-NO_2$, -CN - OR^{34}, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

R^{51} y R^{52} se seleccionan independientemente del grupo que consiste de hidrógeno, flúor, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

o cualesquiera dos de Ra^{51} y R^{52} en el mismo carbono o en carbonos adyacentes pueden combinarse para formar un cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido o heterocicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido;

R^{55} y R^{56} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido; o

R^{55} y R^{56} se combinan para formar un cicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido o heterocicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido;

R^{60} y R^{61} son cada uno hidrógeno, o R^{60} y R^{61} se combinan para formar cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido;

R^{26} se selecciona del grupo que consiste de hidrógeno, alquilo inferior, fenilo, heteroarilo monocíclico de 5-7 miembros, cicloalquilo monocíclico de 3-7 miembros y heterocicloalquilo monocíclico de 5-7 miembros, en donde fenilo, heteroarilo monocíclico, cicloalquilo monocíclico y heterocicloalquilo monocíclico se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, y alquiltio inferior sustituido con flúor, y en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, -OH, $-NH_2$, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor, con la condición, sin embargo, de que cuando R^{26} es alquilo inferior, cualquier sustitución en el carbono del alquilo inferior enlazado al O de OR^{26} es flúor;

R^{27} y R^{28} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior, fenilo, heteroarilo monocíclico de 5-7 miembros, cicloalquilo monocíclico de 3-7 miembros y heterocicloalquilo monocíclico de 5-7 miembros, en donde fenilo, heteroarilo monocíclico, cicloalquilo monocíclico y heterocicloalquilo monocíclico se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor, y en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, -OH, $-NH_2$, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor, con la condición, sin embargo, de que cuando R^{27} y/o R^{28} es alquilo inferior, cualquier sustitución en el carbono del alquilo inferior enlazado al N de $NR^{27}N^{28}$ es flúor; o

R27 y R28, junto con el nitrógeno al cual se unen, forman un heterocicloalquilo monocíclico de 5-7 miembros o un heteroarilo monocíclico que contiene nitrógeno de 5 ó 7 miembros, en donde el heterocicloalquilo monocíclico o heteroarilo que contiene nitrógeno monociclico se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor;

n es 1 ó 2;

m es 1, 2 ó 3; y

Z es O o S, con la condición, sin embargo, de que cuando D es $-S(O)_2-$, R^{30} es $-OCH_3$, R^{31} es H y R^{32} es -COOH o $-COOCH_3$, R^{33} no es tiofenilo no sustituido

En una modalidad de los compuestos de la Fórmula II, R^{33} no es tiofenilo no sustituido. En otra modalidad, R^{33} es heteroarilo sustituido. En otra modalidad, R^{33} es heteroarilo sustituido con uno o más sustituyentes seleccionados del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, -

$C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$, en donde uno de R^{36} y R^{37} se selecciona del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$ y $-S(O)_2NR^{38}R^{39}$, y el otro de R^{36} y R^{37} es hidrógeno o alquilo inferior, uno de R^{38} y R^{39} se selecciona del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, y el otro de R^{38} y R^{39} es hidrógeno o alquilo inferior, y en donde R^{34}, R^{35}, R^{40} y R^{41} se seleccionan independientemente del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido.

En una modalidad de los compuestos de la Fórmula II, R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido, ariloxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, o R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2, y cada R^{29} es hidrógeno. En una modalidad, R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno y alcoxi inferior opcionalmente sustituido, de preferencia en donde R^{31} es hidrógeno y R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior.

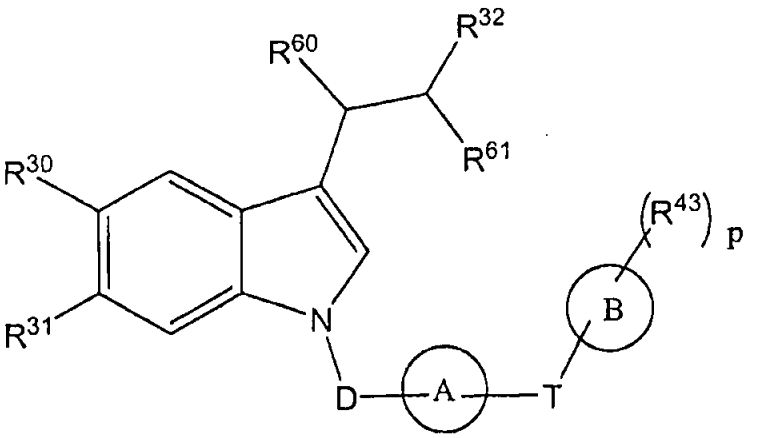
En una modalidad de los compuestos de la Fórmula II, D es $-CR^{51}R^{52}-$, en donde cada R^{51} y R^{52} son independientemente halógeno o alquilo inferior opcionalmente sustituido, o cualesquiera dos de R^{51} y R^{52} en el mismo carbono o en carbonos adyacentes, se combinan para formar un cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido o heterocicloalquilo

monociclico de 3-7 miembros opcionalmente sustituido, R^{33} es heteroarilo sustituido, y R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, y alcoxi inferior opcionalmente sustituido, de preferencia en donde D es $-CH_2-$, R^{31} es hidrógeno y R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior.

En una modalidad de los compuestos de la Fórmula II, D es $-S(O)_2-$, R^{33} es heteroarilo sustituido y R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno y alcoxi inferior opcionalmente sustituido, de preferencia en donde R^{31} es hidrógeno y R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior.

Con relación a cualquiera de las modalidades anteriores de los compuestos de la Fórmula II, R^{60} y R^{61} son hidrógeno y R^{32} es $-C(O)OR^{26}$, de preferencia -COOH.

En algunas modalidades, la invención involucra compuestos de la Fórmula III como sigue:



Fórmula III

todas las sales, profármacos, tautómeros e isómeros de los mismos, en donde:

D, R^{30}, R^{31}, R^{32}, R^{60} y R^{61} son como se define en la Fórmula II;

A es arileno o heteroarileno, en donde el arileno o heteroarileno se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, alquilo inferior, alcoxi inferior y alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con uno o más

sustituyentes seleccionados del grupo que consiste de flúor, -OH, alcoxi inferior y alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor;

T es un enlace covalente o se selecciona del grupo que consiste de $-(CR^{51}R^{52})_m-$, $-(CR^{51}R^{52})_qO(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{53}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(O)_n(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}S(O)_2(CR^{51}R^{52})_r-$, $(CR^{51}R^{52})_qS(O)_2NR^{54}(CR^{51}R^{52})_r-$ y $-(CR^{51}R^{52})_qNR^{54}S(O)_2NR^{54}(CR^{51}R^{52})_r$, en donde R^{51}, R^{52} y m son como se define en la Fórmula II en lo anterior;

q y r son independientemente 0, 1 ó 2;

B se selecciona del grupo que consiste de cicloalquilo, heterocicloalquilo, arilo y heteroarilo;

R^{43} en cada caso se selecciona independientemente del grupo que consiste de halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

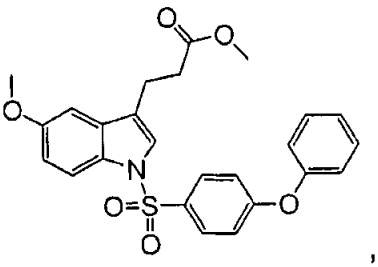
R^{53} se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{53} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $-NR^{53}-$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{53} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $-NR^{53}-$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_2R^{41}$;

R^{54}, en cada caso, se selecciona independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono

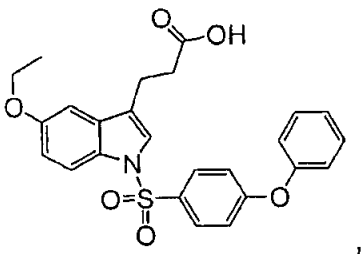
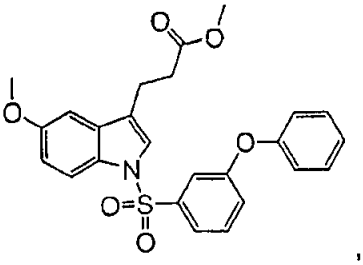
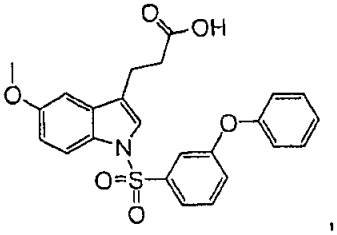
opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{54} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $-NR^{54}-$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{54} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $-NR^{54}-$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

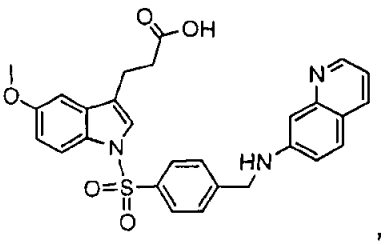
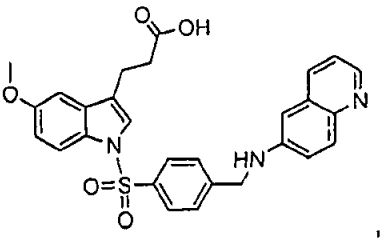
p es 0, 1, 2 ó 3; y

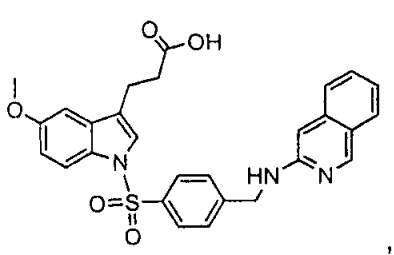
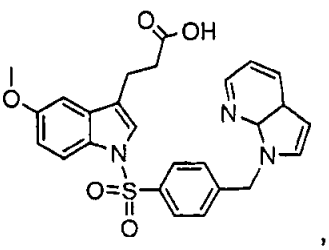
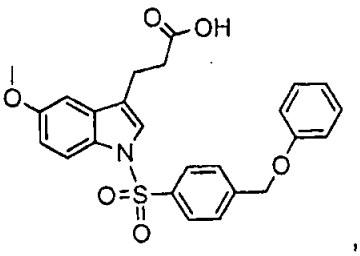
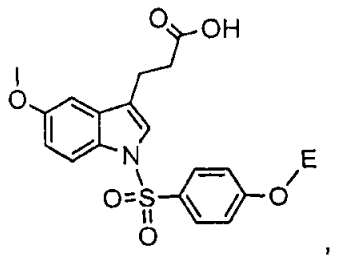
n, Z, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} y R^{41} son como se define para la Fórmula II en lo anterior,

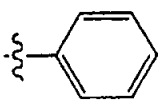
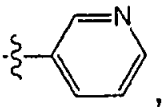
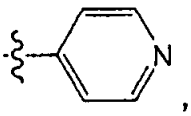
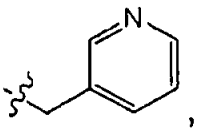
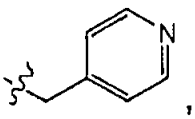


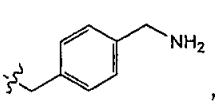
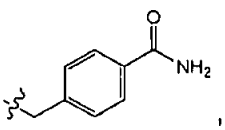
con la condición, sin embargo, de que el compuesto no sea

en donde E es  ,  ,  ,  ,  ,

 , o  , en donde  indica el punto de unión de E a O.

En una modalidad de los compuestos de la Fórmula III, cuando A es fenilo, T es meta o para hacia D y B es fenilo, piridinilo, 7-azaindolilo o quinolinilo, entonces p es 1, 2 ó 3, con la condición, sin embargo, de que cuando T es $-OCR^{51}R^{52}-$ y para hacia D, B es fenilo, p es 1 y R^{43} es para hacia T, R^{43} no es CH_2NH_2 o $C(O)NH_2$. En otra modalidad, A es diferente a fenilo. En otra modalidad, B es diferente a fenilo, piridinilo, 7-azaindolilo o quinolinilo.

En una modalidad de los compuestos de la Fórmula III, A es heteroarilo opcionalmente sustituido con halógeno, -OH, alquilo inferior, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor.

En una modalidad, R^{43} se selecciona del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$, en donde R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} y R^{41} no son cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o alquilo inferior sustituido con cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido. En una modalidad, A es heteroarilo opcionalmente sustituido con halógeno, -OH, alquilo inferior, alcoxi inferior, o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior, o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor, y R^{43} se selecciona del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$, en donde R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} y R^{41} no son cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o alquilo inferior sustituido con cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido.

En una modalidad de los compuestos de la Fórmula III, R^{30} y R^{31} se seleccionan del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido, ariloxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, o R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2 y cada R^{29} es hidrógeno. En una modalidad, R^{30} y R^{31} en forma independiente son alcoxi inferior opcionalmente sustituido, o R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2 y cada R^{29} es hidrógeno. En una modalidad, R^{30} y R^{31} se seleccionan independientemente del grupo que consiste

de hidrógeno, halógeno y alcoxi inferior opcionalmente sustituido, de preferencia en donde R^{31} es hidrógeno y R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior.

En otra modalidad de los compuestos de la Fórmula III, A es fenilo y T-B son orto hacia D. En una modalidad, A es heteroarilo opcionalmente sustituido con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor. En una modalidad, A es fenilo opcionalmente sustituido con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior o alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor y T-B son orto hacia D.

En otra modalidad de los compuestos de la Fórmula III, R^{53} y R^{54} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido. En otra modalidad, R^{53} y R^{54} son independientemente hidrógeno o alquilo inferior opcionalmente sustituido, donde el alquilo inferior de preferencia se sustituye opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que la sustitución del carbono que se enlaza al N de $-NR^{53}-$ o $-NR^{54}-$ es flúor.

En una modalidad de los compuestos de la Fórmula III, D es $-S(O)_2-$, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A se sustituye opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor y T es un enlace covalente, -O- o NCH_3-. En una

modalidad, D es $-S(O)_2-$, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A se sustituye opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior, o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior, o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor, T es un enlace covalente, -O- o $-NCH_3-$ y cada R^{43} se selecciona independientemente del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido y alquiltio inferior opcionalmente sustituido, de preferencia halógeno, alquilo inferior, -OH, alcoxi inferior, o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior, o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor.

En una modalidad de los compuestos de la Fórmula III, D es $-S(O)_2-$, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A es fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo, en donde fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo se sustituyen opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor, T es un enlace covalente, -O- o NCH_3- y B es fenilo, piridinilo, pirazolilo o isoxazolilo. En una modalidad, D es $-S(O)_2-$, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A es fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo, en donde fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo se sustituyen opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o

S del alquiltio inferior es flúor, T es un enlace covalente, -O- o -NCH_3-, B es fenilo, piridinilo, pirazolilo o isoxazolilo y cada R^{43} se selecciona independientemente del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido y alquiltio inferior opcionalmente sustituido, de preferencia halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor.

En una modalidad de los compuestos de la Fórmula III, D es -$S(O)_2$-, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A es fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo, en donde fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo se sustituyen opcionalmente con flúor, cloro, alquilo inferior opcionalmente sustituido con flúor, o alcoxi inferior opcionalmente sustituido con flúor, T es un enlace covalente, -O-, o -NCH_3-, B es fenilo, piridinilo, pirazolilo o isoxazolilo y cada R^{43} se selecciona independientemente del grupo que consiste de flúor, cloro, alquilo inferior opcionalmente sustituido con flúor y alcoxi inferior opcionalmente sustituido con flúor.

En una modalidad de los compuestos de la Fórmula III, D es -$CR^{51}R^{52}$-, de preferencia -CH_2-, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A se sustituye opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor y T es un enlace covalente, -O- o NCH_3-. En una modalidad, D es -$CR^{51}R^{52}$-, de preferencia -CH_2-, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A se sustituye opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior, o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior, o alquiltio

inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor, T es un enlace covalente, -O- o -NCH_3- y cada R^{43} se selecciona independientemente del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido y alquiltio inferior opcionalmente sustituido, de preferencia halógeno, alquilo inferior, -OH, alcoxi inferior, o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior, o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor.

En una modalidad de los compuestos de la Fórmula III, D es -$CR^{51}R^{52}$-, de preferencia -CH_2-, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A es fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo, en donde fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo se sustituyen opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor, T es un enlace covalente, -O- o NCH_3- y B es fenilo, piridinilo, pirazolilo o isoxazolilo. En una modalidad, D es -$CR^{51}R^{52}$-, de preferencia -CH_2-, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A es fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo, en donde fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo se sustituyen opcionalmente con halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor, T es un enlace covalente, -O- o -NCH_3-, B es fenilo, piridinilo, pirazolilo o isoxazolilo y cada R^{43} se selecciona independientemente del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido y alquiltio inferior

opcionalmente sustituido, de preferencia halógeno, alquilo inferior, -OH, alcoxi inferior o alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con flúor, -OH, alcoxi inferior o alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor.

En una modalidad de los compuestos de la Fórmula III, D es $-CR^{51}R^{52}-$, de preferencia $-CH_2-$, R^{60} y R^{61} son hidrógeno, R^{31} es hidrógeno, R^{30} es halógeno o alcoxi inferior opcionalmente sustituido con flúor, de preferencia alcoxi inferior, A es fenilo, tiofenilo, piridinilo, tiazolilo u oxazolilo opcionalmente sustituido con flúor, cloro, alquilo inferior opcionalmente sustituido con flúor o alcoxi inferior opcionalmente sustituido con flúor, T es un enlace covalente, -O- o $-NCH_3-$, B es fenilo, piridinilo, pirazolilo o isoxazolilo y cada R^{43} se selecciona independientemente del grupo que consiste de flúor, cloro, alquilo inferior opcionalmente sustituido con flúor y alcoxi inferior opcionalmente sustituido con flúor.

Con relación a cualquiera de las modalidades anteriores de los compuestos de la Fórmula III, R^{32} es $-C(O)OR^{26}$, de preferencia -COOH.

En algunas modalidades de los compuestos anteriores, se excluyen compuestos donde N (excepto donde N es un átomo de anillo heteroarilo), O o S se enlaza a un carbono que también se enlaza a N (excepto donde N es un átomo de anillo heteroarilo), O o S; o donde N (excepto donde N es un átomo de anillo heteroarilo), O, C(S), C(O), o S(O)n (n es 0-2) se enlaza a un carbono de alqueno de un grupo alquenilo o se enlaza a un carbono de alquino de un grupo alquinilo; por consiguiente, en algunas modalidades, los compuestos que incluyen enlazamientos tales como los siguientes se excluyen de la presente invención: $-NR-CH_2-NR-$, $-O-CH_2-NR-$, $-S-CH_2-NR-$, $-NR-CH_2-O-$, $-O-CH_2-O-$, $-S-CH_2-O-$, $-NR-CH_2-S-$, $-O-CH_2-S-$, $-S-CH_2-S-$, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, $-S(O)_{0-2}-CH=CH-$, $-CH=CH-S(O)_{0-2}-$, $-S(O)_{0-2}-C≡C-$, $-C≡C-S(O)_{0-2}-$, -C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)- o -C(S)-C≡C-.

Con referencia a los compuestos de las Fórmulas I, II y III en la presente, se incluye una referencia específica a sub-grupos y especies de los compuestos de las Fórmulas I, II y III descritas en la presente (incluyendo todas las modalidades como se describe en lo anterior, por ejemplo, la referencia a la Fórmula I incluye referencia a las Fórmulas Ia y Ib) a menos que se indique lo contrario. Al especificar un compuesto o compuestos de las Fórmulas I, II o III, a menos que se indique claramente lo contrario, la especificación de tal o tales compuestos incluye sales farmacéuticamente aceptables del o los compuestos.

Otro aspecto de la invención se relaciona con el uso novedoso de compuestos de las Fórmulas I, Ia, Ib, II o III para el tratamiento de enfermedades asociadas con los PPARs.

Otro aspecto de esta invención proporciona composiciones que incluyen una cantidad terapéuticamente efectiva de un compuesto de las Fórmulas II o III y por lo menos un portador, excipiente y/o diluyente farmacéuticamente aceptable. La composición puede incluir una pluralidad de diferentes compuestos farmacológicamente activos, incluyendo uno o más compuestos de las Fórmulas I, II o III.

En otro aspecto, los compuestos de las Fórmulas II o III pueden usarse en la preparación de un medicamento para el tratamiento de una enfermedad o padecimiento mediado por PPAR, o una enfermedad o padecimiento en el cual la modulación de un PPAR proporciona un beneficio terapéutico. En un aspecto adicional, la enfermedad o padecimiento se selecciona del grupo que consiste de trastornos de peso (por ejemplo, obesidad, condición de sobrepeso, bulimia y anorexia nerviosa), trastornos de lípidos (por ejemplo, hiperlipidemia, dislipidemia incluyendo dislipidemia diabética asociada y dislipidemia-hipoalfalipoproteinemia mixta, hipertrigliceridemia, hipercolesterolemia y baja HDL (lipoproteína de alta densidad)), trastornos metabólicos (por ejemplo, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, complicación diabética incluyendo neuropatía, nefropatía, retinopatía, úlcera de pies y cataratas por diabetes), enfermedad cardiovascular (por ejemplo, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, apoplejía, enfermedad cerebrovascular, infarto del miocardio, enfermedad vascular periférica), enfermedades inflamatorias (por ejemplo, enfermedades

autoinmunes tales como vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren y esclerosis múltiple, enfermedades que involucran inflamación de vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica, e inflamación en otros órganos, tales como enfermedad renal poliquística (PKD), síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), trastornos cutáneos (por ejemplo, enfermedades hiperproliferativas epiteliales tales como eccema y psoriasis, dermatitis, incluyendo dermatitis atópica, dermatitis por contacto, dermatitis alérgica y dermatitis crónica y cicatrización defectuosa), trastornos neurodegenerativos (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal y enfermedad desmielinizante, incluyendo encefalomielitis diseminada aguda y síndrome de Guillain-Barre), trastornos de coagulación (por ejemplo, trombosis), trastornos gastrointestinales (por ejemplo, infarto del intestino grueso o delgado), trastornos genitourinarios (por ejemplo, insuficiencia renal, disfunción eréctil, incontinencia urinaria y vejiga neurogénica), trastornos oftálmicos (por ejemplo, inflamación oftálmica, degeneración macular y neovascularización patológica), infecciones (por ejemplo, HCV, HIV y Helicobacter pylori), dolor neuropático o inflamatorio, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de obesidad, condición de sobrepeso, bulimia, anorexia nerviosa, hiperlipidemia, dislipidemia, hipoalfalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, una complicación diabética de neuropatía, nefropatía, retinopatía, cataratas, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, eccema, psoriasis, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, trombosis, degeneración macular, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de

vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático, dolor inflamatorio e infertilidad. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular

En otro aspecto, la invención proporciona equipos que incluyen un compuesto o composición como se describe en la presente. En algunas modalidades, el compuesto o composición se empaca, por ejemplo, en un frasco, una botella, un matraz, el cual puede empacarse además, por ejemplo, dentro de una caja, envoltura o bolsa; el compuesto o composición se aprueba por la Administración de Alimentos y Fármacos de los Estados Unidos, o agencia reguladora similar, para su administración a un mamífero, por ejemplo, un humano; el compuesto o composición se aprueba para su administración a un mamífero, por ejemplo, un humano para una enfermedad o padecimiento mediado por PPAR; el equipo incluye instrucciones escritas u otra indicación de que el compuesto o composición es adecuado o se aprueba para su administración a un mamífero, por ejemplo, un humano, para una enfermedad o padecimiento mediado por PPAR; el compuesto o composición se empaca en forma de dosis unitaria o dosis única, por ejemplo, píldoras, cápsulas o similares de dosis única. En algunas modalidades, el compuesto o composición de los equipos de la invención se aprueba para una indicación médica

seleccionada del grupo que consiste de obesidad, condición de sobrepeso, bulimia, anorexia nerviosa, hiperlipidemia, dislipidemia, hipoalfalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, baja HDL, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, una complicación diabética de neuropatía, nefropatía, retinopatía, úlcera de pies por diabetes o cataratas, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, apoplejía, enfermedad cerebrovascular, infarto del miocardio, enfermedad vascular periférica, vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis, hepatitis, eccema, psoriasis, dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, trombosis, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático o inflamatorio, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica,

inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático, dolor inflamatorio e infertilidad En algunas modalidades, el compuesto o composición de los equipos de la invención se aprueba para una indicación médica seleccionada del grupo que consiste de obesidad, condición de sobrepeso, bulimia, anorexia nerviosa, hiperlipidemia, dislipidemia, hipoalfalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, una complicación diabética de neuropatía, nefropatía, retinopatía, cataratas, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, eccema, psoriasis, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, trombosis, degeneración macular, infertilidad y cáncer. En algunas modalidades, el compuesto o composición de los equipos de la invención se aprueba para una indicación médica seleccionada del grupo que consiste de vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático, dolor inflamatorio e infertilidad. En algunas modalidades, el compuesto o composición de los equipos de la invención se aprueba para una indicación médica seleccionada del grupo que consiste de enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del

intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular.

En otro aspecto, la invención proporciona un método de tratamiento o profilaxis de una enfermedad o condición en un animal objeto, por ejemplo, una enfermedad o condición mediada por PPAR o una enfermedad o condición en la cual la modulación de un PPAR proporciona un beneficio terapéutico, administrando al sujeto una cantidad terapéuticamente efectiva de un compuesto de las Fórmulas I, II o III, un profármaco de tal compuesto, o una sal farmacéuticamente aceptable de tal compuesto o profármaco. El compuesto puede administrarse solo o puede administrarse como parte de una composición. En un aspecto, el método involucra administrar al sujeto una cantidad efectiva de un compuesto de las Fórmulas I, II o III, en combinación con una o más terapias distintas para la enfermedad o padecimiento.

En otro aspecto, la invención proporciona un método de tratamiento o profilaxis de una enfermedad o padecimiento mediado por PPAR o una enfermedad o padecimiento en el cual la modulación de un PPAR proporciona un beneficio terapéutico, en donde el método involucra administrar al sujeto una cantidad terapéuticamente efectiva de una composición que incluye un compuesto de las Fórmulas I, II o III.

En aspectos y modalidades que involucran el tratamiento o profilaxis de una enfermedad o padecimiento, la enfermedad o padecimiento se selecciona del grupo que consiste de trastornos de peso (por ejemplo, obesidad, condición de sobrepeso, bulimia y anorexia nerviosa), trastornos de lípidos (por ejemplo, hiperlipidemia, dislipidemia incluyendo dislipidemia diabética asociada y dislipidemia-hipoalfalipoproteinemia mixta, hipertrigliceridemia, hipercolesterolemia y baja HDL (lipoproteína de alta densidad)), trastornos metabólicos (por ejemplo, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, complicación diabética incluyendo neuropatía, nefropatía, retinopatía, úlcera de pies y cataratas por diabetes), enfermedad cardiovascular (por ejemplo, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, apoplejía, enfermedad cerebrovascular, infarto del miocardio, enfermedad vascular periférica), enfermedades inflamatorias (por ejemplo, enfermedades

autoinmunes tales como vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren y esclerosis múltiple, enfermedades que involucran inflamación de vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica, e inflamación en otros órganos, tales como enfermedad renal poliquística (PKD), síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), trastornos cutáneos (por ejemplo, enfermedades hiperproliferativas epiteliales tales como eccema y psoriasis, dermatitis, incluyendo dermatitis atópica, dermatitis por contacto, dermatitis alérgica y dermatitis crónica y cicatrización defectuosa), trastornos neurodegenerativos (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal y enfermedad desmielinizante, incluyendo encefalomielitis diseminada aguda y síndrome de Guillain-Barre), trastornos de coagulación (por ejemplo, trombosis), trastornos gastrointestinales (por ejemplo, infarto del intestino grueso o delgado), trastornos genitourinarios (por ejemplo, insuficiencia renal, disfunción eréctil, incontinencia urinaria y vejiga neurogénica), trastornos oftálmicos (por ejemplo, inflamación oftálmica, degeneración macular y neovascularización patológica), infecciones (por ejemplo, HCV, HIV y Helicobacter pylori), dolor neuropático o inflamatorio, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de obesidad, condición de sobrepeso, bulimia, anorexia nerviosa, hiperlipidemia, dislipidemia, hipoalfalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, una complicación diabética de neuropatía, nefropatía, retinopatía, cataratas, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, eccema, psoriasis, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, trombosis, degeneración macular, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de

vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático, dolor inflamatorio e infertilidad. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular.

En ciertos aspectos y modalidades, los compuestos de las Fórmulas II o III se usan en el tratamiento o profilaxis de una enfermedad o padecimiento seleccionado del grupo que consiste de trastornos de peso (por ejemplo, obesidad, condición de sobrepeso, bulimia y anorexia nerviosa), trastornos de lípidos (por ejemplo, hiperlipidemia, dislipidemia incluyendo dislipidemia diabética asociada y dislipidemia-hipoalfalipoproteinemia mixta, hipertrigliceridemia, hipercolesterolemia y baja HDL (lipoproteína de alta densidad)), trastornos metabólicos (por ejemplo, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, complicación diabética incluyendo neuropatía, nefropatía, retinopatía, úlcera de pies y cataratas por diabetes), enfermedad cardiovascular (por ejemplo, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, apoplejía, enfermedad cerebrovascular, infarto del miocardio, enfermedad vascular periférica), enfermedades inflamatorias (por ejemplo, enfermedades autoinmunes tales como vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos inclusión, polimiositis,

dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren y esclerosis múltiple, enfermedades que involucran inflamación de vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica, e inflamación en otros órganos, tales como enfermedad renal poliquística (PKD), síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), trastornos cutáneos (por ejemplo, enfermedades hiperproliferativas epiteliales tales como eccema y psoriasis, dermatitis, incluyendo dermatitis atópica, dermatitis por contacto, dermatitis alérgica y dermatitis crónica y cicatrización defectuosa), trastornos neurodegenerativos (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal y enfermedad desmielinizante, incluyendo encefalomielitis diseminada aguda y síndrome de Guillain-Barre), trastornos de coagulación (por ejemplo, trombosis), trastornos gastrointestinales (por ejemplo, infarto del intestino grueso o delgado), trastornos genitourinarios (por ejemplo, insuficiencia renal, disfunción eréctil, incontinencia urinaria y vejiga neurogénica), trastornos oftálmicos (por ejemplo, inflamación oftálmica, degeneración macular y neovascularización patológica), infecciones (por ejemplo, HCV, HIV y Helicobacter pylori), dolor neuropático o inflamatorio, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de obesidad, condición de sobrepeso, bulimia, anorexia nerviosa, hiperlipidemia, dislipidemia, hipoalfalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, una complicación diabética de neuropatía, nefropatía, retinopatía, cataratas, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, eccema, psoriasis, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, trombosis, degeneración macular, infertilidad y cáncer. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis,

esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático, dolor inflamatorio e infertilidad. En algunas modalidades, la enfermedad o padecimiento se selecciona del grupo que consiste de enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular.

En ciertos aspectos y modalidades, los compuestos de las Fórmulas I, Ia, Ib, II o III se usan en el tratamiento o profilaxis de una enfermedad o padecimiento seleccionado del grupo que consiste de enfermedades inflamatorias (por ejemplo, enfermedades autoinmunes tales como vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren y esclerosis múltiple, enfermedades que involucran inflamación de vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica, e inflamación en otros órganos, tales como enfermedad renal poliquística (PKD), síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), trastornos cutáneos (por ejemplo, dermatitis, incluyendo dermatitis atópica, dermatitis por contacto, dermatitis alérgica y dermatitis crónica y cicatrización defectuosa), trastornos neurodegenerativos (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal y enfermedad desmielinizante, incluyendo encefalomielitis diseminada aguda y síndrome de Guillain-Barre),

trastornos gastrointestinales (por ejemplo, infarto del intestino grueso o delgado), trastornos genitourinarios (por ejemplo, insuficiencia renal, disfunción eréctil, incontinencia urinaria y vejiga neurogénica), trastornos oftálmicos (por ejemplo, inflamación oftálmica, degeneración macular y neovascularización patológica), infecciones (por ejemplo, HCV, HIV y Helicobacter pylori), dolor neuropático o inflamatorio e infertilidad. En algunos aspectos y modalidades, los moduladores de PPAR con la estructura química de las Fórmulas I, Ia o Ib se usan en el tratamiento o profilaxis de una enfermedad o padecimiento seleccionado del grupo que consiste de enfermedades neurodegenerativas, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular.

En algunas modalidades de aspectos que involucran compuestos de las Fórmulas I, II o III, el compuesto es específico para cualquiera o dos cualesquiera de PPARα, PPARγ y PPARδ, por ejemplo, específico para PPARα; específico para PPARδ; específico para PPARγ; específico para PPARα y PPARδ; específico para PPARα y PPARγ; o específico para PPARδ y PPARγ. Tal especificidad significa que el compuesto tiene una actividad por lo menos 5 veces mayor (de preferencia una actividad mayor de por lo menos 5, 10, 20, 50 o 100 veces o más) sobre el o los PPARs específicos que sobre el o los otros PPARs, donde la actividad se determina usando un ensayo bioquímico adecuado para determinar la actividad de PPAR, por ejemplo, cualquier ensayo conocido por un experto en la técnica o como se describe en la presente. En otra modalidad, los compuestos tienen actividad significativa sobre la totalidad de PPARα, PPARδ y PPARγ.

En algunas modalidades, un compuesto de las Fórmulas I, II o III tendrá una EC_{50} de menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM o menos de 1 nM con respecto a por lo menos uno de PPARα, PPARγ y PPARδ, tal como se determina en un ensayo de actividad de PPAR generalmente aceptado. En una modalidad, un compuesto de cualquiera de las Fórmulas I, II o III tendrá una EC_{50} de menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM o menos de 1 nM con respecto a por

lo menos dos cualesquiera de PPARα, PPARγ y PPARδ. En una modalidad, un compuesto de cualquiera de las Fórmulas I, II o III tendrá una EC_{50} de menos de 100 nM, menos de 50 nM, menos de 20 nM, menos de 10 nM, menos de 5 nM o menos de 1 nM con respecto a la totalidad de PPARα, PPARγ y PPARδ. Con relación a cualquiera de las modalidades anteriores, un compuesto de la invención puede ser un agonista específico de cualquiera de PPARα, PPARγ y PPARδ, o dos cualesquiera de PPARα, PPARγ y PPARδ. Un agonista específico de uno de PPARα, PPARγ y PPARδ es tal que la EC_{50} para uno de PPARα, PPARγ y PPARδ será por lo menos aproximadamente 5 veces, también 10 veces, también 20 veces, también 50 veces o por lo menos aproximadamente 100 veces menor que la EC_{50} para los ctros dos de PPARα, PPARγ y PPARδ. Un agonista específico de dos de PPARα, PPARγ y PPARδ es tal que la EC_{50} para cada uno de dos de PPARα, PPARγ y PPARδ será por lo menos aproximadamente 5 veces, también 10 veces, también 20 veces, también 50 veces o por lo menos aproximadamente 100 veces menor que la EC_{50} para el otro de PPARα, PPARγ y PPARδ.

En algunas modalidades de la invención, los compuestos de las Fórmulas I, II o III activos sobre los PPARs también tienen propiedades farmacológicas deseables. En algunas modalidades, la propiedad farmacológica deseada es pan-actividad sobre PPAR, selectividad de PPAR para cualquier PPAR individual (PPARα, PPARδ o PPARγ), selectividad sobre dos cualesquiera de los PPARs (PPARα y PPARδ, PPARα y PPARγ o PPARδ y PPARγ), o cualquiera o más de vida media sérica mayor a 2 horas, también mayor a 4 horas, también mayor a 8 horas, solubilidad acuosa y biodisponibilidad oral de más de 10%, también más de 20%.

Modalidades adicionales serán aparentes a partir de la Descripción Detallada y de las reivindicaciones.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Como se indica en el Arte Previo en lo anterior, la presente invención concierne a receptores activados por el proliferador del peroxisoma (PPARs), los cuales se han identificado en humanos y otros mamíferos. Se ha identificado un grupo de compuestos, que corresponden a las Fórmulas I, II o III, que son activos sobre uno o más de los PPARs, en particular compuestos que

son activos sobre uno o más PPARs humanos. Tales compuestos pueden usarse para una diversidad de aplicaciones, por ejemplo, como agonistas sobre los PPARs, incluyendo agonistas de por lo menos uno de PPARα, PPARδ y PPARγ, así como agonistas de PPAR duales y pan-agonista, tales como agonistas de PPARα y PPARγ, PPARα y PPARδ, PPARγ y PPARδ o agonistas de PPARα, PPARγ y PPARδ.

Como se usan en la presente, se aplican las siguientes definiciones a menos que se indique de otra manera:

"Halógeno" - solo o en combinación, se refiere a todos los halógenos, es decir, cloro (Cl), flúor (F), bromo (Br) o yodo (I).

"Hidroxilo" o "hidroxi" se refiere al grupo -OH.

"Tiol" se refiere al grupo -SH.

"Alquilo inferior", solo o en combinación, significa un radical derivado de alcanos que contiene de 1 a 6 átomos de carbono (a menos que se defina específicamente) que incluye un alquilo de cadena lineal o alquilo ramificado. El grupo alquilo de cadena lineal o ramificado se une en cualquier punto disponible para producir un compuesto estable. En muchas modalidades, un alquilo inferior es un grupo alquilo lineal o ramificado que contiene de 1-6, 1-4 ó 1-2 átomos de carbono, tales como metilo, etilo, propilo, isopropilo, butilo, t-butilo y similares. "Alquilo inferior sustituido" denota un alquilo inferior que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes, unidos en cualquier átomo disponible para producir un compuesto estable, en donde los sustituyentes se seleccionan del grupo que consiste de -F, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^e$ y $-R^f$. Adicionalmente, las sustituciones posibles incluyen subconjuntos de estas sustituciones, tal como se indican en la presente, por ejemplo, en la descripción de los compuestos de las Fórmulas I, II o III, unidas en cualquier átomo disponible para producir un compuesto estable. Por ejemplo, "alquilo inferior sustituido con flúor" denota un grupo alquilo inferior sustituido con uno o más átomos de flúor, tal como perfluoroalquilo, donde de

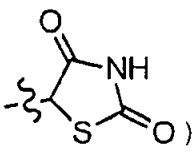
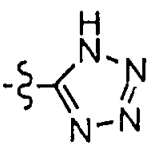
preferencia el alquilo inferior se sustituye con 1, 2, 3, 4 ó 5 átomos de flúor, también 1, 2 ó 3 átomos de flúor. Se entenderá que las sustituciones se unen en cualquier átomo disponible para producir un compuesto estable, cuando el alquilo inferior opcionalmente sustituido es un grupo R de una porción tal como -OR (por ejemplo, alcoxi inferior), -SR (por ejemplo, alquiltio inferior), -NHR (por ejemplo, monoalquilamino), -C(O)NHR, y similares, la sustitución del grupo R del alquilo inferior es tal que la sustitución del carbono del alquilo inferior enlazado a cualquier O, S o N de la porción (excepto donde N es un átomo del anillo heteroarilo) excluye sustituyentes que pueden resultar en que cualquier O, S o N del sustituyente (excepto donde N es un átomo del anillo heteroarilo) se enlace al carbono del alquilo inferior enlazado a cualquier O, S o N de la porción.

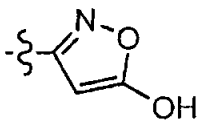
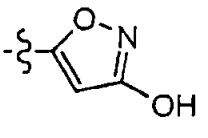
"Alquenilo inferior", solo o en combinación, significa un hidrocarburo lineal o ramificado que contiene 2-6 átomos de carbono (a menos que se defina específicamente) y por lo menos uno, de preferencia 1-3, de más preferencia 1-2, de mayor preferencia uno, doble enlace carbono a carbono. Los dobles enlaces carbono a carbono pueden contenerse dentro de una cadena lineal o porción ramificada. Ejemplos de grupos alquenilo inferior incluyen etenilo, propenilo, isopropenilo, butenilo y similares. "Alquenilo inferior sustituido" denota un alquenilo inferior que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes, unidos en cualquier átomo disponible para producir un compuesto estable, en donde los sustituyentes se seleccionan del grupo que consiste de -F, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^d$ y $-R^f$. Además, las sustituciones posibles incluyen subconjuntos de estas sustituciones, tal como se indican en la presente, por ejemplo, en la descripción de los compuestos de las Fórmulas I, II o III, unidas en cualquier átomo disponible para producir un compuesto estable. Se entiende que las sustituciones se unen en cualquier átomo disponible para producir un compuesto estable, la sustitución de grupos alquenilo inferior es tal que F, C(O), C(S), C(NH), S(O), $S(O)_2$, O, S o N (excepto donde N es un átomo del anillo heteroarilo) no se enlazan a un carbono de alqueno del mismo. Además, donde alquenilo inferior es un sustituyente de otra porción o un grupo R de

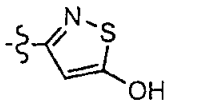
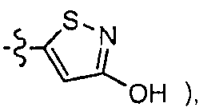
una porción tal como -OR, -NHR, -C(O)R y similares, la sustitución de la porción es tal que cualquier C(O), C(S), S(O), $S(O)_2$, O, S o N de la misma (excepto en donde N es un átomo del anillo heteroarilo) no se enlazan a un carbono de alqueno del sustituyente del alquenilo inferior o grupo R. Además, donde alquenilo inferior es un sustituyente de otra porción o un grupo R de una porción tal como -OR, -NHR, -C(O)NHR y similares, la sustitución del grupo R del alquenilo inferior es tal que la sustitución del carbono del alquenilo inferior enlazado a cualquier O, S o N de la porción (excepto donde N es un átomo del anillo heteroarilo) excluye sustituyentes que pueden resultar en que cualquier O, S o N del sustituyente (excepto donde N es un átomo del anillo heteroarilo) se enlace al carbono del alquenilo inferior enlazado a cualquier O, S o N de la porción. Un "carbono de alquenilo" se refiere a cualquier carbono dentro de un grupo alquenilo inferior, saturado o como parte del doble enlace carbono a carbono. Un "carbono de alqueno" se refiere a un carbono dentro de un grupo alquenilo inferior que es parte de un doble enlace carbono a carbono. "Alquenilo de 3 a 6 átomos de carbono" denota un alquenilo inferior que contiene 3-6 átomos de carbono. Un "alquenilo de 3 a 6 átomos de carbono sustituido" denota un alquenilo inferior opcionalmente sustituido que contiene 3-6 átomos de carbono.

"Alquinilo inferior", solo o en combinación, significa un hidrocarburo lineal o ramificado que contiene 2-6 átomos de carbono (a menos que se defina específicamente) que contiene por lo menos uno, de preferencia uno, triple enlace carbono a carbono. Ejemplos de grupos alquinilo inferior incluyen etinilo, propinilo, butinilo y similares. "Alquinilo inferior sustituido" denota un alquinilo inferior que se sustituye independientemente, a menos que se indique de otra manera, con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes, unidos en cualquier átomo disponible para producir un compuesto estable, en donde los sustituyentes se seleccionan del grupo que consiste de -F, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^d$ y $-R^f$. Además, las sustituciones posibles incluyen subconjuntos de estas sustituciones, tal como se indican en la presente, por ejemplo, en la descripción de los compuestos de las Fórmulas I, II o III, unidas en cualquier átomo disponible para producir un

compuesto estable. Se entiende que las sustituciones se unen en cualquier átomo disponible para producir un compuesto estable, la sustitución de grupos alquinilo inferior es tal que F, C(O), C(S), C(NH), S(O), $S(O)_2$, O, S o N (excepto en donde N es un átomo del anillo heteroarilo) no se enlazan a un carbono de alquino del mismo. Además, donde alquinilo inferior es un sustituyente de otra porción o un grupo R de una porción tal como -OR, -NHR, -C(O)R, y similares, la sustitución de la porción es tal que cualquier C(O), C(S), S(O), $S(O)_2$, O, S o N de la misma (excepto donde N es un átomo del anillo heteroarilo) no se enlaza a un carbono del alquino del sustituyente alquinilo inferior o grupo R. Además, donde alquinilo inferior es un sustituyente de otra porción o un grupo R de una porción tal como -OR, -NHR, -C(O)NHR y similares, la sustitución del grupo R del alquinilo inferior es tal que la sustitución del carbono del alquinilo inferior enlazado a cualquier O, S ó N de la porción (excepto donde N es un átomo del anillo heteroarilo) excluye sustituyentes que pueden resultar en que cualquier O, S o N del sustituyente (excepto donde N es un átomo del anillo heteroarilo) se enlace al carbono del alquinilo inferior enlazado a cualquier O, S o N de la porción. Un "carbono de alquinilo" se refiere a cualquier carbono dentro de un grupo alquinilo inferior, saturado o como parte del triple enlace carbono a carbono. Un "carbono de alquino" se refiere a un carbono dentro de un grupo alquinilo inferior que es parte de un triple enlace carbono a carbono. "Alquinilo de 3 a 6 átomos de carbono" denota un alquinilo inferior que contiene 3-6 átomos de carbono. Un "alquinilo de 3 a 6 átomos de carbono sustituido" denota un alquinilo inferior opcionalmente sustituido que contiene 3-6 átomos de carbono.

"Isóstero del ácido carboxílico" se refiere a una porción seleccionada del grupo que consiste de tiazolidindiona (es decir ), ácido hidroxámico (es decir, -C(O)NHOH), acilcianamida (es decir -C(O)NHCN), tetrazol (es decir, ), 3- o 5-hidroxiisoxazol (es

decir,  o ), 3- o 5-hidroxiisotiazol (es decir,

 o ), sulfonato (es decir, $-S(O)_2OH$) y sulfonamida (es decir $-S(O)_2NH_2$). En términos funcionales, los isósteros del ácido carboxílico imitan ácidos carboxílicos en virtud de propiedades físicas similares incluyendo, pero sin limitarse a tamaño molecular, distribución de carga o forma molecular. El 3- ó 5-hidroxiisoxazol o 3- ó 5 hidroxiisotiazol pueden sustituirse opcionalmente con alquilo inferior o alquilo inferior sustituido con 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de flúor, arilo y heteroarilo, en donde el arilo o heteroarilo pueden además sustituirse opcionalmente con 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor. El nitrógeno de la sulfonamida puede sustituirse opcionalmente con un sustituyente seleccionado del grupo que consiste de alquilo inferior, alquilo inferior sustituido con flúor, acetilo (es decir, $-C(O)CH_3$), arilo y heteroarilo, en donde el arilo o heteroarilo pueden además sustituirse opcionalmente con 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor.

"Arilo", solo o en combinación, se refiere a un sistema de anillo monocíclico o bicíclico que contiene hidrocarburos aromáticos tales como fenilo o naftilo, el cual puede fusionarse opcionalmente con un cicloalquilo o heterocicloalquilo de preferencia de 5-7, de más preferencia de 5-6, miembros de anillo. "Arileno" se refiere a un arilo divalente.

"Heteroarilo", solo o en combinación, se refiere a una estructura de anillo aromático monocíclico que contiene 5 ó 6 átomos de nitrógeno, o un grupo aromático bicíclico que tiene 8 a 10 átomos, que contiene uno o más, de preferencia 1-4, de más preferencia 1-3, incluso de más preferencia 1-2 heteroátomos independientemente seleccionados del grupo que consiste de O, S y

N. Heteroarilo pretende también incluir S o N oxidado, tales como sulfinilo, sulfonilo y N-óxido de un nitrógeno del anillo terciario. Un átomo de carbono o nitrógeno es el punto de unión de la estructura de anillo heteroarilo, de modo que se produzca un compuesto estable. Ejemplos de grupos heteroarilo incluyen, pero no se limitan a, piridinilo, piridazinilo, pirazinilo, quinoxalinilo, indolizinilo, benzo[b]tienilo, quinazolinilo, purinilo, indolilo, quinolinilo, pirimidinilo, pirrolilo, pirazolilo, oxazolilo, tiazolilo, tienilo, isoxazolilo, oxatiadiazolilo, isotiazolilo, tetrazolilo, imidazolilo, triazolilo, furanilo, benzofurilo e indolilo. "Heteroarilo que contiene nitrógeno" se refiere a un heteroarilo en donde cualesquiera heteroátomos son N. "Heteroarileno" se refiere a un heteroarilo divalente.

"Cicloalquilo" se refiere a sistemas de anillos de carbono monocíclicos, bicíclicos o tricíclicos, no aromáticos, saturados o insaturados de 3-10, también 3-8, de más preferencia 3-6 miembros de anillo por anillo, tales como ciclopropilo, ciclopentilo, ciclohexilo, adamantilo y similares.

"Heterocicloalquilo" se refiere a un grupo cicloalquilo no aromático, saturado o insaturado que tiene de 5 a 10 átomos en el cual de 1 a 3 átomos de carbono del anillo se reemplazan por heteroátomos de O, S o N, y se fusionan opcionalmente con benzo o heteroarilo de 5-6 miembros de anillo. Heterocicloalquilo pretende también incluir S o N oxidado, tales como sulfinilo, sulfonilo y N-óxido de un nitrógeno de anillo terciario. Heterocicloalquilo pretende también incluir compuestos en los cuales uno de los carbonos del anillo se sustituye con oxo, es decir, el carbono del anillo es un grupo carbonilo, tal como lactonas y lactamas. El punto de unión del anillo heterocicloalquilo está en un átomo de carbono o nitrógeno de modo que se retiene un anillo estable. Ejemplos de grupos heterocicloalquilo incluyen, pero no se limitan a morfolino, tetrahidrofuranilo, dihidropiridinilo, piperidinilo, pirrolidinilo, pirrolidonilo, piperazinilo, dihidrobenzofurilo y dihidroindolilo.

"Arilo opcionalmente sustituido", "heteroarilo opcionalmente sustituido", "cicloalquilo opcionalmente sustituido" y "heterocicloalquilo opcionalmente sustituido" se refieren a grupos arilo, heteroarilo, cicloalquilo y heterocicloalquilo, respectivamente, los cuales se sustituyen opcionalmente de forma independiente, a menos que se indique de otra manera, con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes, unidos en cualquier átomo disponible

para producir un compuesto estable, en donde los sustituyentes se seleccionan del grupo que consiste de halógeno, $-NO_2$, -CN, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-OC(S)R^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)OR^a$, $-C(S)OR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-C(O)NR^aR^a$, $-C(S)NR^aR^a$, $-S(O)_2NR^aR^a$, $-C(NH)NR^bR^c$, $-NR^aC(O)R^a$, $-NR^aC(S)R^a$, $-NR^aS(O)_2R^a$, $-NR^aC(O)NR^aR^a$, $-NR^aC(S)NR^aR^a$, $-NR^aS(O)_2NR^aR^a$, $-NR^aR^a$, $-R^d$, $-R^e$ y $-R^f$.

Las variables, como se usan en la descripción de sustituyentes opcionales para alquilo inferior, alquenilo inferior, alquinilo inferior, cicloalquilo, heterocicloalquilo, arilo y heteroarilo se definen como sigue:

$-R^a$, $-R^b$ y R^c en cada caso se seleccionan independientemente del grupo que consiste de hidrógeno, $-R^d$, $-R^e$ y $-R^f$, con la condición, sin embargo, de que R^a enlazado a S, S(O), $S(O)_2$, C(S) o C(O) no es hidrógeno, o

$-R^b$ y $-R^c$ combinados con el nitrógeno al cual se unen, forman un heterocicloalquilo de 5-7 miembros o un heteroarilo que contiene nitrógeno de 5 ó 7 miembros, en donde el heterocicloalquilo de 5-7 miembros ó heteroarilo que contiene nitrógeno de 5 ó 7 miembros se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de halógeno, cicloalquilamino, $-NO_2$, -CN, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-R^m$ y $-R^o$;

$-R^d$ en cada caso es independientemente alquilo inferior opcionalmente sustituido con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de flúor, $-OR^g$, $-SR^g$, $-NR^gR^g$, $-C(O)R^g$, $-C(S)R^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NR^gR^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NR^gS(O)_2R^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NR^gS(O)_2NR^gR^g$ y $-R^f$;

$-R^e$ en cada caso se selecciona independientemente del grupo que consiste de alquenilo inferior y alquinilo inferior, en donde el alquenilo inferior o alquinilo inferior se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de flúor, $-OR^g$, $-SR^g$, $-NR^gR^g$, $-C(O)R^g$, $-C(S)R^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NR^gR^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NR^gS(O)_2R^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-R^d$ y $-R^f$;

-R^f en cada caso se selecciona independientemente del grupo que consiste de cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo y heteroarilo se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de halógeno, $-NO_2$, -CN, $-OR^g$, $-SR^g$, $-NR^gR^g$, $-C(O)R^g$, $-C(S)R^g$, $-S(O)R^g$, $-S(O)_2R^g$, $-C(O)NR^gR^g$, $-C(S)NR^gR^g$, $-S(O)_2NR^gR^g$, $-NR^gC(O)R^g$, $-NR^gC(S)R^g$, $-NR^gS(O)_2R^g$, $-NR^gC(O)NR^gR^g$, $-NR^gC(S)NR^gR^g$, $-NR^gS(O)_2NR^gR^g$, $-R^m$ y $-R^o$;

-R^g en cada caso se selecciona independientemente del grupo que consiste de hidrógeno, $-R^h$, $-R^i$ y $-R^j$, con la condición, sin embargo, de que R^g enlazado a S, S(O), $S(O)_2$, C(S) o C(O) no es hidrógeno;

-R^h en cada caso es independientemente alquilo inferior opcionalmente sustituido con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de flúor, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-C(O)R^k$, $-C(S)R^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NR^kR^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NR^kS(O)_2R^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NR^kS(O)_2NR^kR^k$ y $-R^o$, con la condición, sin embargo, de que cualquier sustitución en el carbono del alquilo inferior enlazado a cualquier O, S o N de cualquier OR^h, SR^h o NR^h se selecciona del grupo que consiste de flúor y $-R^o$;

-R^i en cada caso se selecciona independientemente del grupo que consiste de alquenilo de 3 a 6 átomos de carbono y alquinilo de 3 a 6 átomos de carbono, en donde el alquenilo de 3 a 6 átomos de carbono o alquinilo de 3 a 6 átomos de carbono se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de flúor, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-C(O)R^k$, $-C(S)R^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NR^kR^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NR^kS(O)_2R^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, $-R^m$ y $-R^o$, con la condición, sin embargo, de que cualquier sustitución en el carbono del alquenilo o alquinilo enlazado a cualquier O, S o N de cualquier OR^i, SR^i o NR^i se selecciona del grupo que consiste de flúor, $-R^m$ y $-R^o$;

-R^j en cada caso se selecciona independientemente del grupo que consiste de cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo y heteroarilo se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó

3 sustituyentes seleccionados del grupo que consiste de halógeno, $-NO_2$, -CN, $-OR^k$, $-SR^k$, $-NR^kR^k$, $-C(O)R^k$, $-C(S)R^k$, $-S(O)R^k$, $-S(O)_2R^k$, $-C(O)NR^kR^k$, $-C(S)NR^kR^k$, $-S(O)_2NR^kR^k$, $-NR^kC(O)R^k$, $-NR^kC(S)R^k$, $-NR^kS(O)_2R^k$, $-NR^kC(O)NR^kR^k$, $-NR^kC(S)NR^kR^k$, $-NR^kS(O)_2NR^kR^k$, $-R^m$ y $-R^o$;

$-R^m$ en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, alquenilo inferior y alquinilo inferior, en donde el alquilo inferior se sustituye opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de $-R^o$, flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, monoalquilamino, dialquilamino y cicloalquilamino, y en donde el alquenilo inferior o alquinilo inferior se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de $-R^o$, flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, monoalquilamino, dialquilamino y cicloalquilamino;

$-R^k$ en cada caso se selecciona independientemente del grupo que consiste de hidrógeno, $-R^n$ y $-R^o$, con la condición, sin embargo, de que R^k enlazado a S, S(O), $S(O)_2$, C(S) o C(O) no es hidrógeno;

$-R^n$ en cada caso se selecciona independientemente del grupo que consiste de alquilo inferior, alquenilo de 3 a 6 átomos de carbono y alquinilo de 3 a 6 átomos de carbono, en donde el alquilo inferior se sustituye opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de $-R^o$, flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, monoalquilamino, dialquilamino y cicloalquilamino, con la condición, sin embargo, de que cualquier sustitución del carbono del alquilo inferior enlazado al O de OR^n, S de SR^n o N de cualquier NR^n es flúor o $-R^o$, y en donde el alquenilo de 3 a 6 átomos de carbono o alquinilo de 3 a 6 átomos de carbono se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de $-R^o$, flúor, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, monoalquilamino, dialquilamino y cicloalquilamino, con la condición, sin

embargo, de que cualquier sustitución del carbono del alquenilo de 3 a 6 átomos de carbono o alquinilo de 3 a 6 átomos de carbono enlazado al O de OR^n, S de SR^n o N de cualquier NR^n es flúor, alquilo inferior, alquilo inferior sustituido con flúor o $-R^o$;

R^o en cada caso se selecciona independientemente del grupo que consiste de cicloalquilo, heterocicloalquilo, arilo y heteroarilo, en donde el cicloalquilo, heterocicloalquilo, arilo y heteroarilo se sustituyen opcionalmente con uno o más, de preferencia 1, 2, 3, 4 ó 5, también 1, 2 ó 3 sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, $-NO_2$, -CN, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, alquiltio inferior sustituido con flúor, monoalquilamino, dialquilamino y cicloalquilamino.

"Alcoxi inferior" denota el grupo $-OR^p$, donde R^p es alquilo inferior. "Alcoxi inferior opcionalmente sustituido" denota alcoxi inferior en el cual R^p es alquilo inferior opcionalmente sustituido. De preferencia, la sustitución del alcoxi inferior es con 1, 2, 3, 4 ó 5 sustituyentes, también 1, 2 ó 3 sustituyentes. Por ejemplo, "alcoxi inferior sustituido con flúor" denota un alcoxi inferior en el cual el alquilo inferior se sustituye con uno o más átomos de flúor donde, de preferencia, el alcoxi inferior se sustituye con 1, 2, 3, 4 ó 5 átomos de flúor, también 1, 2 ó 3 átomos de flúor. Se entiende que las sustituciones en el alcoxi inferior se unen en cualquier átomo disponible para producir un compuesto estable, la sustitución del alcoxi inferior es tal que O, S o N (excepto donde N es un átomo del anillo heteroarilo), no se enlazan al carbono del alquilo inferior enlazado al O del alcoxi inferior. Además, donde el alcoxi inferior se describe como un sustituyente de otra porción, el oxígeno del alcoxi inferior no se enlaza a un átomo de carbono que se enlaza a un O, S o N de la otra porción (excepto donde N es un átomo del anillo heteroarilo), o a un carbono del alqueno o alquino de la otra porción.

"Ariloxi" denota el grupo $-OR^q$, donde R^q es arilo. "Ariloxi opcionalmente sustituido" denota ariloxi en el cual R^q es arilo opcionalmente sustituido. "Heteroariloxi" denota el grupo $-OR^r$, donde R^r es heteroarilo. "Heteroariloxi opcionalmente sustituido" denota heteroariloxi en el cual R^r es heteroarilo opcionalmente sustituido.

"Alquiltio inferior" denota el grupo $-SR^s$, donde R^s es alquilo inferior. "Alquiltio inferior sustituido" denota alquiltio inferior en el cual R^s es alquilo inferior opcionalmente sustituido.

De preferencia, la sustitución del alquiltio inferior es con 1, 2, 3, 4 ó 5 sustituyentes, también 1, 2 ó 3 sustituyentes. Por ejemplo, "alquiltio inferior sustituido con flúor" denota un alquiltio inferior en el cual el alquilo inferior se sustituye con uno o más átomos de flúor donde, de preferencia, el alquiltio inferior se sustituye con 1, 2, 3, 4 ó 5 átomos de flúor, también 1, 2 ó 3 átomos de flúor. Se entiende que las sustituciones en el alquiltio inferior se unen en cualquier átomo disponible para producir un compuesto estable, la sustitución del alquiltio inferior es tal que O, S o N (excepto donde N es un átomo del anillo heteroarilo), no se enlazan al carbono del alquilo inferior enlazado al S del alquiltio inferior. Además, donde el alquiltio inferior se describe como un sustituyente de otra porción, el azufre del alquiltio inferior no se enlaza a un átomo de carbono que se enlaza a un O, S o N de la otra porción (excepto donde N es un átomo del anillo heteroarilo), o a un carbono del alqueno o alquino de la otra porción.

"Amino" o "amina" denota el grupo $-NH_2$. "Monoalquilamino" denota el grupo $-NHR^t$ donde R^t es alquilo inferior. "Dialquilamino" denota el grupo $-NR^tR^u$, donde R^t y R^u son independientemente alquilo inferior. "Cicloalquilamino" denota el grupo $-NR^vR^w$, donde R^v y R^w se combinan con el nitrógeno para formar un heterocicloalquilo de 5-7 miembros, donde el heterocicloalquilo puede contener un heteroátomo adicional dentro del anillo, tal como O, N o S, y también puede sustituirse además con alquilo inferior. Ejemplos de cicloalquilamino incluyen, pero no se limitan a, piperidina, piperazina, 4-metilpiperazina, morfolina y tiomorfolina. Se entiende que cuando monoalquilamino, dialquilamino o cicloalquilamino son sustituyentes en otras porciones que se unen en cualquier átomo disponible para producir un compuesto estable, el nitrógeno del monoalquilamino, dialquilamino o cicloalquilamino como sustituyentes no se enlaza a un átomo de carbono que se enlaza a un O, S o N de la otra porción (excepto donde N es un átomo del anillo heteroarilo) o a un carbono del alqueno o alquino de la otra porción.

Como se usa en la presente en relación con el compuesto de modulación, compuestos de unión o ligandos de PPAR, el término "específico para PPAR" y términos de acepción similar, significan que un compuesto particular se une a un PPAR en un grado estadísticamente mayor que a otras biomoléculas que pueden presentarse en, o aislarse originalmente a partir de, un organismo particular, por ejemplo, una unión por lo menos 2, 3, 4, 5,

10, 20, 50, 100 ó 1000 veces mayor. También, donde se indica actividad biológica diferente a unión, el término "específico para PPAR" indica que un compuesto particular tiene mayor actividad biológica asociada con la unión a un PPAR que a otras biomoléculas (por ejemplo, en un nivel como se indica para especificidad de unión). De manera similar, la especificidad puede ser para un PPAR específico con respecto a otros PPARs que pueden presentarse en, o aislarse originalmente a partir de, un organismo particular.

También, en el contexto de los compuestos que se unen a un objetivo biomolecular, el término "mayor especificidad" indica que un compuesto se une a un objetivo especificado en un grado mayor que otra biomolécula o biomoléculas que pueden presentarse bajo condiciones de unión relevantes, donde la unión a tales otras biomoléculas produce una actividad biológica diferente a la unión al objetivo especificado. En algunos casos, la especificidad es con referencia a un conjunto limitado de otras biomoléculas, por ejemplo, en el caso de los PPARs, en algunos casos la referencia puede ser otros receptores o, para un PPAR particular, puede ser otros PPARs. En algunas modalidades, la especificidad mayor es una especificidad por lo menos 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500 ó 1000 veces mayor. En el contexto de los ligandos que interactúan con los PPARs, los términos "actividad sobre" o "actividad hacia" y términos similares, significan que tales ligandos tienen IC_{50} EC_{50} menor a 10 μM, menor a 1 μM, menor a 100 nM, menor a 50 nM, menor a 20 nM, menor a 10 nM, menor a 5 nM o menor a 1 nM con respecto a por lo menos un PPAR, tal como se determina en un ensayo de actividad de PPAR generalmente aceptado.

El término "composición" o "composición farmacéutica" se refiere a una formulación adecuada para su administración a un sujeto animal pretendido para propósitos terapéuticos. La formulación incluye una cantidad terapéuticamente significativa (es decir, una cantidad terapéuticamente efectiva) de por lo menos un compuesto activo y por lo menos un portador o excipiente farmacéuticamente aceptable, la cual se prepara en una forma adaptada para su administración a un sujeto. De esta manera, la preparación es "farmacéuticamente aceptable", lo que indica que no tiene propiedades que pueden ocasionar que un médico razonablemente prudente evite la administración del material a un paciente, tomando en consideración la

enfermedad o padecimientos que deben tratarse y la ruta de administración respectiva. En muchos casos, tal composición farmacéutica es una preparación estéril, por ejemplo, para inyectables.

El término enfermedad o padecimiento "mediado por PPAR" y términos similares, se refieren a una enfermedad o padecimiento en el cual la función biológica de un PPAR afecta el desarrollo y/o transcurso de la enfermedad o padecimiento, y/o en el cual la modulación del PPAR altera el desarrollo, transcurso y/o síntomas de la enfermedad o padecimiento. En algunos casos, la enfermedad o padecimiento puede mediarse por cualquiera o más de las isoformas de PPAR, por ejemplo, PPARγ, PPARα, PPARδ, PPARγ y PPARα, PPARγ y PPARδ, PPARα y PPARδ o PPARγ, PPARα y PPARδ.

El término "terapéuticamente efectivo" o "cantidad efectiva" indica que los materiales o la cantidad de material son efectivos para prevenir, aliviar o mejorar uno o más síntomas de una enfermedad o condición médica, y/o para prolongar la supervivencia del sujeto que se está tratando.

El término "PPAR" se refiere a un receptor activado por el proliferador del peroxisoma, como se reconoce en la técnica. Como se indica en lo anterior, la familia del PPAR incluye PPARα (también referido como PPARa o PPARalfa), PPARδ (también referido como PPARd o PPARdelta) y PPARγ (también referido como PPARg o PPARgamma). Los PPARs individuales pueden identificarse por sus secuencias, donde los números de acceso de secuencias de referencia ejemplares son como sigue:

Receptor	Secuencia	No. de Acceso	SEQ ID NO:
hPPARa	**ADNc**	NM_005036	
hPPARa	**proteína**	NP_005027	
hPPARg **isoforma 2**	**ADNc**	NM_015869	
hPPARg **isoforma 2**	**proteína**	NP_056953	
hPPARd	**ADNc**	NM_006238	
hPPARd	**proteína**	NP_006229	

Alguien con experiencia ordinaria en la técnica reconocerá que existirán diferencias en secuencias debido a la variación alélica, y también reconocerá que otros animales, particularmente otros mamíferos, tienen PPARs correspondientes, los cuales se han identificado o pueden identificarse fácilmente usando alineación de secuencias y confirmación de actividad. Tales PPARs homólogos también pueden usarse en la presente invención, cuyos PPARs homólogos tienen identidad de secuencias de, por ejemplo, al menos 50%, 60%, 70%, 80%, 90%, 95%, 99% o incluso 100%, sobre una región que abarca 50, 100, 150, 200, 250, 300, 350, 400, 450, 500 o incluso más aminoácidos o nucleótidos, para proteínas o ácidos nucleicos, respectivamente. Alguien con experiencia en la técnica reconocerá también que pueden intrcducirse modificaciones en una secuencia de PPAR sin destruir la actividad de PPAR. Tales PPARs modificados también pueden usarse en la presente invención, por ejemplo, si las modificaciones no alteran la conformación del sitio de unión al grado que el PPAR modificado carezca de unión de ligando sustancialmente normal.

Como se usa en la presente en relación con el diseño o desarrollo de ligandos, el término "unir" y "unión" y términos similares, se refieren a una asociación no covalente, energéticamente favorable, entre las moléculas especificadas (es decir, el estado unido tiene una energía libre menor que el estado separado, lo cual puede medirse en forma calorimétrica). Para unirse a un objetivo, la unión es por lo menos selectiva, es decir, el compuesto se une en forma preferencial a un objetivo particular o a miembros de una familia objetivo en un sitio de unión, en comparación con la unión inespecífica a proteínas no relacionadas que no tienen un sitio de unión similar. Por ejemplo, a menudo se usa BSA para evaluar o controlar la unión inespecífica. Además, para que una asociación se considere como unión, la disminución en la energía libre que va de un estado separado al estado unido debe ser suficiente, de modo que la asociación pueda detectarse en un ensayo bioquímico adecuado para las moléculas involucradas.

Por "examinar" se quiere decir la creación de condiciones experimentales y la acumulación de datos con respecto a un resultado particular de las condiciones experimentales. Por ejemplo, pueden examinarse enzimas con base en su capacidad de actuar sobre un sustrato que puede detectarse. Asimismo, por ejemplo, puede examinarse un compuesto o ligando con base en su capacidad para unirse a una molécula o moléculas objetivo particulares y/o para modular una actividad de una molécula objetivo.

Por "señal de fondo", en referencia a un ensayo de unión, se quiere decir la señal que se registra bajo condiciones estándar para el ensayo particular en ausencia de un compuesto de prueba, andamiaje molecular o ligando que se une a la molécula objetivo. Las personas con experiencia ordinaria en la técnica comprenderán que existen métodos aceptados y se encuentran disponibles ampliamente para determinar la señal de fondo.

Por "clog P" se quiere decir el logaritmo P calculado de un compuesto, "P" refiriéndose al coeficiente de partición del compuesto entre una fase lipofílica y una acuosa, usualmente entre octanol y agua.

En el contexto de los compuestos que se unen a un objetivo, el término "mayor afinidad" indica que el compuesto se une más estrechamente que un compuesto de referencia, o que el mismo compuesto en una condición de referencia, es decir, con una constante de disociación menor. En algunas modalidades, la mayor afinidad es una afinidad por lo menos 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000 ó 10,000 veces mayor.

Por unión con "afinidad moderada" se quiere decir unión con una K_D de aproximadamente 200 nM a aproximadamente 1 μM bajo condiciones estándar. Por "afinidad moderadamente alta" se quiere decir unión a una K_D de aproximadamente 1 nM a aproximadamente 200 nM. Por unión a "alta afinidad" se quiere decir unión a una K_D por debajo de aproximadamente 1 nM bajo condiciones estándar. Las condiciones estándar para la unión son en pH 7.2 a 37°C durante una hora. Por ejemplo, las condiciones típicas de unión en un volumen de 100 μl/pozo pueden comprender un PPAR, un compuesto de prueba, tampón HEPES 50 mM a pH 7.2, NaCl 15 mM, ATP 2 μM y albúmina sérica bovina (1 ug/pozo), a 37 °C durante una hora.

Los compuestos de unión también pueden caracterizarse por su efecto sobre la actividad de la molécula objetivo. De esta manera, un compuesto de "baja actividad" tiene una concentración inhibitoria (IC_{50}) (para inhibidores o antagonistas) o concentración efectiva (EC_{50}) (aplicable a agonistas) de más de 1 μM bajo condiciones estándar. Por "actividad moderada" se quiere decir una IC_{50} o EC_{50} de 200 nM a 1 μM bajo condiciones estándar. Por "actividad moderadamente alta" se quiere decir una IC_{50} o EC_{50} de 1 nM a 200 nM. Por "alta actividad" se quiere decir una IC_{50} o EC_{50} por debajo de 1 nM bajo condiciones estándar. La IC_{50} (o EC_{50}) se define como la concentración del compuesto en la cual se pierde (o gana) el 50% de actividad de la actividad de la molécula objetivo (por ejemplo, enzima u otra proteína) que se está midiendo, con relación a la actividad cuando no se presenta ningún compuesto. La actividad puede medirse usando métodos conocidos por aquellos con experiencia ordinaria en la técnica, por ejemplo, al medir cualquier producto o señal que puede detectarse, producidos por la presentación de una reacción enzimática, u otra actividad, por una proteína que se está midiendo. Para los agonistas del PPAR, las actividades pueden determinarse como se describe en los Ejemplos, o usando otros métodos de ensayo conocidos en la técnica.

Por "proteína" se quiere decir un polímero de aminoácidos. Los aminoácidos pueden presentarse en forma natural o no natural. Las proteínas también pueden contener modificaciones, tales como estar glicosiladas, fosforiladas, u otras modificaciones comunes.

Por "familia de proteínas" se quiere decir una clasificación de proteínas con base en similitudes estructurales y/o funcionales. Por ejemplo, cinasas, fosfatasas, proteasas y agrupaciones similares de proteínas son familias de proteínas. Las proteínas pueden agruparse en una familia de proteínas con base en tener uno o más plegamientos proteínicos en común, una similitud sustancial en conformación entre los plegamientos de las proteínas, homología o con base en tener una función común. En muchos casos, se especificarán familias más pequeñas, por ejemplo, la familia PPAR.

Por "efecto bioquímico específico" se quiere decir un cambio bioquímico terapéuticamente significativo en un sistema biológico, ocasionando un resultado que puede detectarse. Este efecto bioquímico específico puede ser, por ejemplo, la inhibición o activación de

una enzima, la inhibición o activación de una proteína que se une a un objetivo deseado, o tipos similares de cambios en la bioquímica del cuerpo. El efecto bioquímico específico puede ocasionar alivio de síntomas de una enfermedad o padecimiento, u otro efecto deseable. El resultado que puede detectarse, también puede detectarse a través de una etapa intermedia.

Por "condiciones estándar" se quiere decir condiciones bajo las cuales se realiza un ensayo para obtener datos científicamente significativos. Las condiciones estándar son dependientes del ensayo particular, y pueden ser generalmente subjetivas. Normalmente, las condiciones estándar de un ensayo serán aquellas condiciones que son óptimas para obtener datos útiles a partir del ensayo particular. Las condiciones estándar generalmente minimizarán la señal de fondo y maximizarán la señal buscada que debe detectarse.

Por "desviación estándar" se quiere decir la raíz cuadrada de la varianza. La varianza es una medida de qué tanto se dispersa una distribución. Se calcula como la desviación cuadrada promedio de cada número a partir de su media. Por ejemplo, para los números 1, 2 y 3, la media es 2 y la varianza es:

$$\sigma^2 = \frac{(1-2)^2 + (2-2)^2 + (3-2)^2}{3} = 0.667 .$$

En el contexto de esta invención, por "molécula objetivo" se quiere decir una molécula de la que un compuesto, andamiaje molecular o ligando se está examinando para su unión a la misma. La molécula objetivo tiene una actividad que se alterará o cambiará por la unión del andamiaje molecular o ligando a la molécula objetivo. La unión del compuesto, andamiaje o ligando a la molécula objetivo puede ocasionar de preferencia un efecto bioquímico específico cuando se presenta en un sistema biológico. Un "sistema biológico" incluye, pero no se limita a, un sistema vivo tal como un humano, animal, planta o insecto. En la mayoría, pero no en todos los casos, la molécula objetivo será una molécula de proteína o ácido nucleico.

Por "farmacóforo" se quiere decir una representación de características moleculares que se consideran como responsables de una actividad deseada, tal como interacción o unión con un receptor. Un farmacóforo puede incluir propiedades tridimensionales (grupos

hidrofóbicos, grupos cargados/ionizables, donadores/aceptores de enlaces de hidrógeno), 2D (subestructuras) y 1D (físicas o biológicas).

Como se usan en la presente en relación con valores numéricos, los términos "aproximadamente" y "alrededor de" significan ±10% del valor indicado.

I. Aplicaciones de Agonistas de PPAR

Los PPARs se han reconocido como objetivos adecuados para una serie de diferentes enfermedades y padecimientos. Algunas de esas aplicaciones se describen brevemente en lo siguiente. Se conocen aplicaciones adicionales y los compuestos presentes también pueden usarse para aquellas enfermedades y padecimientos.

(a) Resistencia a insulina y diabetes

En relación con resistencia a la insulina y diabetes, el PPARγ es necesario y suficiente para la diferenciación de adipocitos *in vitro* e *in vivo*. En adipocitos, el PPARγ incrementa la expresión de numerosos genes involucrados en metabolismo de lípidos y incorporación de lípidos. En contraste, el PPARγ subregula la leptina, una proteína selectiva de adipocitos, secretada, de la que se ha mostrado que inhibe la ingestión y aumenta el metabolismo catabólico de lípidos. Esta actividad de receptor puede explicar la incorporación y almacenamiento calórico incrementado, observado *in vivo* con el tratamiento con agonistas de PPARγ. Clínicamente, las TZDs, incluyendo troglitazona, rosiglitazona y pioglitazona, y los no TZDs, incluyendo farglitazar, tienen actividad de sensibilización a insulina y antidiabética. (Berger, et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

El PPARγ se ha asociado con varios genes que afectan la acción de la insulina. El TNFα, una citocina proinflamatoria que se expresa por los adipocitos, se ha asociado con resistencia a la insulina. Los agonistas de PPARγ inhiben la expresión de TNFα en tejido adiposo de roedores obesos, y extirpan las acciones del TNFα en adipocitos *in vitro*. Se demostró que los agonistas de PPARγ inhiben la expresión de 11β-hidroxiesteroide deshidrogenasa 1 (11β-HSD-1), la enzima que convierte cortisona en el agonista de glucocorticoides cortisol, en adipocitos y tejido adiposo de modelos de ratón de diabetes tipo 2. Esto es notable ya que el hipercorticosteroidismo exacerba la resistencia a la insulina. La Proteína Relacionada con el Complemento de Adipocitos

de 30 kDa (Acrip30 o adiponectina) es una proteína secretada específica de adipocitos que disminuye la glucosa, triglicéridos y ácidos grasos libres. En comparación con sujetos humanos normales, los pacientes con diabetes tipo 2 tienen niveles plasmáticos reducidos de Acrp30. El tratamiento de ratones diabéticos y sujetos humanos no diabéticos con agonistas de PPARγ incrementa los niveles plasmáticos de Acrp30. La inducción de Acrp30 por agonistas de PPARγ puede, por lo tanto, jugar también un papel clave en el mecanismo de sensibilización a insulina de los agonistas de PPARγ en la diabetes. (Berger, et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

El PPARγ se expresa predominantemente en tejido adiposo. De este modo, se cree que la eficacia neta *in vivo* de los agonistas de PPARγ involucra acciones directas sobre las células adiposas con efectos secundarios en tejidos clave de respuesta a insulina tales como músculo esquelético e hígado. Esto se soporta por la carencia de eficacia en disminución de glucosa de la rosiglitazona en un modelo de ratón de resistencia severa a la insulina donde el tejido adiposo blanco estaba esencialmente ausente. Adicionalmente, el tratamiento *in vivo* de ratas resistentes a insulina produce normalización aguda (<24 horas) de la acción de la insulina del tejido adiposo mientras que la incorporación de glucosa mediada por insulina en el músculo no se mejoró hasta varios días después del inicio de la terapia. Esto es consistente con el hecho que los agonistas de PPARγ pueden producir un incremento en la acción de la insulina del tejido adiposo después de la incubación directa *in vitro*, mientras que tal efecto no pudo demostrarse usando músculos esqueléticos aislados incubados *in vitro*. Los efectos metabólicos benéficos de los agonistas de PPARγ sobre músculo e hígado pueden mediarse por su capacidad para (a) mejorar la incorporación, almacenamiento (y potencialmente catabolismo) mediados por insulina de los ácidos grasos libres en el tejido adiposo; (b) inducir la producción de factores derivados de tejido adiposo con actividad potencial de sensibilización a insulina (por ejemplo, Acrp30); y/o (c) suprimir los niveles circulantes y/o acciones de los factores derivados de tejido adiposo que ocasionan resistencia a insulina, tales como TNFα o resistina. (Berger, et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

(b) Dislipidemia y ateroesclerosis

En relación con dislipidemia y aterosclerosis, se ha mostrado que el PPARα juega un papel crítico en la regulación de la incorporación, activación y β-oxidación celular de ácidos grasos. La activación del PPARα induce la expresión de proteínas y enzimas de transporte de ácidos grasos en la ruta de la β-oxidación del peroxisoma. Varias enzimas mitocondriales involucradas en el catabolismo de recolección de energía de los ácidos grasos, se sobreregulan contundentemente por los agonistas de PPARα. Los proliferadores del peroxisoma también activan la expresión del CYP4As, una subclase de enzimas del citocromo P450 que catalizan la ω-hidroxilación de ácidos grasos, una ruta que es particularmente activa en los estados de ayuno y diabético. En resumen, es claro que el PPARα es un sensor y regulador importante de lípidos del metabolismo celular de recolección de energía. (Berger, et al., 2002, *Diabetes Tech. And Ther.* 4:163-174.)

La ateroesclerosis es una enfermedad muy prevaleciente en las sociedades occidentalizadas. Además de una fuerte asociación con el colesterol LDL elevado, la "dislipidemia", caracterizada por partículas elevadas ricas en triglicéridos y niveles bajos de colesterol HDL, se asocia comúnmente con otros aspectos de un síndrome metabólico que incluye obesidad, resistencia a la insulina, diabetes tipo 2 y un riesgo incrementado de enfermedad de arterias coronarias. De este modo, en 8,500 hombres con enfermedad conocida de arterias coronarias, se encontró que 38% tenían HLD bajo (<35 mg/dL) y 33% tenían triglicéridos elevados (>200 mg/dL). En tales pacientes, el tratamiento con fibratos resultó en una disminución sustancial de triglicéridos y modesta eficacia de elevación de HDL. En forma más importante, una gran prueba prospectiva reciente mostró que el tratamiento con gemfibrozil producía una reducción del 22% en los eventos cardiovasculares o muerte. De este modo, los agonistas de PPARα pueden mejorar efectivamente los factores de riesgo cardiovascular y tener un beneficio neto para mejorar las consecuencias cardiovasculares. De hecho, el fenofibrato se aprobó recientemente en los Estados Unidos para el tratamiento de hiperlipidemia tipo IIA y IIB. Es probable que los mecanismos por los cuales la activación de PPARα ocasiona disminución de triglicéridos incluyan los efectos de agonistas para suprimir la expresión del gen apo-CIII hepático mientras también se estimula la expresión del gen de lipoproteína lipasa. Los agonistas de PPARγ/α duales, incluyendo KRP-297 y DRF 2725,

poseen una potente eficacia de alteración de lípidos además de actividad antihiperglicémica en modelos animales de diabetes y trastornos de lípidos.

La presencia de expresión de PPARα y/o PPARγ en tipos celulares vasculares, incluyendo macrófagos, células endoteliales y células de músculo liso vascular, sugiere que los efectos vasculares directos pueden contribuir a la eficacia antiateroesclerosis potencial. Se ha mostrado que la activación de PPARα y PPARα inhibe la adhesión celular vascular inducida por citocinas y suprime la migración de monocitos-macrófagos. Varios estudios adicionales han mostrado también que los compuestos selectivos de PPARγ tienen la capacidad de reducir el tamaño de las lesiones arteriales y atenuar el direccionamiento de monocitos-macrófagos hacia lesiones arteriales en modelos animales de aterosclerosis. El PPARγ se presenta en macrófagos en lesiones ateroescleróticas humanas, y puede jugar un papel en la regulación de la expresión de la metaloproteinasa-9 de matriz (MMP-9), la cual se implica en ruptura de placas ateroescleróticas (Marx et al., *Am J Pathol.* 1998, 153(1):17- 23). La subregulación de la secreción inducida por LPS de MMP-9 se observó también para los agonistas de PPARα y PPARγ, los cuales pueden contribuir a los efectos benéficos observados con los agonistas de PPAR en modelos animales de ateroesclerosis (Shu et al., *Biochem Biophys Res Commun.* 2000, 267(1):345-9). También se ha mostrado que PPARγ tiene un papel en la expresión de la proteína molécula 1 de adhesión intercelular (ICAM-I) (Chen et al., *Biochem Biophys Res Commun.* 2001, 282(3):717-22) y expresión de la proteína molécula 1 de adhesión celular vascular (VCAM-I) (Jackson et al., *Arterioscler Thromb Vasc Biol.* 1999, 19(9):2094-104) en células endoteliales, las cuales juegan un papel en la adhesión de los monocitos a las células endoteliales. Además, dos estudios recientes han sugerido que la activación de PPARα o PPARγ en macrófagos puede inducir la expresión de una proteína "bomba" de afluencia de colesterol.

Se ha encontrado que los agonistas de PPARδ relativamente selectivos producen, si la hay, mínima actividad de disminución de glucosa o triglicéridos en modelos murinos de diabetes tipo 2 en comparación con agonistas eficaces de PPARγ o PPARα. Subsecuentemente, un incremento modesto en los niveles de colesterol HDL se detectó con agonistas de PPARδ en ratones db/db. Recientemente, Oliver, et al. (*supra*) reportó que un potente agonista de PPARδ

selectivo puede inducir un incremento sustancial en niveles de colesterol HDL mientras se reducen los niveles de triglicéridos y la resistencia a la insulina en monos obesos de la India.

De este modo, mediante mecanismos multifactoriales que incluyen mejoramientos en lípidos circulantes, efectos anti-inflamatorios sistémicos y locales, e inhibición de la proliferación celular vascular, los agonistas de PPARα, PPARγ, y PPARδ pueden usarse en el tratamiento o prevención de la ateroesclerosis. (Berger, et al., *supra*).

(c) Inflamación

Se sabe que los monocitos y macrófagos toman parte importante en el proceso inflamatorio a través de la liberación de citocinas inflamatorias y la producción de óxido nítrico por la sintasa de óxido nítrico inducible. Se ha demostrado que la rosiglitazona induce apoptosis de macrófagos en concentraciones que paralelizan su afinidad por PPARγ. Se ha demostrado también que este ligando bloquea la síntesis de citocinas inflamatorias en líneas celulares colónicas.

Esta última observación sugiere una explicación mecanística para las acciones anti-inflamatorias observadas de las TZDs en modelos de roedores de colitis.

Estudios adicionales han examinado la relación entre macrófagos, citocinas y PPARγ y los agonistas del mismo (Jiang et al., *Nature* 1998, 391(6662):82-6., Ricote et al., *Nature* 1998, 391(6662):79-82, Hortelano et al., *J Immunol.* 2000, 165(11):6525-31, y Chawla et al., *Nat Med.* 2001, 7(1):48-52) lo que sugiere un papel para los agonistas de PPARγ en el tratamiento de respuestas inflamatorias, por ejemplo en enfermedades autoinmunes.

La migración de monocitos y macrófagos juega un papel en el desarrollo de respuestas inflamatorias también. Se han demostrado que los ligandos de PPAR tienen un efecto sobre una diversidad de quimiocinas. La migración de monocitos dirigida por la proteína-1 quimiotáctica de monocitos (MCP-1) se atenúa por los ligandos de PPARγ y PPARα en una línea celular de leucemia monocítica (Kintscher et al., *Eur J Pharmacol.* 2000, 401(3):259-70). Se demostró que la expresión del gen MCP-1 se suprime por el ligando de PPARγ 15-desoxi-Delta(12,14)PGJ2 (15d-PGJ2) en dos líneas celulares monocíticas, lo cual también demostró inducción de la expresión del gen IL-8 (Zhang et al., *J Immunol.* 2001, 166(12):7104-11).

Se han descrito acciones anti-inflamatorias para los ligandos de PPARα que pueden ser importantes en el mantenimiento de la salud vascular. El tratamiento de macrófagos humanos activados por citocinas con agonistas de PPARα induce apoptosis de las células. Se reportó que los agonistas de PPARα inhiben la activación de células de músculo liso aórtico en respuesta a estímulos inflamatorios. (Staels et al., 1998, *Nature* 393:790-793.) En pacientes hiperlipidémicos, el tratamiento con fenofibrato disminuye las concentraciones plasmáticas de la citocina inflamatoria interleucina 6.

Se investigaron rutas anti-inflamatorias en células de músculo liso de vías respiratorias con respecto a PPARα y PPARγ (Patel et al., 2003, *The Journal of Immunology*, 170:2663-2669). Este estudio demostró un efecto anti-inflamatorio de un ligando de PPARγ que puede ser útil en el tratamiento de COPD y de asma insensible a esteroides.

Los efectos anti-inflamatorios de moduladores de PPAR se han estudiado también con respecto a enfermedades autoinmunes, tales como síndrome crónico del intestino inflamado, artritis, enfermedad de Crohn y esclerosis múltiple, y en enfermedades neuronales tales como enfermedad de Alzheimer y enfermedad de Parkinson.

(d) Hipertensión

La hipertensión es un trastorno complejo del sistema cardiovascular que se ha mostrado asociado con resistencia a la insulina. Los pacientes con diabetes tipo 2 demuestran un incremento de 1.5-2 veces en hipertensión en comparación con la población general. Se ha demostrado que la terapia con troglitazona, rosiglitazona y pioglitazona disminuye la presión sanguínea en pacientes diabéticos así como la terapia con troglitazona en sujetos obesos, resistentes a la insulina. Ya que se mostró que tales reducciones en presión sanguínea se correlacionan con disminuciones en niveles de insulina, pueden mediarse por una mejoría en la sensibilidad a insulina. Sin embargo, ya que las TZDs también disminuyeron la presión sanguínea en ratas Sprague Dawley de un riñón un clip, las cuales no son resistentes a la insulina, se propuso que la acción hipotensiva de agonistas de PPARγ no se ejerce únicamente a través de su capacidad para mejorar la sensibilidad a la insulina. Otros mecanismos a los que se ha apelado para explicar los efectos anti-hipertensivos de los agonistas de PPARγ incluyen su capacidad para

(a) subregular la expresión de péptidos que controlan el tono vascular tales como PAI-I, endotelina y péptido C natriurético tipo c o (b) alterar las concentraciones de calcio y la sensibilidad al calcio de las células vasculares. (Berger et al., *supra*).

(e) Cáncer

La modulación del PPAR se ha correlacionado también con el tratamiento del cáncer. (Burstein, et al.; *Breast Cancer Res. Treat.,* 2003, 79(3):391-7; Alderd, et al.; *Oncogene*, 2003, 22(22):3412-6).

(f) Control de Peso

La administración de agonistas de PPARα puede inducir saciedad y, de este modo, son útiles en la pérdida o mantenimiento del peso. Tales agonistas de PPARα pueden actuar en forma preferencial sobre PPARα, o pueden también actuar sobre otro PPAR, o pueden ser pan-agonistas de PPAR. De este modo, el efecto de inducción de saciedad de los agonistas de PPARα puede utilizarse para el control o pérdida de peso.

(g) Enfermedades autoinmunes

Los agonistas de PPAR pueden proporcionar beneficios en el tratamiento de enfermedades autoinmunes. Los agonistas de las isoformas de PPAR pueden involucrarse en el tráfico o actividad de células T y células B, la alteración de la función o diferenciación de oligodendrocitos, la inhibición de la actividad de macrófagos, la reducción de respuestas inflamatorias y efectos neuroprotectores, algunos o todos los cuales pueden ser importantes en una diversidad de enfermedades autoinmunes.

La esclerosis múltiple (MS) es una enfermedad autoinmune neurodegenerativa que involucra la desmielinización de axones y la formación de placas. Se ha demostrado que el ARNm de PPARδ se expresa fuertemente en oligodendrocitos inmaduros (Granneman et al., *Neurosci Res.* 1998, 51(5):563-73). Se demostró que los agonistas selectivos de PPARδ o pan-agonistas aceleran la diferenciación de los oligodendrocitos, sin ningún efecto sobre la diferenciación observada con un agonista selectivo de PPARγ. Una alteración en la mielinización del cuerpo calloso se observó en ratones anulados en PPARδ (Peters et al., *Mol Cell Biol.* 2000, 20(14):5119-28). Se mostró también que el ARNm y la proteína de PPARδ se expresan en todo el cerebro en

neuronas y oligodendrocitos, pero no en astrocitos (Woods et al., *Brain Res.* 2003, 975(1-2):10-21). Estas observaciones sugieren que el PPARδ tiene un papel en la mielinización, donde la modulación de tal papel puede utilizarse para tratar la esclerosis múltiple al alterar la diferenciación de oligodendrocitos, lo cual puede resultar en la desaceleración de la desmielinización, o incluso promover la re-mielinización de los axones. Se ha demostrado también que las células B12 similares a oligodendrocitos, así como oligodendrocitos de médula espinal aislados de rata, se afectan por agonistas de PPARγ. La alquildihidroxiacetona fosfato sintasa, una enzima clave del peroxisoma implicada en la síntesis de plasmológenos, los cuales son un componente clave de la mielina, se incrementa en células B12 tratadas con agonistas de PPARγ, mientras el número de células maduras en los oligodendrocitos de médula espinal aislados se incrementa con el tratamiento con agonistas de PPARγ.

El papel del PPAR en la regulación de células B y T también puede proporcionar beneficios terapéuticos en enfermedades tales como la MS. Por ejemplo, se ha mostrado que los agonistas de PPARγ pueden inhibir la secreción de IL-2 por las células T (Clark et al., *J Immunol.* 2000, 164(3):1364-71) o pueden inducir apoptosis en células T (Harris et al., *Eur J Immunol.* 2001, 31 (4): 1098- 105), lo que sugiere un papel importante en las respuestas inmunes mediadas por células. Un efecto antiproliferativo y citotóxico sobre células B por los agonistas de PPARγ se ha observado también (Padilla et al., *Clin Immunol.* 2002, 103(1):22-33).

Los efectos anti-inflamatorios de los moduladores de PPAR, como se discute en la presente, también pueden ser útiles para tratar MS, así como una diversidad de otras enfermedades autoinmunes tales como diabetes mellitus Tipo 1, psoriasis, vitiligo, uveítis, enfermedad de Sjogren, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome del intestino inflamado y enfermedad de Crohn. Usando un modelo de ratón, se demostró que el gemfibrozil y fenofibrato, agonistas de PPARα, inhiben los signos clínicos de encefalomielitis autoinmune experimental, lo que sugiere que los agonistas de PPARα pueden ser útiles para tratar padecimientos inflamatorios, tal como esclerosis múltiple (Lovett-Racke et al., *J Immunol.* 2004, 172(9):5790-8).

Los efectos neuroprotectores que parecen asociarse con los PPARs también pueden ayudar en el tratamiento de la MS. Los efectos de los agonistas de PPAR sobre la muerte celular neuronal inducida por LPS se estudiaron usando co-cultivos de neuronas corticales-glía. Se mostró que los agonistas de PPARγ, 15d-PGJ2, ciglitazona y troglitazona evitan la muerte celular neuronal inducida por LPS, así como que suprimen la liberación de NO y PGE2 y una reducción en la expresión de iNOS y COx-2 (Kim et al., *Brain Res.* 2002, 941(1-2):1-10).

La artritis reumatoide (RA) es una enfermedad inflamatoria autoimmune que resulta en la destrucción de las articulaciones. Además de la inflamación crónica y el daño a las articulaciones debido en parte a mediadores tales como IL-6 y TNF-alfa, la diferenciación de osteoclastos se implica también en el daño a articulaciones. Los agonistas de PPAR pueden regular estas rutas, proporcionando beneficios terapéuticos en tratamiento de la RA. En estudios usando el agonista de PPARγ, troglitazona, en células sinoviales similares a fibroblastos (FLS) aisladas a partir de pacientes con artritis reumatoide, se observó una inhibición de respuestas inflamatorias mediadas por citocinas (Yamasaki et al., *Clin Exp Immunol.*, 2002, 129(2):379-84). Los agonistas PPARγ han demostrado también efectos benéficos en un modelo de rata o ratón de RA (Kawahito et al., *J Clin Invest.* 2000, 106(2): 189-97; Cuzzocrea et al.. *Arthritis Rheum.* 2003, 48(12):3544-56). Los efectos del ligando de PPARα, fenofibrato, sobre fibroblastos sinoviales reumatoides de pacientes con RA también mostraron inhibición de la producción de citocinas, así como activación NF-KappaB y diferenciación de osteoclastos. Se mostró también que el fenofibrato inhibe el desarrollo de artritis en un modelo de rata (Okamoto et al., *Clin Exp Rheumatol.* 2005, 23(3):323-30).

La psoriasis es una enfermedad autoinmune mediada por células T, donde la activación de las células T conduce a la liberación de citocinas y resulta en la proliferación de queratinocitos. Además de los efectos anti-inflamatorios, la diferenciación de queratinocitos puede también ser un objetivo terapéutico para los agonistas de PPAR. Estudios en un modelo de ratón anulado en PPARδ sugieren usar el ligando de PPARδ para inducir selectivamente la diferenciación de queratinocitos e inhibir la proliferación celular (Kim et al., *Cell Death Differ.* 2005). Se ha demostrado que los ligandos de PPARγ de tiazolidindiona inhiben la proliferación de

queratinocitos psoriáticos en monocapas y cultivos de órganos, y cuando se aplican tópicamente inhiben hiperplasia epidérmica de piel psoriática humana transplantada a ratones SCID (Bhagavathula et al., *J Pharmacol Exp Ther.* 2005,315(3):996-1004).

(h) Enfermedades neurodegenerativas:

La modulación de los PPARs puede proporcionar beneficios en el tratamiento de enfermedades neuronales. Por ejemplo, los efectos anti-inflamatorios de los moduladores de PPAR discutidos en la presente se han estudiado también con respecto a enfermedades neuronales tales como enfermedad de Alzheimer y enfermedad de Parkinson.

Además de los procesos inflamatorios, la enfermedad de Alzheimer se caracteriza por depósitos de péptidos amiloides-beta (Abeta) y nudos neurofibrilares. Una disminución en los niveles de péptido Abeta en células neuronales y no neuronales se observó con la expresión inducida de PPARγ, o por la activación de PPARγ utilizando una tiazolidindiona (Camacho et al., *J Neurosci.* 2004, 24(48):10908-17). El tratamiento de ratones APP7171 con el agonista de PPARγ, pioglitazona, mostró varios efectos benéficos, incluyendo la reducción en microglía activada y astrocitos reactivos en el hipocampo y corteza, reducción en ciclooxigenasa 2 pro-inflamatoria y sintasa de óxido nítrico inducible, niveles disminuidos de ARNm y proteína de β-secretasa-1 y una reducción en los niveles de péptido Abeta1-42 soluble (Heneka et al., *Brain.* 2005, 128(Pt 6):1442-53).

Las regiones de degeneración de neuronas de dopamina en la enfermedad de Parkinson se han asociado con niveles incrementados de citocinas inflamatorias (Nagatsu et al., *J Neural Transm Suppl.* 2000;(60):277-90). El efecto del agonista de PPARγ, pioglitazona, sobre la muerte de células nerviosas dopaminérgicas y la activación de la glía, se estudió en un modelo de ratón MPTP de la enfermedad de Parkinson, en donde la pioglitazona administrada en forma oral resultó en la activación reducida de la glía, así como en prevención de la pérdida de células dopaminérgicas (Breidert et al. *Journal of Neurochemistry*, 2002, 82: 615).

(i) Otras indicaciones

Los moduladores de PPARγ han demostrado inhibición de angiogénesis coroideo inducida por VEGF así como represión de efectos de neovascularización coroideo, lo que sugiere

un potencial para el tratamiento de trastornos retinianos. Se ha mostrado que el PPARδ se expresa en sitios de implante y en células deciduales en ratas, lo que sugiere un papel en el embarazo, tal como para mejorar la fertilidad. Estos estudios se revisaron en Kota, et al., 2005, *Pharmacological Research,* 51: 85-94.

El manejo de dolor, ya sea neuropático o inflamatorio, también se sugiere como un posible objetivo para los moduladores de PPAR. Burstein, S., Life Sci. 2005, **77**(14):1674-84, sugiere que el PPARγ proporciona una función de receptor para la actividad de algunos canabinoides. Lo Verme et al., *Mol Pharmacol.* 2005, 67(1):15-9, identifica a PPARα como un objetivo responsable de efectos que reducen el dolor e inflamación de la palmitoiletanolamida (PEA). La PEA activa selectivamente a PPARα *in vitro*, e induce la expresión del ARMn de PPARα cuando se aplica tópicamente a ratones. En modelos animales de edema de pata inducido por carragenina y edema de oreja inducido por ésteres de forbol, la inflamación en ratones tipo silvestre se atenúa por PEA, la cual no tiene efecto sobre ratones deficientes en PPARα. Los agonistas de PPARα, OEA, GW7647 y Wy-14643 demostraron efectos similares. Benani et al., *Neurosci Lett.* 2004, 369(1):59-63, usa un modelo de inflamación en ratas para valorar la respuesta de PPAR en la médula espinal de ratas después de la inyección de adyuvante completo de Freund en la pata trasera. Se demostró que PPARα se activó, lo que sugiere un papel en las rutas de dolor.

Los PPARs se involucran también en algunas infecciones, y pueden dirigirse para tratar tales infecciones. Dharancy et al. reporta que la infección por VHC se relaciona con expresión y función alterada del receptor nuclear anti-inflamatorio PPARalfa, e identifica el PPARalfa hepático como un mecanismo subyacente a la patogénesis de la infección por HCV, y como un nuevo objetivo terapéutico en el tratamiento tradicional de daño hepático inducido por HCV (Dharancy et al., Gastroenterology 2005, 128(2):334-42). J Raulin reporta que, entre otros efectos, la infección por HIV induce alteración de lípidos celulares, incluyendo desestabilización de la regulación de PPARγ (J. Raulin, Prog Lipid Res 2002, 41(1):27-65). Slomiany y Slomiany reportan que la activación de PPARgamma que conduce a la impedancia del efecto inhibitorio del lipopolisacárido (LPS) de Helicobacter pylori sobre la síntesis de mucina salival, requiere la

participación del receptor del factor de crecimiento epidérmico (EGFR). Además, demostraron que la impedancia por ciglitazona se despuntó en una forma dependiente de la concentración por un agonista de PPAR gamma. (Slomiany and Slomiany, *Inflammopharmacology* 2004, 12(2):177-88).

Muto et al. (*Human Molecular Genetics* 2002, 11(15):1731-1742) demostró que los defectos moleculares observados en embriones $Pkd1^{-/-}$ contribuyen a la patogénesis de la enfermedad renal poliquística dominante autosómica (ADPKD) y que las tiazolidindionas tienen un efecto compensatorio sobre la ruta afectada por la pérdida de policistina-1. De este modo, las rutas activadas por tiazolidindionas pueden proporcionar nuevos objetivos terapéuticos en la ADPKD (Muto et al., *supra*). Glintborg et al. muestra un incremento en los niveles de la hormona del crecimiento en sujetos con síndrome ovárico poliquístico tratado con pioglitazona (Glintborg et al., *J Clin Endocrinol Metab* 2005, 90(10):5605-12).

De acuerdo con la descripción en lo anterior, las isoformas de la familia de PPAR de los receptores nucleares se involucran claramente en la regulación sistémica del metabolismo de lípidos y sirven como "sensores" para ácidos grasos, metabolitos prostanoideos, eicosanoides y moléculas relacionadas. Estos receptores funcionan para regular una amplia colección de genes en una forma coordinada. Las rutas bioquímicas importantes que regulan la acción de la insulina, oxidación de lípidos, síntesis de lípidos, diferenciación de adipocitos, función del peroxisoma, apoptosis celular e inflamación pueden modularse a través de las isoformas individuales del PPAR. Los fuertes efectos terapéuticos de los agonistas de PPARα y PPARγ para influenciar favorablemente los niveles sistémicos de lípidos, homeostasis de glucosa y riesgo de ateroesclerosis (en el caso de la activación de PPARα en humanos) se han descubierto recientemente. Los agonistas de PPARα y PPARγ se utilizan clínicamente en la actualidad para alterar de manera favorable los niveles sistémicos de lípidos y la homeostasis de la glucosa, respectivamente. También, recientes observaciones hechas usando ligandos de los PPARS sugieren que esta isoforma también es un objetivo terapéutico importante para dislipidemia y resistencia a insulina.

De este modo, los moduladores de PPAR, tales como aquellos descritos en la presente, pueden utilizarse en la profilaxis y/o el tratamiento terapéutico de una variedad de

diferentes enfermedades y condiciones, tales como trastornos de peso (por ejemplo, obesidad, condición de sobrepeso, bulimia y anorexia nerviosa), trastornos por lípidos (por ejemplo, hiperlipidemia, dislipidemia incluyendo dislipidemia diabética asociada e hipoalfalipoproteinemia mezclada con dislipidemia, hipertrigliceridemia, hipercolesterolemia y HDL baja (lipoproteína de densidad elevada)), trastornos metabólicos (por ejemplo, Síndrome Metabólico, diabetes mellitus del tipo II, diabetes del tipo I, hiperinsulinemia, tolerancia a glucosa deteriorada, resistencia a la insulina, complicación diabética incluyendo neuropatía, nefropatía, retinopatía, úlceras diabetes en pies y cataratas), enfermedad cardiovascular (por ejemplo, hipertensión, enfermedad cardiaca coronaria), falla cardiaca, falla cardiaca congestiva, aterosclerosis, arteriosclerosis, apoplejía, enfermedad cerebrovascular, infarto al miocardio, enfermedad vascular periférica), enfermedades inflamatorias (por ejemplo, enfermedades autoinmunes tales como vitiligo, uveítis, pénfigo foliáceo, miositis corporal por inclusión, polimiositis, dermatomiositis, escleroderma, enfermedad de Grave, enfermedad de Hashimoto, enfermedad huésped contra injerto crónico, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren y esclerosis múltiple, enfermedades que implican inflamación de las vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica, e inflamación en otros órganos, tales como enfermedad renal policística (PKD), síndrome de ovario policístico, pancreatitis, nefritis y hepatitis), trastornos de la piel (por ejemplo, enfermedades hiperproliferativas epiteliales tales como eczema y soriasis, dermatitis, incluyendo dermatitis atópica, dermatitis por contacto, dermatitis alérgica y dermatitis crónica y cicatrización afectada de heridas), trastornos neurodegenerativos (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, daño de médula espinal y enfermedad desmielizante, incluyendo encefalomielitis diseminada aguda y síndrome de Guillain-Barre), trastornos de coagulación (por ejemplo, trombosis), trastornos gastrointestinales (por ejemplo, infarto del intestino grueso y delgado), trastornos genitourinarios (por ejemplo, insuficiencia renal, disfunción eréctil, incontinencia urinaria y vejiga neurogénica), trastornos oftálmicos (por ejemplo, inflamación oftálmica, degeneración macular y neovascularización patológica), infecciones (por ejemplo, HCV, VIH, y Helicobacter pylori), dolor neuropático o inflamatorio, infertilidad y cáncer.

II. Compuestos Activos en PPAR

Como se indica en el Arte Previo y en relación con enfermedades y padecimientos aplicables, se ha identificado una serie de diferentes agonistas de PPAR. Además, la presente invención proporciona compuestos agonistas de PPAR descritos por las Fórmulas I, Ia, Ib, II o III tal como se proporcionan en el Arte Previo en lo anterior. Dentro de la Fórmula I se incluyen subgrupos y compuestos descritos en la Solicitud de Patente Norteamericana con Número de Serie 10/937,791, cuya descripción se incorpora por esto para referencia en la presente en su totalidad. Estos compuestos pueden usarse en el tratamiento o profilaxis de una enfermedad o padecimiento seleccionado del grupo que consiste de enfermedades inflamatorias (por ejemplo, enfermedades autoinmunes tales como vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren y esclerosis múltiple, enfermedades que involucran inflamación de vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica, e inflamación en otros órganos, tales como enfermedad renal poliquística (PKD), síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), trastornos cutáneos (por ejemplo, dermatitis, incluyendo dermatitis atópica, dermatitis por contacto, dermatitis alérgica y dermatitis crónica y cicatrización defectuosa), trastornos neurodegenerativos (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal y enfermedad desmielinizante, incluyendo encefalomielitis diseminada aguda y síndrome de Guillain-Barre), trastornos gastrointestinales (por ejemplo, infarto del intestino grueso o delgado), trastornos genitourinarios (por ejemplo, insuficiencia renal, disfunción eréctil, incontinencia urinaria y vejiga neurogénica), trastornos oftálmicos (por ejemplo, inflamación oftálmica, degeneración macular y neovascularización patológica), infecciones (por ejemplo, HCV, HIV y Helicobacter pylori), dolor neuropático o inflamatorio e infertilidad, de preferencia enfermedades neurodegenerativas, tales como enfermedad de Alzheimer, enfermedad de Parkinson y esclerosis lateral amiotrófica, enfermedades autoinmunes tales como artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn y esclerosis múltiple,

infertilidad, enfermedades que involucran células de músculo liso de vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica y padecimientos relacionados con angiogénesis, tal como degeneración macular. Los compuestos de las Fórmulas II o III también pueden usarse en el tratamiento de estas enfermedades, así como en el tratamiento o profilaxis de una enfermedad o padecimiento seleccionado del grupo que consiste de trastornos de peso (por ejemplo, obesidad, condición de sobrepeso, bulimia y anorexia nerviosa), trastornos de lípidos (por ejemplo, hiperlipidemia, dislipidemia incluyendo dislipidemia diabética asociada y dislipidemia-hipoalfalipoproteinemia mixta, hipertrigliceridemia, hipercolesterolemia y baja HDL (lipoproteína de alta densidad)), trastornos metabólicos (por ejemplo, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, complicación diabética incluyendo neuropatía, nefropatía, retinopatía, úlcera de pies y cataratas por diabetes), enfermedad cardiovascular (por ejemplo, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva, ateroesclerosis, arterioesclerosis, apoplejía, enfermedad cerebrovascular, infarto del miocardio, enfermedad vascular periférica), trastornos cutáneos (por ejemplo, enfermedades hiperproliferativas epiteliales tales como eccema y psoriasis, trastornos de coagulación (por ejemplo, trombosis) y cáncer. Compuestos ejemplares descritos por las Fórmulas II y III se proporcionan en los Ejemplos en lo siguiente. Compuestos adicionales dentro de las Fórmulas I, Ia, Ib, II o III también pueden prepararse y probarse para confirmar la actividad usando métodos convencionales y la guía proporcionada en la presente.

La actividad de los compuestos puede valorarse utilizando métodos conocidos por aquellos expertos en la técnica, así como los métodos descritos en la presente. Los ensayos de selección pueden incluir controles para propósitos de calibración y confirmación de manipulación apropiada de los componentes del ensayo. Los pozos de referencia, que contienen todos los reactivos pero no el miembro de la biblioteca química, se incluyen usualmente. Como otro ejemplo, un inhibidor (o activador) conocido de una enzima para la cual se buscan moduladores, puede incubarse con una muestra del ensayo, y utilizarse la disminución (o incremento) resultante en la actividad de la enzima como un comparador o control. Se apreciará que los moduladores pueden también combinarse con los activadores o inhibidores de enzimas para encontrar moduladores que

inhiben la activación o represión de la enzima que se provoca de otro modo por la presencia del modulador conocido de la enzima. De modo similar, cuando se buscan ligandos para un objetivo, los ligandos conocidos del objetivo pueden presentarse en los pozos de ensayo de control/calibración.

(a) Ensayos de Actividad Enzimática

Una serie de ensayos diferentes puede utilizarse para valorar la actividad de los moduladores de PPAR y/o determinar la especificidad de un modulador para un PPAR particular. Además de los ensayos mencionados en los Ejemplos en lo siguiente, alguien con experiencia ordinaria en la técnica sabrá de otros ensayos que pueden utilizarse y podrá modificar un ensayo para una aplicación particular. Por ejemplo, el ensayo puede utilizar un formato AlphaScreen (ensayo homogéneo de proximidad luminiscente amplificada), por ejemplo, el sistema AlphaScreening (Packard BioScience). AlphaScreen se describe en general en Seethala and Prabhavathi, *Homogenous Assays*: *AlphaScreen*, Handbook of Drug Screening, Marcel Dekkar Pub. 2001, pp. 106-110. Las aplicaciones de la técnica a los ensayos de unión del ligando del receptor PPAR se describen por ejemplo en Xu, et al., *Nature,* 2002, 415:813-817.

(b) Valoración de la eficacia de los compuestos en sistemas modelo de enfermedad.

La utilidad de los compuestos de la Fórmula I para el tratamiento de enfermedades tales como enfermedades autoinmunes y enfermedades neurológicas, puede valorarse fácilmente usando sistemas modelo conocidos para aquellos experimentados en la técnica. Por ejemplo, la eficacia de los moduladores de PPAR en modelos de la enfermedad de Alzheimer puede probarse al imitar la lesión inflamatoria a los tejidos neuronales, y medir la recuperación usando marcadores moleculares y farmacológicos (Heneka, et al., *J. Neurosci.*, 2000, 20:6862-6867). La eficacia de los moduladores de PPAR en la esclerosis múltiple se ha monitoreado utilizando el modelo aceptado de encefalomielitis autoinmune experimental (EAE) (Storer, et al., *J. Neuroimmunol.,* 2004, 161:113-122. Véase también: Niino, et al., *J. Neuroimmunol.*, 2001, 116:40–48; Diab, et al. *J. Immunol.*, 2002, 168:2508–2515; Natarajan, et al., *Genes Immun.*, 2002, 3, 59–70; Feinstein, et al., *Ann. Neurol.*, 2002, 51:694–702.)

(c) Isómeros, Profármacos y Metabolitos Activos

Los compuestos contemplados en la presente se describen con referencia a las fórmulas genéricas y compuestos específicos. Además, los compuestos de la invención pueden existir en una serie de diferentes formas o derivados, todos dentro del alcance de la presente invención. Estos incluyen, por ejemplo, tautómeros, estereoisómeros, mezclas racémicas, regioisómeros, sales, profármacos (por ejemplo, ésteres de ácido carboxílico), formas solvatadas, diferentes formas o polimorfos cristalinos y metabolitos activos.

(d) Tautómeros, Estereoisómeros, Regioisómeros y Formas Solvatadas

Se entiende que algunos compuestos pueden exhibir tautomerismo. En tales casos, las fórmulas proporcionadas en la presente representan expresamente sólo una de las posibles formas tautoméricas. Debe entenderse, por lo tanto, que las fórmulas proporcionadas en la presente pretenden representar cualquier forma tautomérica de los compuestos representados y no deben limitarse meramente a la forma tautomérica específica representada por los dibujos de las fórmulas.

Asimismo, algunos de los compuestos de acuerdo con la presente invención, pueden existir como estereoisómeros, es decir, que tienen la misma conectividad atómica de átomos enlazados en forma covalente, difiriendo aún en la orientación espacial de los átomos. Por ejemplo, los compuestos pueden ser estereoisómeros ópticos, los cuales contienen uno o más centros quirales y, por lo tanto, pueden existir en dos o más formas estereoisoméricas (por ejemplo, enantiómeros o diastereómeros). De este modo, tales compuestos pueden presentarse como estereoisómeros únicos (es decir, esencialmente libres de otros estereoisómeros), racematos y/o mezclas de enantiómeros y/o diastereómeros. Como otro ejemplo, los estereoisómeros incluyen isómeros geométricos, tales como orientación *cis* o *trans* de sustituyentes en carbonos adyacentes de un doble enlace. Todos los estereoisómeros únicos, racematos y mezclas de los mismos pretenden estar dentro del alcance de la presente invención. A menos que se especifique lo contrario, todas las formas estereoisoméricas se incluyen dentro de las fórmulas proporcionadas en la presente.

En algunas modalidades, un compuesto quiral de la presente invención está en una forma que contiene por lo menos 80% de un isómero único (60% de exceso enantiomérico ("e.e") o exceso diastereomérico ("d.e.")), o por lo menos 85% (70% de e.e. o d.e.), 90% (80% de e.e. o d.e.), 95% (90% de e.e. o d.e.), 97.5% (95% de e.e. o d.e.) o 99% (98% de e.e. o d.e.). Como se entiende generalmente por aquellos expertos en la técnica, un compuesto ópticamente puro que tiene un centro quiral es uno que consiste esencialmente de uno de los dos posibles enantiómeros (es decir, es enantioméricamente puro) y un compuesto ópticamente puro que tiene más de un centro quiral es uno que es diastereoméricamente puro y enantioméricamente puro. En algunas modalidades, el compuesto se presenta en forma ópticamente pura.

Para los compuestos en los cuales la síntesis involucra la adición de un grupo único en un doble enlace, particularmente un doble enlace carbono-carbono, la adición puede ocurrir en cualquiera de los átomos enlazados por el doble enlace. Para tales compuestos, la presente invención incluye ambos regioisómeros.

Adicionalmente, las fórmulas pretenden cubrir formas solvatadas así como no solvatadas de las estructuras identificadas. Por ejemplo, las estructuras indicadas incluyen formas hidratadas y no hidratadas. Otros ejemplos de solvatos incluyen las estructuras en combinación con un solvente adecuado, tal como isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético o etanolamina.

(e) Profármacos y Metabolitos

Además de las presentes fórmulas y compuestos descritos en la presente, la invención también incluye profármacos (generalmente profármacos farmacéuticamente aceptables), derivados metabólicos activos (metabolitos activos) y sus sales farmacéuticamente aceptables.

Los profármacos son compuestos o sales farmacéuticamente aceptables de los mismos los cuales, cuando se metabolizan bajo condiciones fisiológicas o cuando se convierten por solvólisis, producen el compuesto activo deseado. Los profármacos incluyen, sin limitación, ésteres, amidas, carbamatos, carbonatos, ureidos, solvatos o hidratos del compuesto activo. Típicamente, el profármaco es inactivo, o menos activo que el compuesto activo, pero puede

proporcionar una o más propiedades favorables de manejo, administración y/o metabólicas. Por ejemplo, algunos profármacos son ésteres del compuesto activo; durante la metabólisis, el grupo éster se escinde para producir el fármaco activo. También, algunos profármacos se activan en forma enzimática para producir el compuesto activo, o un compuesto el cual, con una reacción química posterior, produce el compuesto activo. En este contexto, un ejemplo común es un alquiléster de un ácido carboxílico.

Como se describe en *The Practice of Medicinal Chemistry*, Cap. 31-32 (Ed. Wermuth, Academic Press, San Diego, CA, 2001), los profármacos pueden dividirse conceptualmente en dos categorías no exclusivas, profármacos bioprecursores y profármacos portadores. Generalmente, los profármacos bioprecursores son compuestos que son inactivos o tienen baja actividad en comparación con el compuesto del fármaco activo correspondiente, que contiene uno o más grupos protectores y se convierten en una forma activa por metabolismo o solvólisis. Tanto la forma del fármaco activo como cualesquier productos metabólicos liberados deben tener una toxicidad aceptablemente baja. Típicamente, la formación del compuesto del fármaco activo involucra un proceso o reacción metabólica que es de uno de los siguientes tipos:

Reacciones oxidativas: Las reacciones oxidativas se ejemplifican sin limitación a reacciones tales como oxidación de alcohol, carbonilo y funcionalidades ácido, hidroxilación de carbonos alifáticos, hidroxilación de átomos de carbono alicíclicos, oxidación de átomos de carbono aromáticos, oxidación de dobles enlaces carbono-carbono, oxidación de grupos funcionales que contienen nitrógeno, oxidación de silicio, fósforo, arsénico y azufre, N-desalquilación oxidativa, O- y S-desalquilación oxidativa, desaminación oxidativa, así como otras reacciones oxidativas.

Reacciones reductivas: Las reacciones reductivas se ejemplifican sin limitación a reacciones tales como reducción de funcionalidades carbonilo, la reducción de funcionalidades alcohol y dobles enlaces carbono-carbono, reducción de grupos funcionales que contienen nitrógeno y otras reacciones de reducción.

Reacciones sin cambio en el estado de oxidación: Las reacciones sin cambio en el estado de oxidación se ejemplifican sin limitación a reacciones tales como hidrólisis de ésteres y éteres, escisión hidrolítica de enlaces sencillos carbono-nitrógeno, escisión hidrolítica de

heterociclos no aromáticos, hidratación y deshidratación en enlaces múltiples, nuevos enlazamientos atómicos que resultan de reacciones de deshidratación, deshalogenación hidrolítica, remoción de molécula de haluro de hidrógeno y otras reacciones.

Los profármacos portadores son compuestos de fármacos que contienen una porción de transporte que, por ejemplo, mejora la incorporación y/o suministro ubicado hacia uno del o los sitios de acción. De modo deseable para tal profármaco portador, el enlazamiento entre la porción del fármaco y la porción de transporte es un enlace covalente, el profármaco es inactivo o menos activo que el compuesto del fármaco, el profármaco y cualquier porción de transporte de liberación son aceptablemente no tóxicos. Para los profármacos donde la porción de transporte pretende mejorar la incorporación, típicamente la liberación de la porción de transporte debe ser rápida. En otros casos, es deseable utilizar una porción que proporciona liberación lenta, por ejemplo, ciertos polímeros u otras porciones, tales como ciclodextrinas. (Véase, por ejemplo, Cheng et al., Publicación de Patente Norteamericana No. 20040077595, Solicitud No. 10/656,838, incorporada en la presente para referencia.) Tales fármacos portadores son a menudo ventajosos para los fármacos administrados en forma oral. Los profármacos portadores pueden, por ejemplo, usarse para mejorar una o más de las siguientes propiedades: carácter lipofílico incrementado, duración incrementada de los efectos farmacológicos, especificidad de sitio incrementada, toxicidad y reacciones adversas disminuidas, y/o mejora en la formulación del fármaco (por ejemplo, estabilidad, solubilidad en agua, supresión de una propiedad organoléptica o fisicoquímica indeseable). Por ejemplo, el carácter lipofílico puede incrementarse por la esterificación de grupos hidroxilo con ácidos carboxílicos lipofílicos o de grupos de ácido carboxílico con alcoholes, por ejemplo, alcoholes alifáticos. Wermuth, *supra*.

Los profármacos pueden proceder a partir de la forma de profármaco hacia una forma activa en una sola etapa, o pueden tener una o más formas intermedias las cuales pueden, por sí mismas, tener actividad o pueden ser inactivas.

Los metabolitos, por ejemplo, metabolitos activos, se superponen con los profármacos como se describe en lo anterior, por ejemplo, profármacos bioprecursores. De esta manera, tales metabolitos son compuestos farmacológicamente activos, o compuestos que se

metabolizan además hacia compuestos farmacológicamente activos, que son derivados resultantes de procesos metabólicos en el cuerpo de un sujeto. De estos, los metabolitos activos son tales compuestos derivados farmacológicamente activos. Para los profármacos, el compuesto del profármaco es generalmente inactivo o de actividad menor que el producto metabólico. Para los metabolitos activos, el compuesto progenitor puede ser un compuesto activo o puede ser un profármaco inactivo. Los metabolitos de un compuesto pueden identificarse usando técnicas rutinarias conocidas en el arte, y sus actividades determinarse usando pruebas tales como aquellas descritas en la presente. Por ejemplo, en algunos compuestos, uno o más grupos alcoxi pueden metabolizarse hacia grupos hidroxilo mientras que retienen actividad farmacológica, y/o los grupos carboxilo pueden esterificarse, por ejemplo, glucuronidación. En algunos casos, puede haber más de un metabolito, en donde uno del o los metabolitos intermedios se metabolizan además para proporcionar un metabolito activo. Por ejemplo, en algunos casos un compuesto derivado que resulta de la glucuronidación metabólica puede ser inactivo o de baja actividad, y puede metabolizarse además para proporcionar un metabolito activo.

Los profármacos y metabolitos activos pueden identificarse usado técnicas rutinarias conocidas en el arte. Véase, por ejemplo, Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, *supra*.

(f) Sales farmacéuticamente aceptables

Los compuestos pueden formularse como, o estar en forma de, sales farmacéuticamente aceptables. Las formas de sales farmacéuticamente aceptables contempladas incluyen, sin limitación, mono, bis, tris, tetrakis, y asi sucesivamente. Las sales farmacéuticamente aceptables son no tóxicas en las cantidades y concentraciones a las cuales se administran. La preparación de tales sales puede facilitar el uso farmacológico al alterar las características físicas de un compuesto sin evitar que ejerza su efecto fisiológico. Las alteraciones útiles en las propiedades físicas incluyen disminución del punto de fusión para facilitar la administración transmucosal e incremento de la solubilidad para facilitar la administración de concentraciones más altas del fármaco. Un compuesto de la invención puede poseer un grupo funcional suficientemente

ácido, uno suficientemente básico o ambos y, por consiguiente, reaccionar con cualquiera de una serie de bases inorgánicas u orgánicas y ácidos inorgánicos y orgánicos, para formar una sal farmacéuticamente aceptable.

Las sales farmacéuticamente aceptables incluyen sales de adición ácida tales como aquellas que contienen sulfato, pirosulfato, bisulfato, sulfito, bisulfito, cloruro, bromuro, yoduro, clorhidrato, fumarato, maleato, fosfato, fosfato monoácido, fosfato diácido, metafosfato, pirofosfato, sulfamato, acetato, citrato, lactato, tartrato, sulfonato, metansulfonato, propansulfonato, etansulfonato, bencensulfonato, *p*-toluensulfonato, naftalen-1-sulfonato, naftalen-2-sulfonato, xilensulfonatos, ciclohexilsulfamato, quinato, propionato, decanoato, caprilato, acrilato, formiato, isobutirato, caproato, heptanoato, propiolato, oxalato, malonato, succinato, suberato, sebacato, fumarato, maleato, butin-1,4-dioato, hexin-1,6-dioato, benzoato, clorobenzoato, metilbenzoato, dinitrobenzoato, hidroxibenzoato, metoxibenzoato, ftalato, fenilacetato, fenilpropionato, fenilbutirato, gamma-hidroxibutirato, glicolato y mandelato. Las sales farmacéuticamente aceptables pueden obtenerse a partir de ácidos tales como ácido clorhídrico, ácido maleico, ácido sulfúrico, ácido fosfórico, ácido sulfámico, ácido acético, ácido cítrico, ácido láctico, ácido tartárico, ácido malónico, ácido metansulfónico, ácido etansulfónico, ácido bencensulfónico, ácido p-toluensulfónico, ácido ciclohexilsulfámico, ácido fumárico y ácido quínico.

Las sales farmacéuticamente aceptables incluyen también sales de adición básica tales como aquellas que contienen benzatina, cloroprocaína, colina, dietanolamina, etanolamina, t-butilamina, etilendiamina, meglumina, procaína, aluminio, calcio, litio, magnesio, potasio, sodio, amonio, alquilamina y zinc, cuando se presentan grupos funcionales ácidos, tales como ácido carboxílico o fenol. Por ejemplo, véase *Remington's Pharmaceutical Sciences*, 19ª ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Tales sales pueden prepararse usando las bases correspondientes apropiadas.

Las sales farmacéuticamente aceptables pueden prepararse por técnicas estándar. Por ejemplo, la forma de base libre de un compuesto puede disolverse en un solvente adecuado, tal como una solución acuosa o de acuosa-alcohol que contiene el ácido apropiado y luego aislarse

al evaporar la solución. En otro ejemplo, una sal puede prepararse al hacer reaccionar la base libre y el ácido en un solvente orgánico.

De este modo, por ejemplo, si el compuesto particular es una base, la sal farmacéuticamente aceptable deseada puede prepararse por cualquier método adecuado disponible en la técnica, por ejemplo, el tratamiento de la base libre con un ácido inorgánico, tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, o con un ácido orgánico, tales como ácido acético, ácido maleico, ácido succínico, ácido mandélico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, un ácido de piranosidilo, tal como ácido glucurónico o ácido galacturónico, un ácido alfa-hidroxi, tal como ácido cítrico o ácido tartárico, un aminoácido tal como ácido aspártico o ácido glutámico, un ácido aromático, tal como ácido benzoico o ácido cinámico, un ácido sulfónico, tal como ácido p-toluensulfónico o ácido etansulfónico o similares.

De manera similar, si el compuesto particular es un ácido, la sal farmacéuticamente aceptable deseada puede prepararse por cualquier método adecuado, por ejemplo, tratamiento del ácido libre con una base inorgánica u orgánica, tal como una amina (primaria, secundaria o terciaria), un hidróxido de metal de álcali o hidróxido de metal alcalinotérreo o similares. Ejemplos ilustrativos de sales adecuadas incluyen sales orgánicas derivados de aminoácidos, tales como L-glicina, L-lisina y L-arginina, amoniaco, aminas primarias, secundarias y terciarias, y aminas cíclicas, tales como hidroxietilpirrolidina, piperidina, morfolina o piperizina, y sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, zinc, aluminio y litio.

La sal farmacéuticamente aceptable de los diferentes compuestos puede presentarse como un complejo. Ejemplos de complejos incluyen el complejo 8-cloroteofilina (análogo a, por ejemplo, el complejo dimenhidrinato:difenhidramina 8-cloroteofilina (1:1); Dramamina) y diversos complejos de inclusión de ciclodextrinas.

A menos que se especifique lo contrario, la especificación de un compuesto en la presente incluye sales farmacéuticamente aceptables de tal compuesto.

(g) Formas Polimórficas

En el caso de agentes que son sólidos, se entiende por aquellos expertos en la técnica que los compuestos y sales pueden existir en diferentes formas cristalinas o polimórficas, cuya totalidad pretende estar dentro del alcance de la presente invención y fórmulas especificadas.

III. Administración

Los métodos y los compuestos se usarán típicamente en la terapia para sujetos humanos. Sin embargo, también pueden usarse para tratar indicaciones similares o idénticas en otros sujetos animales. En este contexto, los términos "sujeto", "sujeto animal" y similares se refieren a vertebrados humanos y no humanos, por ejemplo, mamiferos tales como primates no humanos, animales para deporte y comerciales, por ejemplo, bovinos, equinos, porcinos, ovinos, roedores y mascotas, por ejemplo, caninos y felinos.

Las formas adecuadas de dosificación, en parte, dependen del uso o la ruta de administración, por ejemplo, oral, transdérmica, transmucosal, inhalante o por inyección (parenteral). Tales formas de dosificación deben permitir al compuesto alcanzar las células objetivo. Otros factores se conocen bien en la técnica, e incluyen consideraciones tales como toxicidad y formas de dosificación que retardan al compuesto o la composición para ejercer sus efectos. Las técnicas y formulaciones pueden encontrarse en general en Remington: *The Science and Practice of Pharmacy*, 21ª edición, Lippincott, Williams and Wilkins, Philadelphia, PA, 2005 (incorporada por esto para referencia en la presente).

Los compuestos de la presente invención (es decir, la Fórmula I, incluyendo las Fórmulas Ia-Im, y todas las submodalidades descritas en la presente) pueden formularse como sales farmacéuticamente aceptables.

Los portadores o excipientes pueden usarse para producir las composiciones. Los portadores o excipientes pueden elegirse para facilitar la administración del compuesto. Ejemplos de portadores incluyen carbonato de calcio, fosfato de calcio, diversos azúcares tales como lactosa, glucosa o sacarosa, o tipos de almidón, derivados de celulosa, gelatina, aceites vegetales, polietilenglicoles y solventes fisiológicamente compatibles. Ejemplos de solventes fisiológicamente compatibles incluyen soluciones estériles de agua para inyección (WFI), solución salina y dextrosa.

Los compuestos pueden administrarse por diferentes rutas incluyendo intravenosa, intraperitoneal, subcutánea, intramuscular, oral, transmucosal, rectal, transdérmica o inhalante. En algunas modalidades, se prefiere la administración oral. Para administración oral, por ejemplo, los compuestos pueden formularse en formas convencionales de dosificación oral tales como cápsulas, tabletas y preparaciones líquidas tales como jarabes, elíxires y gotas concentradas.

Las preparaciones farmacéuticas para uso oral pueden obtenerse, por ejemplo, al combinar los compuestos activos con excipientes sólidos, moliendo opcionalmente una mezcla resultante y procesando la mezcla de gránulos, agregando después auxiliares adecuados, si se desea, para obtener tabletas o centros de grageas. Los excipientes adecuados son, en particular, rellenos tales como azúcares, incluyendo lactosa, sacarosa, manitol o sorbitol; preparaciones de celulosa, por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de papa, gelatina, goma de tragacanto, metilcelulosa, hidroxipropilmetil-celulosa, carboximetilcelulosa de sodio (CMC) y/o polivinilpirrolidona (PVP: povidona). Si se desea, pueden agregarse agentes desintegrantes, tales como la polivinilpirrolidona reticulada, agar o ácido algínico, o una sal de los mismos tal como alginato de sodio.

Los centros de grageas se proporcionan con recubrimientos adecuados. Para este propósito, pueden usarse soluciones de azúcar concentradas, las cuales pueden contener opcionalmente, por ejemplo, goma arábiga, talco, polivinilpirrolidona, gel de carbopol, polietilenglicol (PEG) y/o dióxido de titanio, soluciones de laca y solventes orgánicos adecuados o mezclas de solventes. Pueden agregarse materiales colorantes o pigmentos a los recubrimientos de tabletas o grageas para su identificación o para caracterizar diferentes combinaciones de dosis de compuestos activos.

Las preparaciones farmacéuticas que pueden usarse en forma oral incluyen cápsulas de ajuste a presión hechas de gelatina ("gelcaps") así como cápsulas selladas suaves hechas de gelatina, y un plastificante, tal como glicerol o sorbitol. Las cápsulas de ajuste a presión pueden contener los ingredientes activos en mezcla con relleno tal como lactosa, aglutinantes tales como almidones y/o lubricantes tales como talco o estearato de magnesio y, opcionalmente, estabilizadores. En las cápsulas suaves, los compuestos activos pueden disolverse o suspenderse

en líquidos adecuados, tales como aceites grasos, parafina líquida o polietilenglicoles (PEGs) líquidos. Además, pueden agregarse estabilizadores.

Alternativamente, puede usarse inyección (administración parenteral), por ejemplo, intramuscular, intravenosa, intraperitoneal y/o subcutánea. Para inyección, los compuestos de la invención se formulan en soluciones líquidas estériles, de preferencia en tampones o soluciones fisiológicamente compatibles, tales como solución salina, solución de Hank o solución de Ringer. Además, los compuestos pueden formularse en forma sólida y volver a disolverse o suspenderse inmediatamente antes de su uso. Pueden producirse también formas liofilizadas.

La administración también puede ser por medio transmucosal, tópico, transdérmico o inhalante. Para administración transmucosal, tópica o transdérmica, en la formulación se usan penetrantes apropiados para la barrera que debe permearse. Tales penetrantes se conocen generalmente en la técnica, e incluyen, por ejemplo, para administración transmucosal, sales biliares y derivados de ácido fusídico. Además, pueden usarse detergentes para facilitar la permeación. La administración transmucosal, por ejemplo, puede ser a través de rocíos nasales o supositorios (rectal o vaginal).

Las composiciones tópicas de esta invención se formulan de preferencia como aceites, cremas, lociones, ungüentos y similares por la elección de portadores apropiados conocidos en la técnica. Los portadores adecuados incluyen aceites vegetales o minerales, vaselina (vaselina filante), grasas o aceites de cadena ramificada, grasas animales y alcohol de alto peso molecular (mayor de 12 átomos de carbono). Los portadores preferidos son aquellos en los cuales el ingrediente activo es soluble. Pueden incluirse también emulsificantes, estabilizadores, humectantes y antioxidantes, así como agentes que imparten color o fragancia, si se desea. Las cremas para aplicación tópica se formulan de preferencia a partir de una mezcla de aceite mineral, cera de abejas auto-emulsificante y agua, en cuya mezcla el ingrediente activo disuelto en un solvente (por ejemplo, un aceite) en cantidades pequeñas, se mezcla. Adicionalmente, la administración por medios transdérmicos puede comprender un parche o apósito transdérmico, tal como un vendaje impregnado con un ingrediente activo, y opcionalmente uno o más portadores o diluyentes conocidos en la técnica. Para administrarse en forma de un

sistema de suministro transdérmico, la administración de la dosificación, por supuesto, será continua en vez de intermitente en todo el régimen de dosificación.

Para inhalantes, los compuestos de la invención pueden formularse como polvo seco o una solución, suspensión o aerosol adecuado. Los polvos y soluciones pueden formularse con aditivos adecuados conocidos en la técnica. Por ejemplo, los polvos pueden incluir una base de polvo adecuada tal como lactosa o almidón, y las soluciones pueden comprender propilenglicol, agua estéril, etanol, cloruro de sodio y otros aditivos, tales como sales ácidas, alcalinas y de tampón. Tales soluciones o suspensiones pueden administrarse al inhalar mediante rocío, bomba, atomizador o nebulizador y similares. Los compuestos de la invención también pueden usarse en combinación con otras terapias inhaladas, por ejemplo, corticosteroides tales como propionato de fluticasona, dipropionato de beclometasona, triamcinolonacetonida, budesonida y furoato de mometasona; agonistas beta tales como albuterol, salmeterol y formoterol; agentes anticolinérgicos tales como bromuro de ipratropio o tiotropio; vasodilatadores tales como treprostinal e iloprost; enzimas tal como ADNasa; proteínas terapéuticas; anticuerpos de inmunoglobulina; un oligonucleótido, tal como ADN o ARN de hebra sencilla o doble, ARNsi; antibióticos tales como tobramicina; antagonistas receptores muscarínicos; antagonistas de leucotrienos; antagonistas de citocinas; inhibidores de proteasas; cromolina sódica; nedocrila sódica; y cromoglicato de sodio.

Las cantidades de los diversos compuestos que se administrarán pueden determinarse por procedimientos estándar, teniendo en cuenta factores tales como la EC_{50} del compuesto, la vida media biológica del compuesto, la edad, tamaño y peso del sujeto y el trastorno asociado con el sujeto. La importancia de estos y otros factores se conoce bien para aquellos con experiencia ordinaria en la técnica. En general, una dosis estará entre aproximadamente 0.01 y 50 mg/kg, de preferencia 0.1 y 20 mg/kg del sujeto que se está tratando. Pueden usarse dosis múltiples.

Los compuestos de la invención también pueden usarse en combinación con otras terapias para tratar la misma enfermedad. Tal uso de combinación incluye la administración de los compuestos y uno o más terapéuticos diferentes en periodos diferentes, o la co-administración del compuesto y una o más terapias diferentes. En algunas modalidades, la dosificación puede

modificarse para uno o más de los compuestos de la invención u otros terapéuticos usados en combinación, por ejemplo, reducción en la cantidad dosificada en relación con un compuesto o terapia usada sola, por métodos bien conocidos por aquellos de experiencia ordinaria en la técnica.

Se entiende que el uso en combinación incluye el uso con otras terapias, fármacos, procedimientos médicos, etc., en donde la otra terapia o procedimiento puede administrarse en períodos diferentes (por ejemplo, dentro de un tiempo corto, tal como en el lapso de horas (por ejemplo, 1, 2, 3, 4-24 horas), o dentro de un tiempo prolongado (por ejemplo, 1-2 días, 2-4 días, 4-7 días, 1-4 semanas)) a los de un compuesto de la presente invención, o al mismo tiempo que un compuesto de la invención. El uso en combinación también incluye el uso con una terapia o procedimiento médico que se administra una vez u ocasionalmente, tal como cirugía, junto con un compuesto de la invención administrado dentro de un período corto o período prolongado, antes o después de la otra terapia o procedimiento. En algunas modalidades, la presente invención permite el suministro de los compuestos de la invención y uno o más fármacos terapéuticos suministrados por una ruta diferente de administración o por la misma ruta de administración. El uso en combinación por cualquier ruta de administración incluye el suministro de compuestos de la invención y uno o más fármacos terapéuticos distintos, suministrados juntos por la misma ruta de administración en cualquier formulación, incluyendo formulaciones donde los dos compuestos se enlazan químicamente en forma tal que mantienen su actividad terapéutica cuando se administran. En un aspecto, la otra terapia de fármaco puede co-administrarse con uno o más de los compuestos de la invención. El uso en combinación por la co-administración incluye la administración de co-formulaciones o formulaciones de compuestos unidos químicamente, o la administración de dos o más compuestos en formulaciones separadas dentro de un período corto de tiempo entre sí (por ejemplo, en el lapso de 2 horas, 3 horas, hasta 24 horas), administrados por la misma o diferentes rutas. La co-administración de formulaciones separadas incluye la co-administración por el suministro mediante un dispositivo, por ejemplo el mismo dispositivo inhalante, la misma jeringa, etc., o la administración desde dispositivos separados dentro de un período corto entre sí. Las co-formulaciones de los compuestos de la invención y una o más terapias de fármacos adicionales suministrados por la misma ruta incluyen la preparación de los

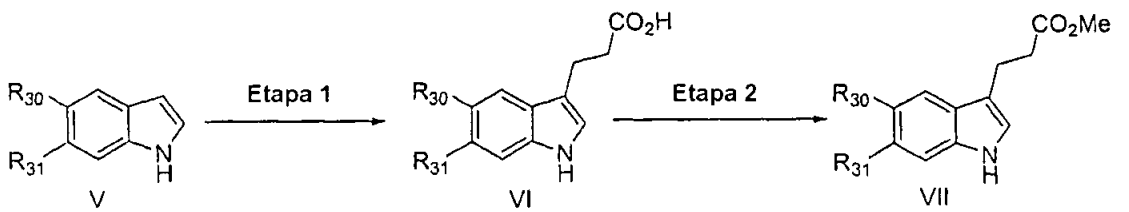
materiales juntos, de modo que puedan administrarse por un dispositivo, incluyendo los compuestos separados combinados en una formulación, o compuestos que se modifican de modo que se unan químicamente, manteniendo aún su actividad biológica. Tales compuestos unidos químicamente pueden tener un enlazamiento que sustancialmente se mantiene *in vivo*, o el enlazamiento puede romperse *in vivo*, separando los dos componentes activos.

IV. Síntesis de Compuestos

Los compuestos con la estructura química de las Fórmulas I, Ia y Ib pueden prepararse por ejemplo, por los esquemas sintéticos descritos en la Solicitud de Patente Norteamericana Número de Serie 10/937,791 (véase también la publicación PCT WO 2005/009958). Compuestos con la estructura química de las Fórmulas II y III pueden prepararse por una serie de rutas sintéticas, incluyendo, por ejemplo los esquemas sintéticos descritos en la presente. Se pueden utilizar rutas sintéticas adicionales por alguien con experiencia en la síntesis química.

Un método para preparar el precursor indol con cadena lateral de ácido 3-propiónico (VII) implica el uso de indol con ácido de Meldrum para producir el éter de ácido propiónico a través de un proceso de dos etapas en una vasija como se muestra en el Esquema I.

Esquema I:



*Etapa 1: Preparación del ácido indol-3-propiónico, **VI***

En un recipiente para microondas, se disuelven indol (1 equivalente), paraformaldehído (1.1 equivalentes), 2,2-dimetil-1,3-dioxan-4,6-diona (1.1 equivalentes), trietilamina (1.1 equivalentes) se disuelven en acetonitrilo (2 ml/mmol). La reacción se calienta a 150°C durante 3 minutos en un reactor de microondas. La reacción se diluye entonces con agua acidificada (pH ~ 5 con ácido acético), y se extrajo la capa acuosa con acetato de etilo. La capa orgánica se lava

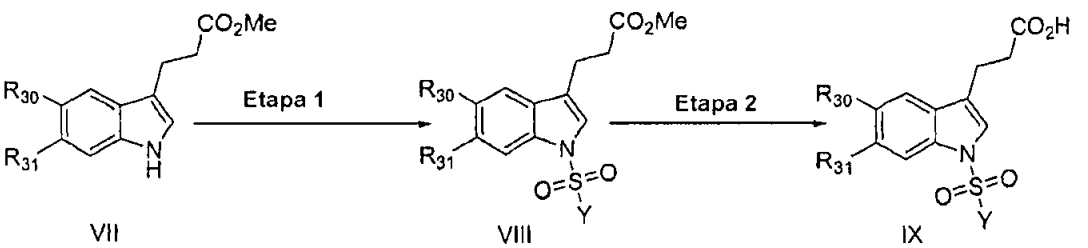
entonces con agua, salmuera, y después se seca sobre sulfato de magnesio. La evaporación del solvente conduce a un sólido. El producto sin purificar se purifica entonces mediante cromatografía instantánea con gradiente en etapas de 2, 4, y 6% de metanol en cloroformo sobre sílice para obtener el compuesto deseado, VI, como un aceite.

*Etapa 2: Preparación del Compuesto **VII**,*

El compuesto **VI** se agita a temperatura ambiente con HCl acuoso (4M), con metanol y dioxano (1:1 equivalentes) durante 1 hora. La mezcla de reacción se extrajo entonces con xilenos. La capa orgánica se evapora, y el compuesto VII se purifica mediante cromatografía instantánea sobre sílice eluyendo con cloroformo para obtener un sólido.

El éster de ácido propiónico resultante puede utilizarse para preparar el indol IX sustituido con 1-sulfona en dos etapas como se muestra en el Esquema II.

Esquema II



VII VIII IX

*Etapa 1: Preparación del Compuesto **VIII***

El compuesto **VII** (1mmol) en THF (5 ml), se combina con BEMP (1.1 mmol), y cloruro de sulfonilo sustituido (1.05 mmol) y mezclado a temperatura ambiente durante 2 horas. El producto **VIII** sin purificar se suministra directamente en la siguiente etapa de saponificación .

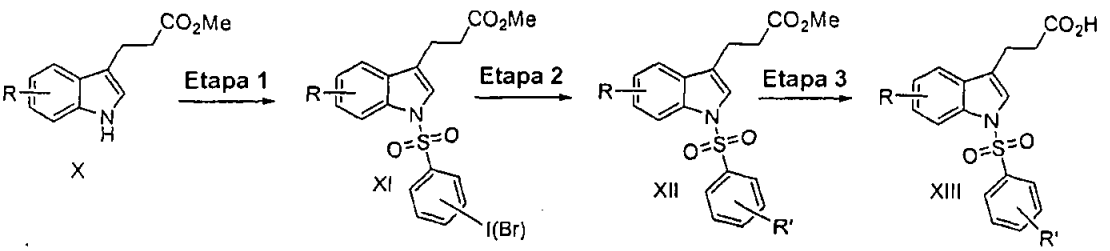
*Etapa 2: Preparación del Compuesto **IX**, desprotección del metiléster.*

En un matraz, se disuelve el reactivo **VIII** sin purificar en NaOH 1M, y se agita durante 4 horas a temperatura ambiente. La hidrólisis puede monitorearse mediante LC-MS. Con la transformación completa, se neutraliza la solución básica con ácido acético. Después, se remueve el solvente bajo presión reducida para producir un sólido sin purificar. El material sin purificar se

recupera en DMSO, y se purifica mediante HPLC de fase inversa con un gradiente de acetonitrilo de 20-100% (gradiente de 12 minutos). El material purificado se analiza entonces mediante HPLC para identificar las fracciones puras. Las fracciones se combinan y se concentran para producir el compuesto **IX** deseado como un sólido.

Los compuestos que tienen una arilsulfona opcionalmente sustituida en el nitrógeno del indol puede prepararse en tres etapas como se muestra en el Esquema III.

Esquema III



*Etapa 1: Preparación del Compuesto **XI***

El compuesto **XI** se prepara mediante desprotonación del nitrógeno del indol del compuesto **X** con el uso de una base, tal como por ejemplo, hidruro de sodio, y acoplamiento con un cloruro de arilsulfonilo sustituido con halógeno en un solvente inerte tal como N,N-dimetilformamida.

*Etapa 2: Preparación del Compuesto **XII***

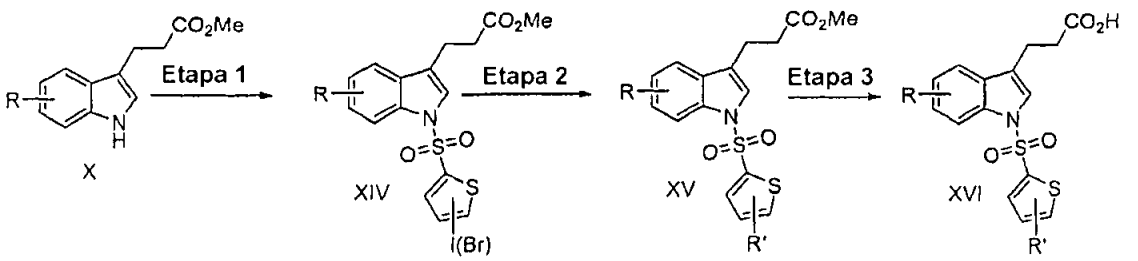
El compuesto **XII** se prepara a través de un acoplamiento biarilo catalizado con metal (tal como paladio) de un ácido borónico con un anillo aromático sustituido con halógeno (yodo o bromo) bajo condiciones básicas (es decir, Suzuki Cross Coupling).

*Etapa 3: Preparación del Compuesto **XIII***

La etapa final de la síntesis del compuesto **XIII** implica la desprotección del (metil o etil) éster bajo condiciones de saponificación con una solución de hidróxido acuoso y un solvente inerte tal como tetrahidrofurano (THF).

En forma similar, la reacción Suzuki Cross Coupling también puede extenderse a tiofenos halogenados. Como se ilustra en el Esquema IV, los tiofenos sustituidos con bi-arilo pueden generarse a través de la misma ruta sintética como se ilustra en el Esquema III.

Esquema IV



*Etapa 1: Preparación del Compuesto **XIV***

El compuesto **XIV** se prepara a través de desprotonación del nitrógeno del indol con el uso de una base, tal como por ejemplo, hidruro de sodio, y acoplamiento con un cloruro de tiofenilsulfonilo sustituido con halógeno en un solvente inerte tal como N,N-dimetilformamida.

*Etapa 2: Preparación del Compuesto **XV***

El compuesto **XV** se prepara a través de un acoplamiento biarilo catalizado con metal (tal como paladio) de un ácido borónico con un anillo aromático sustituido con halógeno (yodo o bromo), bajo condiciones básicas.

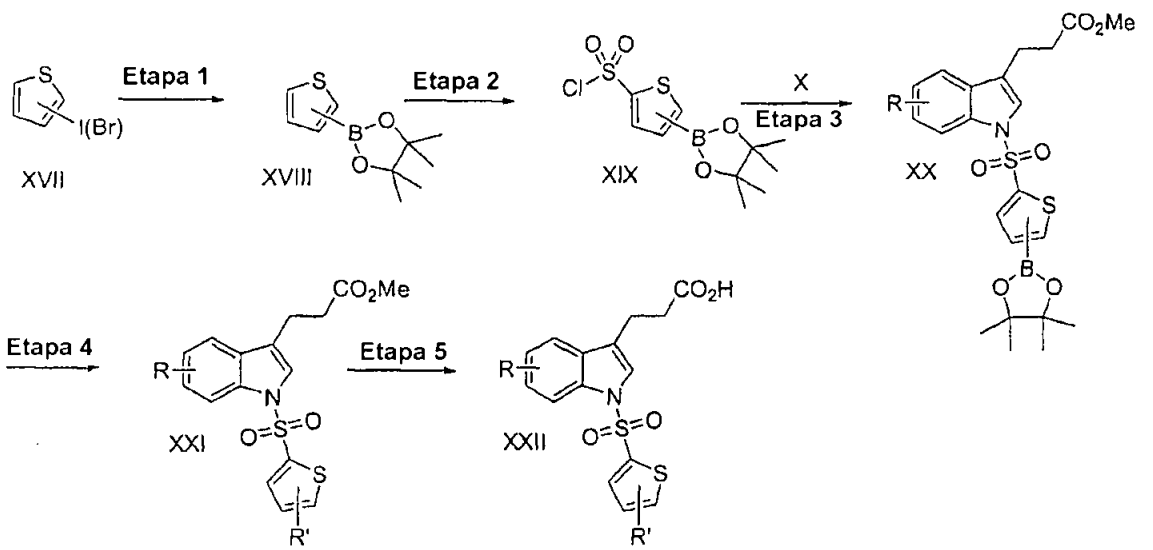
*Etapa 3: Preparación del Compuesto **XVI***

En la etapa final de la síntesis del compuesto **XVI** el (metil o etil) éster se desprotege bajo condiciones de saponificación con una solución de hidróxido acuoso con un solvente inerte tal como tetrahidrofurano (THF).

Una metodología alternativa a la generación del enlazamiento biarilo de las indol-1-sulfonamidas contempla invertir el orden del ácido borónico/éster de los reactivos. Esta estrategia

sintética se ilustra en el Esquema V utilizando un tiofeno como un ejemplo. Compuestos de este tipo pueden prepararse en cinco etapas sintéticas.

Esquema V



Etapa 1: Preparación del Compuesto **XVIII**

A partir de tiofeno halogenado **XVII**, puede ocurrir un intercambio de litio, utilizando reactivos tal como n-butil-litio a –78°C. El tienil-litio puede acoplarse con tricloruro de boro. La hidrólisis subsecuente del dicloruro con un alcohol o un 1,2-dihidroxialcano, tal como por ejemplo, el pinacol puede generar el éster borónico deseado.

*Etapa 2: Preparación del Compuesto **XDC***

El compuesto **XVIII** se trata con ácido clorosulfónico bajo condiciones de baja temperatura (temperatura definida) para agregar el cloruro de sulfonilo al éster borónico de tiofeno.

*Etapa 3: Preparación del Compuesto **XX***

El compuesto **XIX** se acopla al indol **X** como se describe en los Esquemas III y IV utilizando una base para desprotonación del nitrógeno del indol, seguido por acoplamiento con el cloruro de sulfonilo en un solvente inerte tal como N,N-dimetilformamida.

*Etapa 4: Preparación del Compuesto **XXI***

El compuesto **XXI** se prepara a través de acoplamiento de biarilo catalizado con metal (tal como paladio) de un ácido borónico con un anillo aromático sustituido con halógeno (yodo o bromo), bajo condiciones básicas.

*Etapa 5: Preparación del Compuesto **XXII***

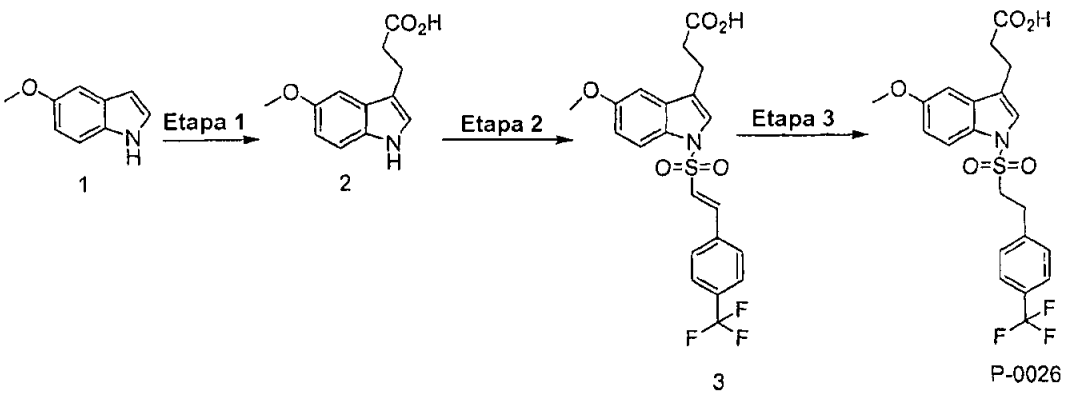
La etapa final de la síntesis implica la desprotección del (metil o etil) éster bajo condiciones de saponificación con una solución de hidróxido acuoso con un solvente inerte tal como tetrahidrofurano (THF).

EJEMPLOS

Ejemplo 1: Síntesis de ácido 3-{5-metoxi-1-[(E)-2-(4-trifluorometil-fenil)-etansulfonil]-1H-indol-3-il}-propiónico (P-0026).

El compuesto **P-0026** se sintetizó en tres etapas a partir de 5-metoxi indol 1 como se muestra en el Esquema 1.

Esquema 1



Etapa 1: Preparación del ácido 3-(5-metoxi-1H-indol-3-il)-propiónico (**2**)

A una solución de 5-metoxiindol (**1**, 4.00 g, 0.0272 mol) disuelta en ácido acético (13 mL, 0.22 mol) que contiene anhídrido acético (5 mL, 0.06 mol), se agregó ácido acrílico (4.06 mL, 0.0592 mol) y la reacción se calentó a 90°C durante 3 hrs. La mezcla de reacción se concentró entonces, 3 ml NaOH (2M) se agregó y la mezcla se agitó durante 5 min. El material insoluble se

removió por filtración. El filtrado se acidificó con 6M HCl. El precipitado se extrajo por filtración para producir el **2** (1.95 g, 33%).

Etapa 2: Preparación del ácido 3-5-Metoxi-1-[(E)-2-(4-trifluorometil-fenil)-etensulfonil]-1H-indol-3-il-propiónico (**3**)

En un matraz de fondo redondo seco y purgado con argón se disolvió ácido 3-(5-Metoxi-1H-indol-3-il)-propiónico (**2**, 90.0 mg, 0.000410 mol) en Tetrahidrofurano seco (4 mL, 0.06 mol). La solución se enfrió hasta -76 °C y 2.5 M de n-Butil-litio en Hexano (328 uL) se agregó por goteo. Después de 15 minutos el cloruro de (E)-2-(4-Trifluorometil-fenil)-etensulfonilo (167 mg, 0.000616 mol) disuelto en 0.5 ml de THF seco se agregó por goteo. La reacción se agitó durante la noche. Se agregó EtOAc a la mezcla y después se acidificó con HCl (1M). La mezcla se agitó durante 1 hora. Se separó la fase orgánica y se extrajo 3 veces la fase acuosa con EtOAc. La fase orgánica combinada se secó (Na2SO4) y la mezcla se concentró, después se colocó en sílice y se purificó con cromatografía instantánea (0.5% MeOH en DCM) para producir 33 mg, 18% de **3**.

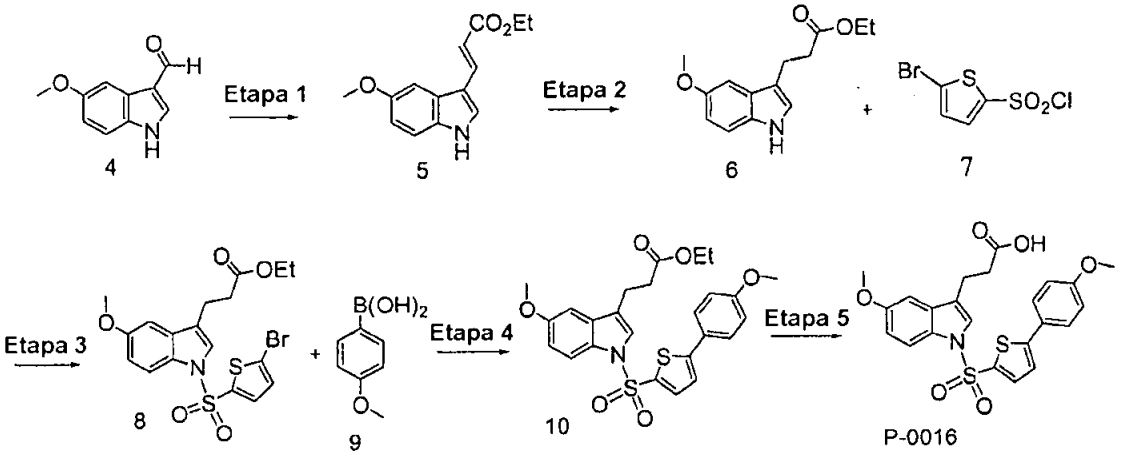
Etapa 3: Preparación del ácido 3-5-Metoxi-1-[(E)-2-(4-trifluorometil-fenil)-etansulfonil]-1H-indol-3-il-propiónico. **(P-0026)**

Al ácido 3-5-Metoxi-1-[(E)-2-(4-trifluorometil-fenil)-etensulfonil]-1H-indol-3-il-propiónico (**3**, 8 mg, 0.00002 mol) disuelto en Tetrahidrofurano (2.0 mL, 0.025 mol), se le agregó a la solución 5% Pd/C (5:95, Paladio:Carbono, 7 mg). La mezcla se agitó durante la noche bajo una atmósfera de gas hidrógeno. El paladio se extrajo por filtración, y la solución se evaporó **P-0026** (8.0 mg, 100%). Peso molecular calculado 455.45, MS (ESI) $[M+H^+]^+$ = 454.0.

Ejemplo 2: Síntesis del ácido 3-{5-metoxi-1-[5-(4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (P-0016).

El compuesto **P-0016** se sintetizó en cinco etapas a partir de 5-metoxiindol-3-carboxaldehído 4 como se muestra en el Esquema 2.

Esquema 2



Etapa 1: Preparación de etiléster del ácido 3-(5-metoxi-1H-indol-3-il)-acrílico (**5**)

En una solución a baja temperatura (baño con hielo) de dietilfosfonoacetato de etilo (30.11 g, 0.134 mol) en tetrahidrofurano (300 mL) bajo nitrógeno, se agregó hidruro de sodio (6.44 g, 0.161 mol, 60%) en cuatro porciones, y se agitó hasta que cesó la evolución de hidrógeno (precaución: evolución de gas muy vigorosa). Una solución de 5-metoxiindol-3-carboxilaldehído (**4**,19.61 g, 0.112 mol) en 350 mL tetrahidrofurano se agregó durante un periodo de 60 minutos a la solución fosfonatada. La mezcla de reacción se calentó a 55°C durante 24 horas, después de lo cual se diluyó la mezcla con 650 mL de diclorometano y se lavó con agua (200 mL; 3X). La capa orgánica se lavó una vez con salmuera, se secó sobre sulfato de sodio anhidro, y se evaporó bajo presión reducida para dar un aceite teñido de amarillo, el cual se purificó al filtrar a través de una columna de sílice. El filtrado se evaporó para producir el compuesto **5** como un sólido blanquecino. ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa 2: — Preparación de etiléster del ácido 3-(5-metoxi-1H-indol-3-il)-propiónico (**6**)

En una solución de etiléster del ácido 3-(5-metoxi-1H-indol-3-il)-acrílico **5** en 250 mL de acetato de etilo se agregó paladio sobre carbón activo (10%; 3 g). La solución se desoxigenó bajo vacío y el hidrógeno se introdujo al matraz de reacción a partir de un balón lleno de hidrógeno. El proceso se repitió tres veces y la mezcla de reacción se agitó durante 16 horas a temperatura ambiente. La mezcla se filtró a través de celite y el filtrado se evaporó bajo presión reducida para

producir el compuesto **6** como un sólido blanco (18.9 g, 68% de rendimiento). 1H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa 3: Preparación de etiléster del ácido 3-[1-(5-bromo-tiofen~2-ilmetil)-5-metoxi-1H-indol-3-il]-propiónico (**8**)

En un matraz de fondo redondo seco, se disolvió etiléster del ácido 3-(5-metoxi-1H-indol-3-il)-propiónico (**6**, 492.0 mg, 1.9 mmol) con diclorometano (12 mL). Sulfato ácido de tetrabutilamonio (30 mg) y 50% de solución KOH (5 mL) se agregaron a continuación. Después de aproximadamente 5 minutos de agitación, se agregó cloruro de 5-bromo tiofen-2-sulfonilo (**7**, 774.0 mg, 2.9 mmol). Esta reacción se dejó agitar a temperatura ambiente durante la noche, después de lo cual se agregaron a la reacción 50 mL de agua y 150 mL acetato de etilo. Las capas se separaron y la capa orgánica se lavó con bicarbonato saturado (3 X 75 mL) y agua (2 X 75 mL) para remover el hidróxido y la sal de sulfonato, después se lavó con salmuera (1 X 75 mL) y se secó sobre sulfato de sodio anhidro. La evaporación bajo presión reducida produjo un compuesto **8** como un aceite café. (820 mg, 87%). ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa 4: Preparación de etiléster del ácido 3-{5-metoxi-1-[5-(4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**10**)

En un matraz de fondo redondo secado al horno de 50 mL, se disolvió etiléster del ácido 3-[1-(5-bromo-tiofen-2-ilmetil)-5-metoxi-1H-indol-3-il]-propiónico (**8**, 300 mg, 0.064 mmol) en tetrahidrofurano seco (8 mL) bajo un flujo de argón. Se agregaron ácido 4-Metoxi-fenil borónico (**9**,. 24.0 mg, 0.16 mmol), tetrakis(trifenilfosfina)paladio(0) (7.2 mg, 0.006 mmol) y 1 N K_2CO_3 (0.4 mL). Un condensador equipado con una linea de gas argón se unió y la reacción se calentó a 48°C durante 3 días. El solvente se removió bajo presión reducida, y el producto sin purificar se purificó por cromatografía instantánea en gel de sílice, utilizando un gradiente de 0-10% acetato de etilo/hexano para proporcionar el compuesto **10**. ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa 5: Síntesis de ácido 3-{5-metoxi-1-[5-(4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0016**)

En una solución de etiléster del ácido 3-{5-metoxi-1-[5-(4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico **10** en tetrahidrofurano (4 mL) se agregó una solución acuosa de hidróxido de potasio (1 mL de 1M) y se agitó a temperatura ambiente durante la noche. El producto ácido se aisló al neutralizar la mezcla de reacción con ácido clorhídrico acuoso, se extrae el producto con acetato de etilo, se seca sobre sulfato de magnesio anhidro, se evapora bajo presión reducida, y se tritura con dietiléter para producir **P-0016** como un sólido blanco (10 mg, 32%) Peso molecular calculado 471.55, MS(ESI) $[M-H^+]^-$= 470.11).

Se prepararon compuestos adicionales siguiendo el protocolo del Esquema 2, reemplazando el ácido 4-metoxi-fenil borónico 9 con un ácido borónico apropiado en la Etapa 4. Los siguientes compuestos se prepararon por este método:

Etiléster del ácido 3-{5-Metoxi-1-[5-(4-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0014**, aislado después de la Etapa 4),

Ácido 3-{5-Metoxi-1-[5-(4-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1 H-indol-3-il}-propiónico (**P-0015**),

Ácido 3-{1-[5-(4-Etoxi-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0017**),

Ácido 3-{5-Metoxi-1-[5-(3-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0019**),

Ácido 3-{5-Metoxi-1-[5-(3-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0018**),

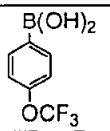
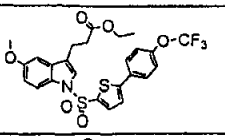
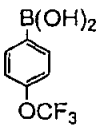
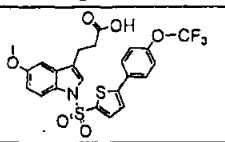
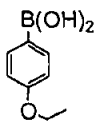
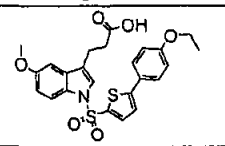
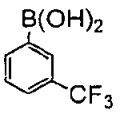
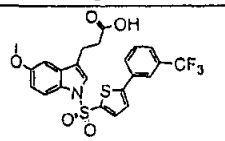
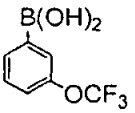
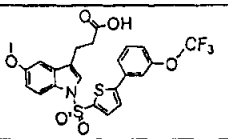
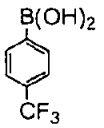
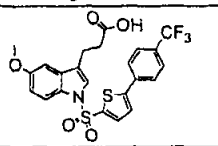
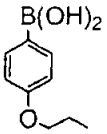
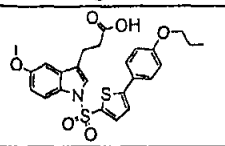
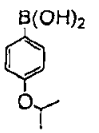
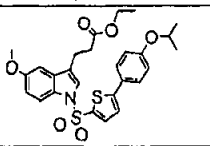
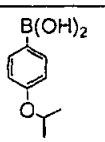
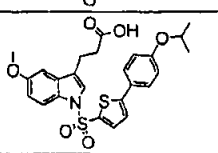
Ácido 3-{5-Metoxi-1-[5-(4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0020**),

Ácido 3-{5-Metoxi-1-[5-(4-propoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0035**),

Etiléster del ácido 3-{1-[5-(4-isopropoxi-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0036**, aislado después de la Etapa 4), y

Ácido 3-{1-[5-(4-Isopropoxi-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0037**).

Estos compuestos se muestran en la siguiente Tabla 1, donde el número de compuesto se proporciona en la Columna 1, el ácido borónico utilizado en la Etapa 4 en la Columna 2, la estructura del compuesto en la Columna 3, y la masa medida y calculada en las Columnas 4 y 5.

Comp. número	Ácido borónico	Estructura del compuesto	Peso molecular	
			Calc.	Medio MS(ESI)
P-0014			525.53	$[M+H^+]^+$ = 526.16
P-0015			471.55	$[M - H^+]^-$ = 470.11
P-0017			485.10	$[M - H^+]^-$ = 484.17
P-0019			509.06	$[M - H^+]^-$ = 508.12
P-0018			525.05	
P-0020			509.52	$[M - H^+]^-$ = 508.12 $[M+H^+]^+$ = 510.20
P-0035			499.61	
P-0036			527.66	
P-0037			499.61	

Se prepararon los compuestos adicionales siguiendo el protocolo del Esquema 2, reemplazando opcionalmente 5-metoxiindol-3-carboxilaldehído 4 con un indol carboxilaldehído

apropiado en la Etapa 1, y/u opcionalmente reemplazando cloruro de 5-bromo tiofen-2-sulfonilo 7 con un cloruro de sulfonilo apropiado en la Etapa 3, y extrayendo el producto de la Etapa 3 directamente a la Etapa 5 para formar el ácido propiónico. Los siguientes compuestos se prepararon por este método, con el peso molecular calculado y la masa medida (MS(ESI)) proporcionados después del compuesto:

Ácido 3-{5-Fluoro-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0002**), PM calculado 501.47, $[M-H^+]^+$ = 500.08,

Ácido 3-{5-Fluoro-1-[5-(5-trifluorometil-isoxazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0003**), PM calculado 488.43, $[M-H^+]^+$ = 487.08,

Ácido 3-{5-Cloro-1-[5-(5-trifluorometil-isoxazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0004**), PM calculado 504.92, $[M+H^+]^+$ = 505.48, $[M-H^+]^+$ =503.06,

Ácido 3-{1-[4-(4-Trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0006**), PM calculado 489.47, $[M+H^+]^+$ = 488.32,

Ácido 3-{1-[5-(1-Metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0007**), PM calculado 483.49, $[M-H^+]^+$ = 482.2,

Ácido 3-{5-Metoxi-1-[5-(5-trifluorometil-isoxazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0008**), PM calculado 500.47, $[M-H^+]^+$ = 499.1,

Etiléster del ácido 3-{5-Etoxi-1-[5-(5-trifluorometil-isoxazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0009**), PM calculado 528.52, $[M-H^+]^+$ = 527.1,

Ácido 3-{5-Cloro-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0033**), PM calculado 517.0, $[M+H^+]^+$ =518.15, $[M-H^+]^+$ = 516.07,

Ácido 3-{5-Metoxi-1-[5-(2-metil-5-trifluorometil-2H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il} propiónico (**P-0034**), PM calculado 513.53, $[M+H^+]^+$ = 514.33, $[M-H^+]^+$ = 512.24,

Ácido 3-{5-Metoxi-1-[4-(piridin-2-iloxi)-bencensulfonil]-1 H-indol-3-il}-propiónico (**P-0047**), PM calculado 452.49, $[M+H^+]^+$ = 453.1,

Ácido 3-{5-Metoxi-1-[4-(4-metoxi-fenoxi)-bencensulfonil]-1-H-indol-3-il}-propiónico (**P-0048**), PM calculado 481.53, $[M+H^+]^+$ = 482.3,

Ácido 3-{1-[4-(3 ,4-Dicloro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0049**), PM calculado 520.39, $[M-H^+]^+$ = 519.9,

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0050**), PM calculado 520.39, $[M-H^+]^+$ = 519.9,

Ácido 3-{5-Metoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0051**), PM calculado 519.50, $[M+H^+]^+$ = 519.9,

Ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0052**), PM calculado 534.42, $[M-H^+]^+$ = 533.9,

Ácido 3-{5-Etoxi-1-[5-(2-metilsulfanil-pirimidin-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0053**), PM calculado 503.62, $[M+H^+]^+$ = 520.3,

Ácido 3-{5-Etoxi-1-[4-(piridin-2-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0055**), PM calculado 466.52, $[M+H^+]^+$ = 467.1,

Ácido 3-{5-Etoxi-1-[4-(piridin-3-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0056**), PM calculado 466.52, $[M+H^+]^+$ = 467.1,

Ácido 3-{5-Etoxi-1-[4-(4-metoxi-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0057**), PM calculado 495.56, $[M+H^+]^+$ = 496.3,

Ácido 3-{1-[4-(3 ,4-Dicloro-fenoxi)-bencensulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0058**), PM calculado 534.42, $[M-H^+]^+$ = 533.9,

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0059**), PM calculado 534.42, $[M-H^+]^+$-533.9,

Ácido 3-{5-Etoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0060**), PM calculado 533.53, $[M+H^+]^+$ = 533.9,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0061**), PM calculado 568.96, $[M+H^+]^+$ = 569.2,

Ácido 3-[5-Etoxi-1-(4'-metoxi-bifenil-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0062**), PM calculado 479.56, $[M+H^+]^+$ = 480.3,

Ácido 3-[5-Etoxi-1-(6-morfolin-4-il-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (P-0063), PM calculado 459.53, $[M+H^+]^+$ = 460.3,

Ácido 3-[5-Etoxi-1-(6-fenoxi-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (P-0064), PM calculado 466.52, $[M+H^+]^+$ = 467.1,

Ácido 3-[5-Etoxi-1-(5-piridin-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0065**), PM calculado 456.54, $[M+H^+]^+$ = 457.1,

Ácido 3-{5-Etoxi-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0066**), PM calculado 527.55, $[M+H^+]^+$ =527.9,

Ácido 3-{5-Metoxi-1-[5-(2-metilsulfanil-pirimidin-4-il)-tiofen-2-sulfonil]-IH-indol-3-il}-propiónico (**P-0067**), PM calculado 489.59, $[M-H^+]^+$ = 489.1,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0068**), PM calculado 554.93, $[M+H^+]^+$ = 555.2,

Ácido 3-{5-Metoxi-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0069**), PM calculado 513.52, $[M-H^+]^+$ =512.09,

Ácido 3-{1-[3-(3 ,4-Dicloro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0071**), PM calculado 520.39, $[M-H^+]^+$ = 520.3,

Ácido 3-[5-Metoxi-1-(4'-metoxi-bifenil-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0072**), PM calculado 465.53, $[M+H^+]^+$ = 466.

Ácido 3,3-[5-Metoxi-1-(5-metil-1-fenil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0146**), PM calculado 439.49, $[M+H^+]^+$ = 440.3,

Ácido 3-{5-Metoxi-1-[3-(piridin-2-carbonil)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0150**), PM calculado 464.50, $[M+H^+]^+$ = 465.1,

Ácido 3-{5-Metoxi-1-[3-(piridin-4-carbonil)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0151**), PM calculado 464.50, $[M+H^+]^+$ = 465.1,

Ácido 3-[l-(Bifenil-2-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico (**P-0152**), PM calculado 435.50, $[M+H^+]^+$ = 436.3,

Ácido 3-[5-Metoxi-1-(4-pirazol-1-il-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0155**), PM calculado 425.47, $[M+H^+]^+$ = 426.3,

Ácido 3-[5-Metoxi-1-(2-fenoxi-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0162**), PM calculado 451.50, $[M+H^+]^+$ = 451.9,

Ácido 3-{5-Etoxi-1-[3-(piridin-4-carbonil)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0168**), PM calculado 478.53, $[M+H^+]^+$ = 479.1,

Ácido 3-[5-Metoxi-1-(6-morfolin-4-il-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (**P-0214**), PM calculado 445.50, $[M+H^+]^+$ = 446.3,

Ácido 3-[5-Metoxi-1-(6-fenoxi-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (**P-0215**), PM calculado 452.49, $[M+H^+]^+$ = 453.1,

Ácido 3-[5-Metoxi-1-(5-piridin-2-il-tiofeno-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0216**), PM calculado 442.52, $[M+H^+]^+$ = 443.5,

Ácido 3-{5-Isopropoxi-1-[5-(2-metilsulfanil-pirimidin-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0311**), PM calculado 517.46, $[M+H^+]^+$ = 517.9,

Ácido 3-{5-Isopropoxi-1-[4-(piridin-2-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0316**), PM calculado 480.54, $[M+H^+]^+$ = 481.1,

Ácido 3-{5-Isopropoxi-1-[4-(piridin-4-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0317**), PM calculado 480.54, $[M+H^+]^+$ = 481.1,

Ácido 3-{5-isopropoxi-1-[4-(4-metoxi-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0318**), PM calculado 509.98, $[M+H^+]^+$ = 510.3,

Ácido 3-{5-Isopropoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0319**), PM calculado 547.55, $[M+H^+]^+$ = 548.3,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5-isopropoxi-1H-indol-3-il}-propiónico (**P-0320**), PM calculado 582.99, $[M+H^+]^+$ = 583.2,

Ácido 3-{1-[3,4-Dicloro-fenoxi)-bencensulfonil]-5-isopropoxi-1H-indol-3-il}-propiónico (**P-0321**), PM calculado 548.45, $[M-H^+]^+$ = 547.9,

Ácido 3-[5-Isopropoxi-1-(4'-metoxi-bifenil-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0322**), PM calculado 493.58, $[M+H^+]^+$ = 494.3,

Ácido 3-[5-Isopropoxi-1-(6-fenoxi-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (**P-0323**), PM calculado 480.54, $[M+H^+]^+$ = 481.1,

Ácido 3-[5-Isopropoxi-1-(5-piridin-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0324**), PM calculado 470.57, $[M+H^+]^+$ = 471.1,

Ácido 3-{5-Isopropoxi-1-fS-Cl-metil-S-trifluorometil-1H-pirazol-S-y^-tiofen-1-sulfonil]-1H-indol-3-il}-propiónico (**P-0326**), PM calculado 541.57, $[M+H^+]^+$ =541.9,

Ácido 3-[1-(Bifenil-2-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico (**P-0332**), PM calculado 463.56, $[M+H^+]^+$ = 463.9,

Ácido 3-[5-Isopropoxi-1-(4'-metil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0338**), PM calculado 477.58, $[M+H^+]^+$ = 478.3,

Ácido 3-[5-Isopropoxi-1-(2-fenoxi-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0339**), PM calculado 479.56, $[M+H^+]^+$ = 479.9,

Ácido 3-(5-Etoxi-1-{4-[(morfolin-4-carbonil)-amino]-bencensulfonil}-1H-indol-3-il)-propiónico (**P-0342**), PM calculado 501.56, $[M+H^+]^+$ = 502.3,

Ácido 3-{5-Etoxi-1-[3-(piridin-2-carbonil)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0344**), PM calculado 478.53, $[M+H^+]^+$ = 479.1,

Ácido 3-{5-Isopropoxi-1-[4-(piridin-3-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0371**), PM calculado 480.54, $[M+H^+]^+$ = 481.1,

Ácido 3-[5-Isopropoxi-1-(4-pirazol-1-il-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0375**), PM calculado 453.52, $[M+H^+]^+$-454.3,

Ácido 3-[5-Etoxi-1-(4'-metil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0386**), PM calculado 463.55, $[M+H^+]^+$ = 464.3,

Ácido 3-[5-Metoxi-1-(4'-trifluorometoxi-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0391**), PM calculado 519.49, $[M-H^+]^+$ = 518.26,

Ácido 3-[5-Metoxi-1-(4'-trifluorometil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0392**), PM calculado 503.50, $[M-H^+]^+$ = 502.25,

Ácido 3-{1-[3-(3 ,5-Dicloro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0560**), PM calculado 520.39, $[M-H^+]^+$ = 518.02,

Ácido 3-{5-Metoxi-1-[3-(4-metoxi-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0561**), PM calculado 481.52, $[M-H^+]^+$ = 480.09,

Etiléster del ácido 3-[5-Metoxi-1-(3-p-toliloxi-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0562**), PM calculado 493.58, $[M+H^+]^+$ = 494.2,

Etiléster del ácido 3-{1-[3-(4-Cloro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0563**), PM calculado 514.00, $[M+H^+]^+$ = 514.9,

Ácido 3-{5-Metoxi-1-[3-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0564**), PM calculado 519.49, $[M+H^+]^+$ = 520.11, $[M-H^+]$-=518.06,

Etiléster del ácido 3-{1-[3-(4-Fluoro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0565**), PM calculado 497.54, $[M+H^+]^+$ = 498.2,

Ácido 3-[5-Metoxi-1-(3-p-toliloxi-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0566**), PM calculado 465.52, $[M-H^+]^-$ = 464.1,

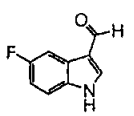
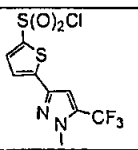
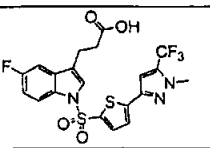
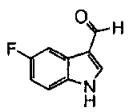
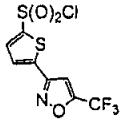
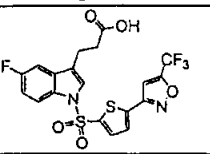
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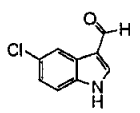
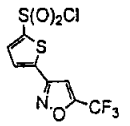
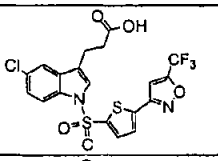
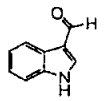
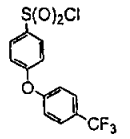
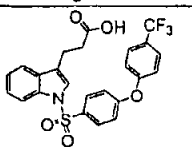
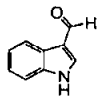
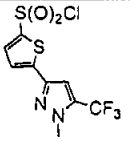
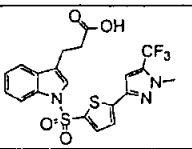
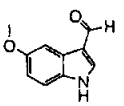
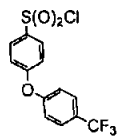
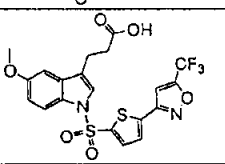
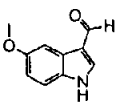
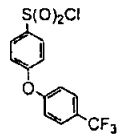
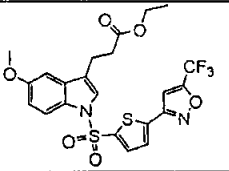
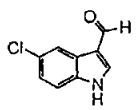
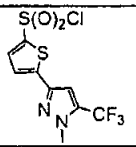
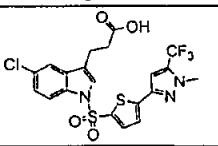
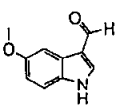
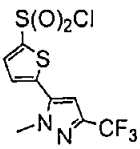
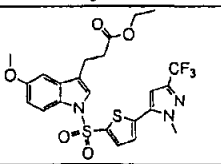
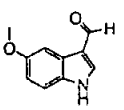
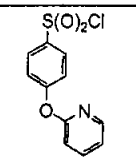
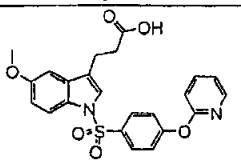
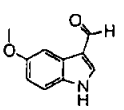
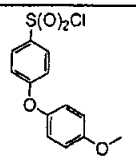
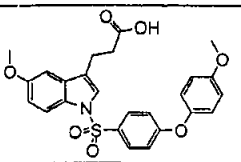
Ácido 3-{1-[3-(4-Fluoro-fenoxi)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0568**), PM calculado 469.49, $[M-H^+]^+$ = 468.1,

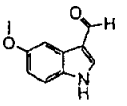
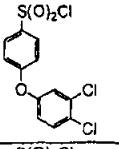
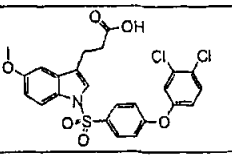
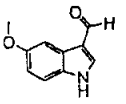
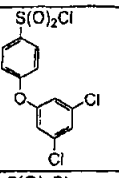
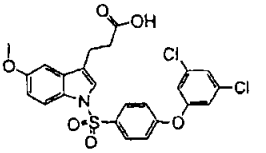
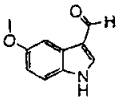
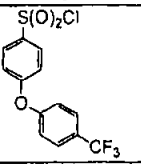
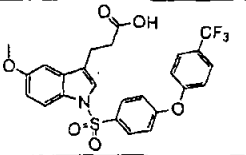
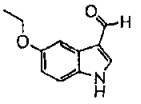
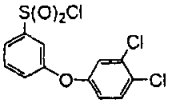
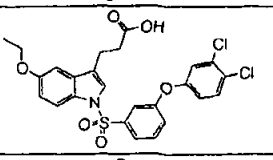
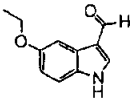
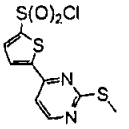
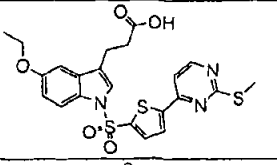
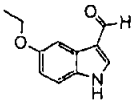
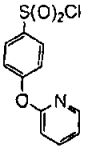
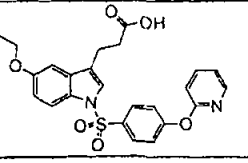
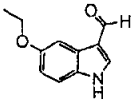
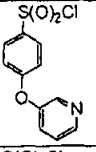
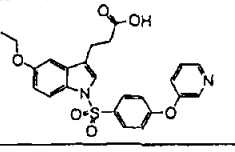
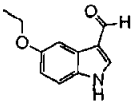
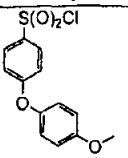
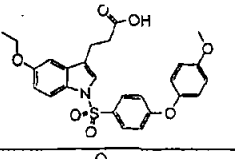
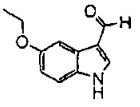
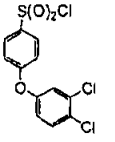
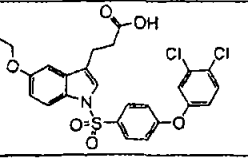
Ácido 3-[5-Metoxi-1-(4'-trifluorometil-bifenil-3-sulfonil)-1H-indol-3-il]-propiónico (**P-0570**), PM calculado 503.50, y

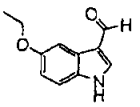
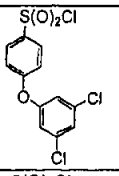
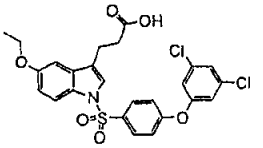
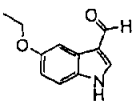
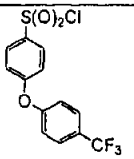
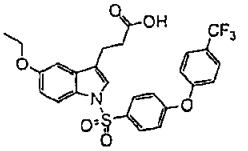
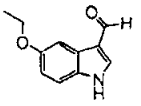
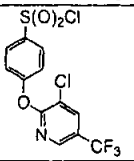
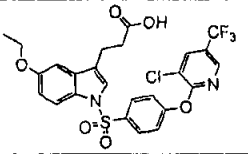
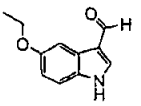
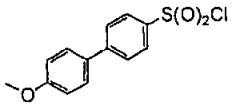
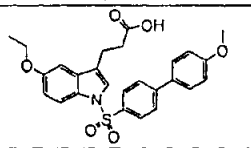
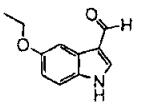
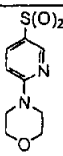
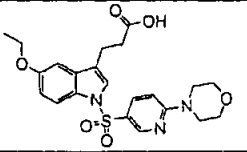
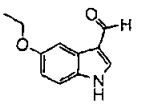
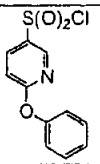
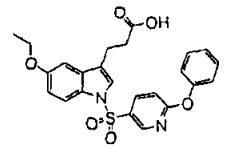
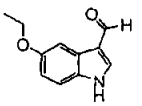
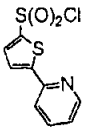
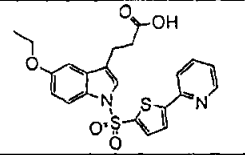
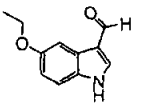
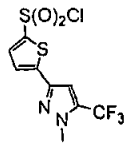
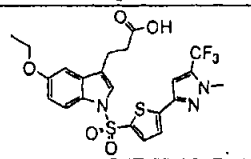
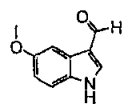
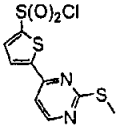
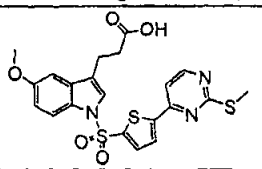
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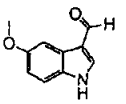
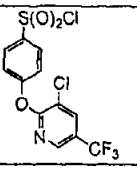
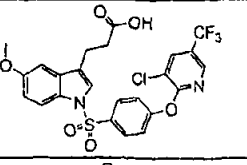
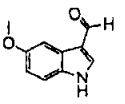
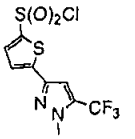
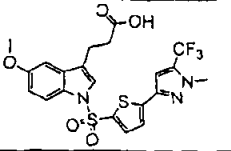
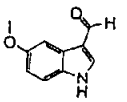
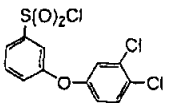
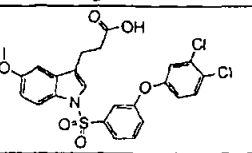
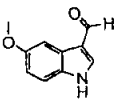
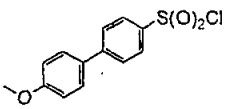
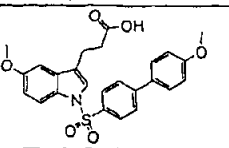
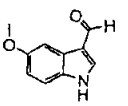
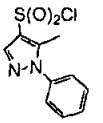
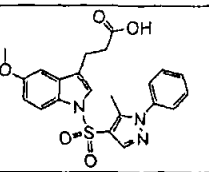
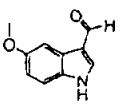
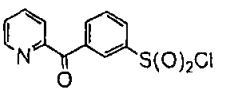
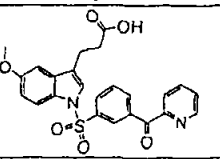
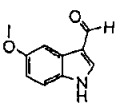
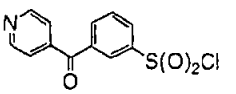
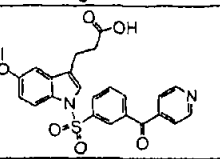
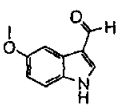
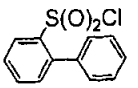
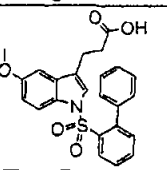
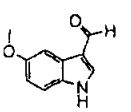
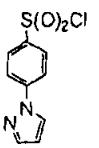
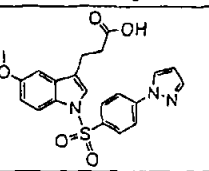
Estos compuestos se muestran en la Tabla 2 siguiente, donde el número de compuesto se proporciona en la Columna 1, el indol carboxilaldehído utilizado en la Etapa 1 en la Columna 2, el cloruro de sulfonilo utilizado en la Etapa 3 en la Columna 3, con la estructura del compuesto en la Columna 4. Tabla 2.

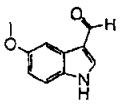
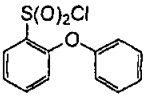
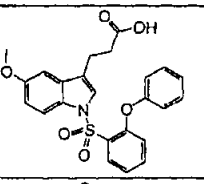
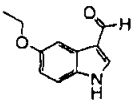
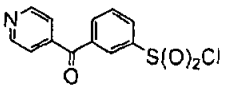
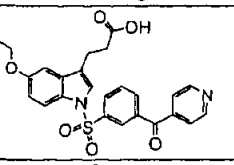
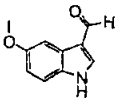
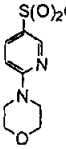
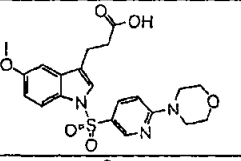
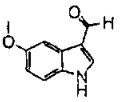
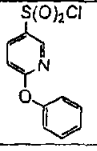
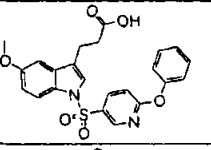
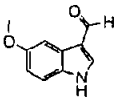
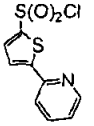
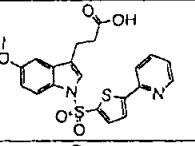
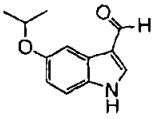
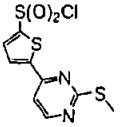
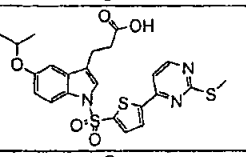
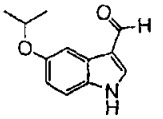
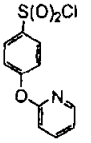
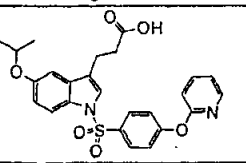
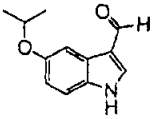
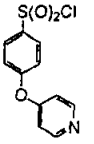
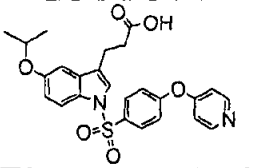
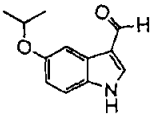
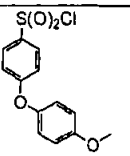
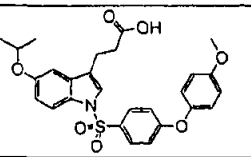
Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0002			
P-0003			

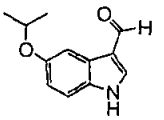
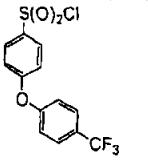
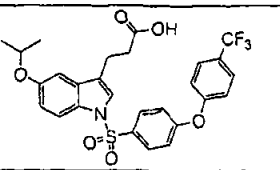
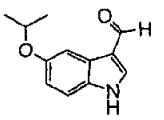
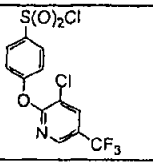
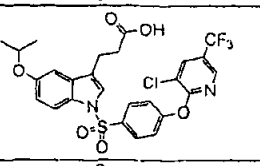
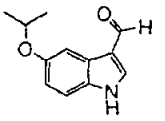
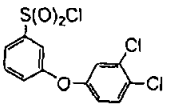
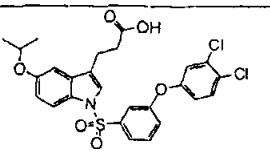
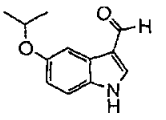
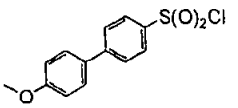
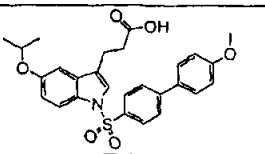
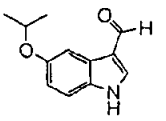
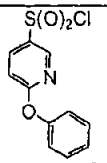
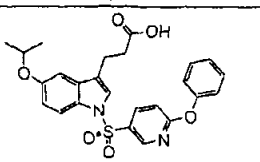
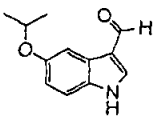
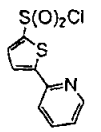
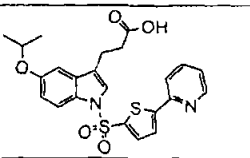
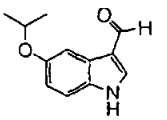
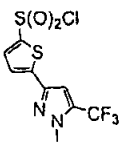
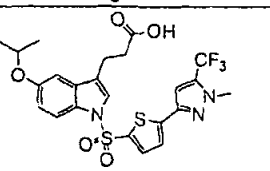
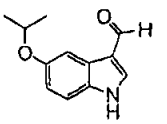
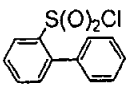
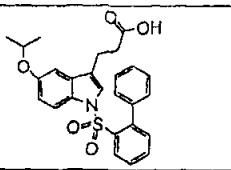
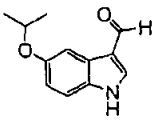
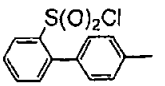
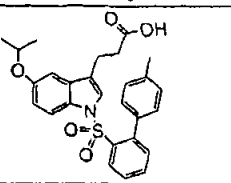
Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0004			
P-0006			
P-0007			
P-0008			
P-0009 *			
P-0033			
P-0034			
P-0047			
P-0048			

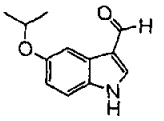
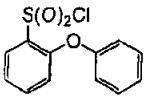
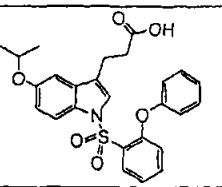
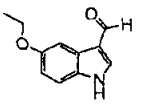
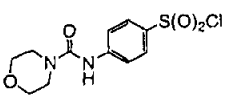
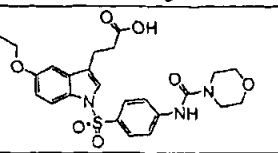
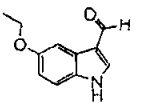
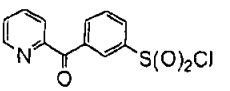
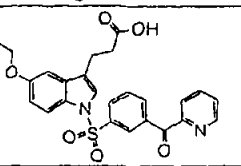
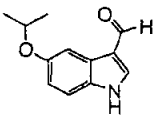
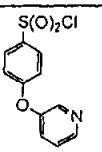
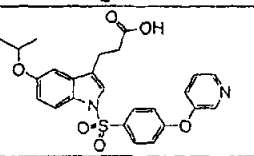
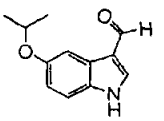
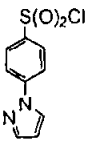
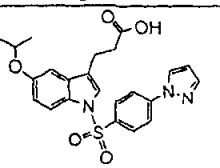
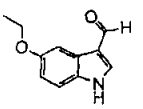
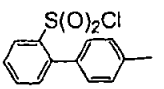
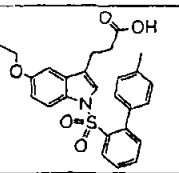
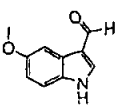
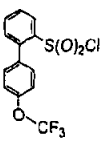
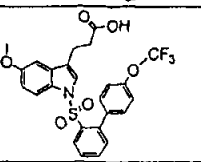
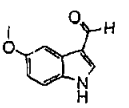
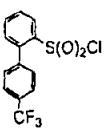
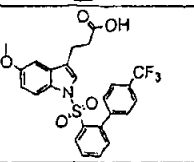
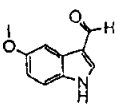
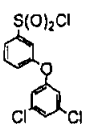
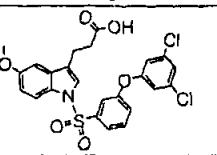
Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
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P-0050			
P-0051			
P-0052			
P-0053			
P-0055			
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P-0058			

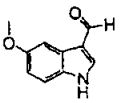
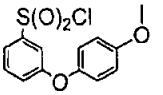
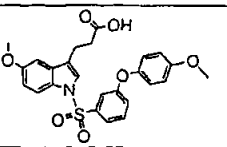
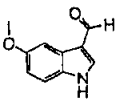
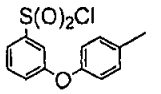
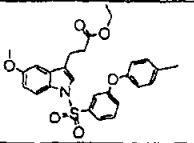
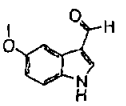
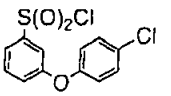
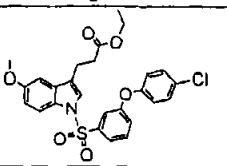
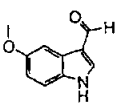
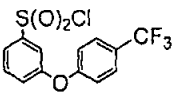
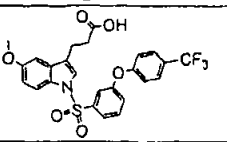
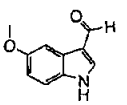
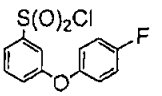
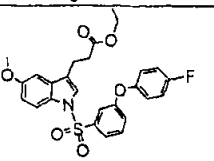
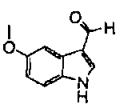
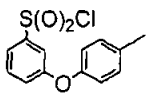
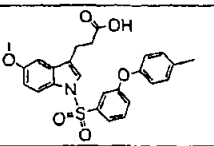
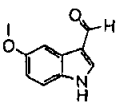
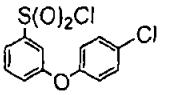
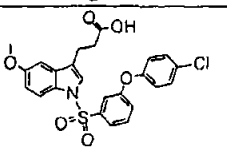
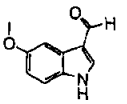
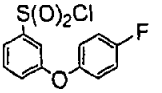
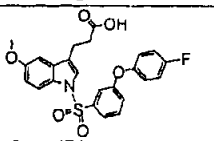
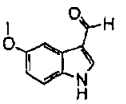
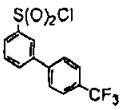
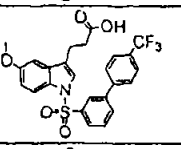
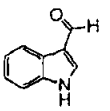
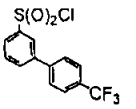
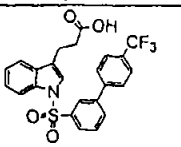
Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0059			
P-0060			
P-0061			
P-0062			
P-0063			
P-0064			
P-0065			
P-0066			
P-0067			

Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0068			
P-0069			
P-0071			
P-0072			
P-0146			
P-0150			
P-0151			
P-0152			
P-0155			

Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0162			
P-0168			
P-0214			
P-0215			
P-0216			
P-0311			
P-0316			
P-0317			
P-0318			

Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
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P-0320			
P-0321			
P-0322			
P-0323			
P-0324			
P-0326			
P-0332			
P-0338			

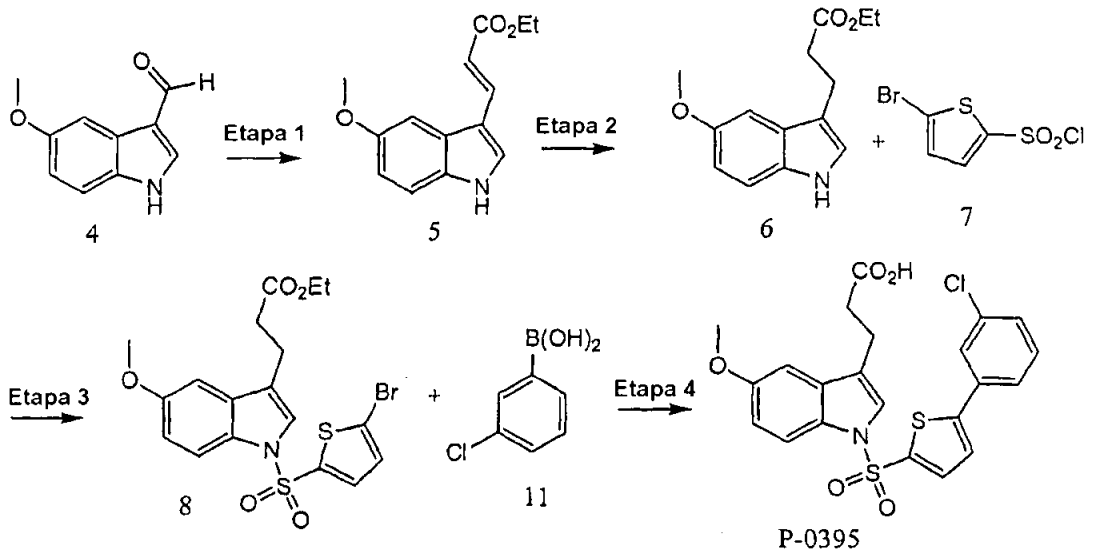
Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0339			
P-0342			
P-0344			
P-0371			
P-0375			
P-0386			
P-0391			
P-0392			
P-0560			

Comp. número	Indol-3-carboxialdehído	Cloruro de sulfonilo	Estructura del compuesto
P-0561			
P-0562 *			
P-0563 *			
P-0564			
P-0565 *			
P-0566			
P-0567			
P-0568			
P-0570			
P-0572			

* Aislado después de la Etapa 3

También se prepararon los compuestos por una ruta alternativa en las Etapas 4 y 5 como se muestra en el Esquema 2a.

Esquema 2a



Etapa — 1 hasta la Etapa-3: Véase el Esquema 2 anterior

Etapa-4: Síntesis de ácido 3-{1-[5-(3-cloro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il)-propiónico (**P-0395**)

Se disolvieron 10 mg de etiléster del ácido 3-[1-(5-bromo-tiofen-2-ilmetil)-5-metoxi-1H-indol-3-il]-propiónico 8 en 400 µL de acetonitrilo y se agregaron 2 equivalentes del ácido 3-cloro-fenil borónico **11**. Se agregaron 200 µL de 1M K_2CO_3 y se agregaron 10 µL de $Pd(AOc)_2$ /di-tbutilbifenilfosfina (0.2 M solución en tolueno). La mezcla de reacción se irradió durante 10 minutos a 160°C en el microondas. La solución se neutralizó con ácido acético y los solventes se removieron bajo vacío. El material sin purificar se disolvió en 500 µL de dimetilsulfóxido y se purificó mediante fase inversa HPLC (Columna C18), se eluye con un gradiente de agua/0.1% de ácido trifluoroacético y acetonitrilo/0.1% de ácido trifluoroacético, 20-100% durante 16 minutos. Peso molecular calculado 475.97, $[M+H^+]^+ = 475.9$.

Se prepararon los compuestos adicionales siguiendo el protocolo del Esquema 2a, opcionalmente reemplazando 5-metoxiindol-3-carboxilaldehído 4 con un indol-3-carboxilaldehído

apropiado en la Etapa 1, y/u opcionalmente reemplazando ácido 3-cloro-fenil borónico 11 con un ácido borónico apropiado en la Etapa 4. Los siguientes compuestos se prepararon por este método, con el peso molecular calculado y masa medida (MS(ESI)) proporcionados después del compuesto:

Ácido 3-{1-[5-(3,5-Bis-trifluorometil-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0001**), PM calculado 577.52, $[M-H^+]^+$ = 575.96,

Metiléster del ácido 3-{1-[5-(4-Trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0038**),

Metiléster del ácido 3-{1-[5-(3-Trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0388**), PM calculado 509.52, $[M+H^+]^+$ = 510.1,

Ácido 3-{1-[5-(4-Trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0393**), PM calculado 495.50, $[M-H^+]^+$ = 494.2,

Ácido 3-{1-[5-(3-Trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0394**), PM calculado 495.50, $[M-H^+]^+$ = 494.2,

Ácido 3-{1-[5-(3-Cloro-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0396**), PM calculado 490.00, $[M+H^+]^+$ = 490.3,

Ácido 3-{5-Cloro-1-[5-(3-cloro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0397**), PM calculado 480.39, $[M-H^+]^+$ = 476.7,

Ácido 3-{1-[5-(3-Cloro-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0398**), PM calculado 463.94, $[M+H^+]^+$ = 466.3,

Ácido 3-{1-[5-(4-Cloro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0399**), PM calculado 475.97, $[M+H^+]^+$ = 475.5,

Ácido 3-{1-[5-(4-Cloro-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0400**), PM calculado 490.00, $[M-H^+]^+$ = 489.9,

Ácido 3-{5-Cloro-1-[5-(4-cloro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0401**), PM calculado 480.39, $[M+H^+]^+$ = 481.5,

Ácido 3-{1-[5-(4-Cloro-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0402**), PM calculado 463.94, $[M-H^+]^+$ = 461.1,

Ácido 3-[l-(5-Furan-2-il-tiofen-2-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico (**P-0403**), PM calculado 431.49, $[M+H^+]^+$ = 432.3,

Ácido 3-[5-Etoxi-1-(5-furan-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0404**), PM calculado 445.51, $[M+H^+]^+$ = 445.9,

Ácido 3-[5-Cloro-1-(5-furan-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0405**), PM calculado 435.91, $[M+H^+]^+$ = 435.9,

Ácido 3-[5-Fluoro-1-(5-furan-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0406**), PM calculado 419.45, $[M+H^+]^+$ = 419.9,

Ácido 3-[1-(5-Furan-3-il-tiofen-2-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico (**P-0407**), PM calculado 431.49, $[M+H^+]^+$ = 432.3,

Ácido 3-[5-Etoxi-1-(5-furan-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0408**), PM calculado 445.51, $[M+H^+]^+$ = 445.9,

Ácido 3-[5-Cloro-1-(5-furan-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0409**), PM calculado 435.91, $[M-H^+]^+$ = 433.9,

Ácido 3-[5-Fluoro-1-(5-furan-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0410**), PM calculado 419.45, $[M+H^+]^+$ = 420.3,

Ácido 3-[5-Metoxi-1-(5-piridin-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0411**), PM calculado 442.51, $[M+H^+]^+$ = 443.1,

Ácido 3-[5-Etoxi-1-(5-piridin-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0412**), PM calculado 456.54, $[M+H^+]^+$ = 457.1,

Ácido 3-[5-Cloro-1-(5-piridin-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0413**), PM calculado 446.93, $[M+H^+]^+$ = 447.1,

Ácido 3-[5-Fluoro-1-(5-piridin-3-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0414**), PM calculado 430.48, $[M+H^+]^+$ = 431.1,

Ácido 3-[5-Etoxi-1-(5-piridin-4-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0415**), PM calculado 456.54, $[M+H^+]^+$ = 457.1,

Ácido 3-[5-Cloro-1-(5-piridin-4-il-tiofen-2-sulfonil)-l H-indol-3-il]-propiónico (**P-0416**), PM calculado 446.93, $[M+H^+]^+$ = 447.1,

Ácido 3-[5-Fluoro-1-(5-piridin-4-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0417**), PM calculado 430.48, $[M+H^+]^+$ = 431.1,

Ácido 3-{1-[5-(3,5-Dicloro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0418**), PM calculado 510.42, $[M-H^+]$-= 509.9,

Ácido 3-{1-[5-(3,5-Dicloro-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0419**), PM calculado 524.44, $[M+H^+]^+$ = 524.3,

Ácido 3-{5-Cloro-1-[5-(3,5-dicloro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0420**), PM calculado 514.84, $[M-H^+]$-= 507.1,

Ácido 3-{1-[5-(3,5-Dicloro-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0421**), PM calculado 498.38, $[M-H^+]$-= 490.3,

Ácido 3-{1-[5-(3 ,4-Difluoro-fenil)-tiofen-2-sulfonil]-5-metoxi-1 H-indol-3-il}-propiónico (**P-0422**), PM calculado 477.51, $[M+H^+]^+$ = 478.3,

Ácido 3-{1-[5-(3,4-Difluoro-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0423**), PM calculado 491.53, $[M+H^+]^+$ = 492.3,

Ácido 3-{5-Cloro-1-[5-(3,4-difluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0424**), PM calculado 481.93, $[M+H^+]^+$ = 481.1,

Ácido 3-{1-[5-(3,4-Difluoro-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0425**), PM calculado 465.47, $[M-H^+]^+$ = 464.7,

Ácido 3-{1-[5-(3,4-Dimetoxi-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0426**), PM calculado 501.58, $[M+H^+]^+$ = 501.9,

Ácido 3-{1-[5-(3,4-Dimetoxi-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0427**), PM calculado 515.60, $[M+H^+]^+$ = 516.3,

Ácido 3-{5-Cloro-1-[5-(3,4-dimetoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0428**), PM calculado 506.00, $[M+H^+]^+$ = 507.5,

Ácido 3-{1-[5-(3 ,4-Dimetoxi-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0429**), PM calculado 489.54, $[M-H^+]^+$ = 485.5,

Ácido 3-{1-[5-(4-Fluoro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0430**), PM calculado 459.52, $[M+H^+]^+$ = 459.9,

Ácido 3-{5-Etoxi-1-[5-(4-fluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0431**), PM calculado 473.54, $[M+H^+]^+$ = 473.9,

Ácido 3-{5-Cloro-1-[5-(4-fluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0432**), PM calculado 463.94, $[M-H^+]^+$ = 458.7,

Ácido 3-{5-Fluoro-1-[5-(4-fluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0433**), PM calculado 447.48, $[M+H^+]^+$ = 447.9,

Ácido 3-{5-Metoxi-1-[5-(4-metilsulfanil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0434**), PM calculado 487.62, $[M+H^+]^+$ = 487.9,

Ácido 3-{5-Etoxi-1-[5-(4-metilsulfanil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0435**), PM calculado 501.65, $[M+H^+]^+$ = 501.9,

Ácido 3-{5-Cloro-1-[5-(4-metilsulfanil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0436**), PM calculado 492.04, $[M-H^+]^+$ = 487.9,

Ácido 3-{5-Fluoro-1-[5-(4-metilsulfanil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0437**), PM calculado 475.58, $[M-H^+]^+$ = 473.9,

Ácido 3-{1-[5-(3-Cloro-4-fluoro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0438**), PM calculado 493.96, $[M+H^+]^+$ = 493.9,

Ácido 3-{1-[5-(3-Cloro-4-fluoro-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0439**), PM calculado 507.99, $[M+H^+]^+$ = 507.5,

Ácido 3-{5-Cloro-1-[5-(3-cloro-4-fluoro-fenil)-tiofen-2-sulfonil-1H-indol-3-il}-propiónico (**P-0440**), PM calculado 498.38, $[M+H^+]^+$ = 503.5,

Ácido 3-{1-[5-(3-Cloro-4-fluoro-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0441**), PM calculado 481.93, $[M-H^+]^-$=479.1,

Ácido 3-[5-Metoxi-1-(5-pirimidin-5-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0442**), PM calculado 443.50, $[M+H^+]^+$ = 444.3,

Ácido 3-[5-Etoxi-1-(5-pirimidin-5-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0443**), PM calculado 457.53, $[M+H^+]^+$ = 458.3,

Ácido 3-[5-Cloro-1-(5-pirimidin-5-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0444**), PM calculado 447.92, $[M+H^+]^+$ = 447.9,

Ácido 3-[5-Fluoro-1-(5-pirimidin-5-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0445**), PM calculado 431.47, $[M+H^+]^+$ = 432.3,

Ácido 3-{5-Metoxi-1-[5-(6-metoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0446**), PM calculado 472.54, $[M+H^+]^+$ = 473.1,

Ácido 3-{5-Etoxi-1-[5-(6-metoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0447**), PM calculado 486.57, $[M+H^+]^+$ = 487.1,

Ácido 3-{5-Cloro-1-[5-(6-metoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0448**), PM calculado 476.96, $[M+H^+]^+$ = 477.1,

Ácido 3-{5-Fluoro-1-[5-(6-metoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0449**), PM calculado 460.50, $[M+H^+]^+$ = 461.1,

Ácido 3-{5-Metoxi-1-[5-(1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0450**), PM calculado 431.49, $[M+H^+]^+$ = 432.3,

Ácido 3-{5-Etoxi-1-[5-(1 H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0451**), PM calculado 445.52, $[M+H^+]^+$ = 445.9,

Ácido 3-{5-Cloro-1-[5-(1H-pirazol-4-il)-thiopriene-2-sulfbnil]-1H-indol-3-il}-propiónico (**P-0452**), PM calculado 435.91, $[M+H^+]^+$ = 435.9,

Ácido 3-{5-Fluoro-1-[5-(1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0453**), PM calculado 419.46, $[M+H^+]^+$ = 419.9,

Ácido 3-{5-Metoxi-1-[5-(1-metil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0454**), PM calculado 445.52, $[M+H^+]^+$ = 445.9,

Ácido 3-{5-Etoxi-1-[5-(1-metil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0455**), PM calculado 459.54, $[M+H^+]^+$ = 460.3,

3-{5-Cloro-1-[5-(1-metil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico Ácido (**P-0456**), PM calculado 449.94, $[M+H^+]^+$ = 449.9,

Ácido 3-{5-Fluoro-1-[5-(1-metil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0457**), PM calculado 433.48, $[M+H^+]^+$ = 434.3,

Ácido 3-{1-[5-(3-Dimetilamino-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0458**), PM calculado 484.59, $[M+H^+]^+$ = 485.1,

Ácido 3-{1-[5-(3-Dimetilamino-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0459**), PM calculado 498.62, $[M+H^+]^+$ = 499.1,

Ácido 3-{5-Cloro-1-[5-(3-dimetilamino-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0460**), PM calculado 489.01, $[M+H^+]^+$ = 489.1,

Ácido 3-{1-[5-(3-dimetilamino-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0461**), PM calculado 472.56, $[M+H^+]^+$ = 473.1,

Ácido 3-{1-[5-(2,6-dimetoxi-piridin-3-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0462**), PM calculado 502.57, $[M+H^+]^+$ = 503.1,

Ácido 3-{1-[5-(2,6-dimetoxi-piridin-3-il)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0463**), PM calculado 516.59, $[M+H^+]^+$ = 517.1,

Ácido 3-{5-Cloro-1-[5-(2,6-dimetoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0464**), PM calculado 506.99, $[M+H^+]^+$ = 507.1,

Ácido 3-{1-[5-(2,6-Dimetoxi-piridin-3-il)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0465**), PM calculado 490.53, $[M+H^+]^+$ = 491.1,

Ácido 3-{1-[5-(2,4-Dimetoxi-pirimidin-5-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0466**), PM calculado 503.55, $[M+H^+]^+$ = 503.9,

Ácido 3-{1-[5-(2,4-Dimetoxi-pirimidin-5-il)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0467**), PM calculado 517.58, $[M+H^+]^+$ = 517.9,

Ácido 3-{5-Cloro-1-[5-(2,4-dimetoxi-pirimidin-5-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0468**), PM calculado 507.97, $[M+H^+]^+$ = 507.9,

Ácido 3-{1-[5-(2,4-Dimetoxi-pirimidin-5-il)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0469**), PM calculado 491.52, $[M+H^+]^+$ = 491.1,

Ácido 3-{1-[5-(6-benciloxi-piridin-3-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0470**), PM calculado 548.64, $[M+H^+]^+$ = 549.1,

Ácido 3-{1-[5-(6-benciloxi-piridin-3-il)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0471**), PM calculado 562.66, $[M+H^+]^+$ = 563.2,

Ácido 3-{1-[5-(6-Benciloxi-piridin-3-il)-tiofen-2-sulfonil]-5-cloro-1H-indol-3-il}-propiónico (**P-0472**), PM calculado 553.06, $[M+H^+]^+$ = 553.2,

Ácido 3-{1-[5-(6-Benciloxi-piridin-3-il)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0473**), PM calculado 536.60, $[M+H^+]^+$ = 537.1,

Ácido 3-{5-Etoxi-1-[5-(4-etoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0474**), PM calculado 499.61, $[M+H^+]^+$ = 499.9,

Ácido 3-{5-Cloro-1-[5-(4-etoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0475**), PM calculado 490.00, $[M-H^+]$-= 489.9,

Ácido 3-{1-[5-(4-Etoxi-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0476**), PM calculado 473.54, $[M+H^+]^+$ = 473.9,

Ácido 3-{1-[5-(3-Fluoro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0477**), PM calculado 459.52, $[M+H^+]^+$ = 460.3,

Ácido 3-{5-Etoxi-1-[5-(3-fluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0478**), PM calculado 473.54, $[M+H^+]^+$ = 473.9,

Ácido 3-{5-Cloro-1-[5-(3-fluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0479**), PM calculado 463.94, $[M-H^+]$-= 457.5,

Ácido 3-{5-Fluoro-1-[5-(3-fluoro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0480**), PM calculado 447.48, $[M+H^+]^+$ = 447.9,

Ácido 3-{5-Etoxi-1-[5-(3-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0481**), PM calculado 539.55, $[M+H^+]^+$ = 539.9,

Ácido 3-{5-Cloro-1-[5-(3-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0482**), PM calculado 529.94, $[M+H^+]^+$ = 525.9,

Ácido 3-{5-Fluoro-1-[5-(3-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0483**), PM calculado 513.49, $[M+H^+]^+$ = 514.3,

Ácido 3-{1-[5-(3,4-Dicloro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0484**), PM calculado 510.42, $[M-H^+]^+$ = 509.9,

Ácido 3-{1-[5-(3,4-Dicloro-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0485**), PM calculado 524.44, $[M+H^+]^+$ = 524.3,

Ácido 3-{5-Cloro-1-[5-(3,4-dicloro-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0486**), PM calculado 514.84, $[M+H^+]^+$ = 511.9,

Ácido 3-{1-[5-(3,4-Dicloro-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0487**), PM calculado 498.38, $[M-H^+]^-$ = 496.3,

Ácido 3-{5-Etoxi-1-[5-(3-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0488**), PM calculado 523.55, $[M+H^+]^+$ = 524.3,

Ácido 3-{5-Cloro-1-[5-(3-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0489**), PM calculado 513.94, $[M-H^+]^+$ = 511.9,

Ácido 3-{5-Fluoro-1-[5-(3-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0490**), PM calculado 497.49, $[M+H^+]^+$ = 497.9,

Ácido 3-{1-[5-(4-Benciloxi-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0491**), PM calculado 561.68, $[M+H^+]^+$ = 562.0,

Ácido 3-{1-[5-(4-Benciloxi-fenil)-tiofen-2-sulfonil]-5-cloro-1H-indol-3-il}-propiónico (**P-0492**), PM calculado 552.07, $[M+H^+]^+$ = 553.6,

Ácido 3-{1-[5-(4-Benciloxi-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0493**), PM calculado 535.61, $[M+H^+]^+$ = 535.9,

Ácido 3-{5-Etoxi-1-[5-(4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0494**), PM calculado 523.55, $[M+H^+]^+$ = 524.3,

Ácido 3-{5-Cloro-1-[5-(4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0495**), PM calculado 513.94, $[M-H^+]^+$ = 512.3,

Ácido 3-{5-Fluoro-1-[5-(4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0496**), PM calculado 497.49, $[M-H^+]^-$ = 490.3,

Ácido 3-{1-[5-(3-Fluoro-4-metoxi-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0497**), PM calculado 489.54, $[M+H^+]^+$ = 490.3,

Ácido 3-{5-Etoxi-1-[5-(3-fluoro-4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0498**), PM calculado 503.57, $[M+H^+]^+$ = 503.9,

Ácido 3-{5-Cloro-1-[5-(3-fluoro-4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0499**), PM calculado 493.96, $[M+H^+]^+$ = 497.1,

Ácido 3-{5-Fluoro-1-[5-(3-fluoro-4-metoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0500**), PM calculado 477.51, $[M+H^+]^+$ = 478.3,

Ácido 3-{5-Metoxi-1-[5-(5-metil-furan-2-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0501**), PM calculado 445.51, $[M+H^+]^+$ = 445.9,

Ácido 3-{5-Etoxi-1-[5-(5-metil-furan-2-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0502**), PM calculado 459.54, $[M+H^+]^+$ = 459.9,

Ácido 3-{5-Cloro-1-[5-(5-metil-furan-2-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0503**), PM calculado 449.93, $[M+H^+]^+$ = 449.5,

Ácido 3-{1-[5-(3,5-Dimetil-isoxazol-4-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0504**), PM calculado 460.53, $[M+H^+]^+$ = 461.1,

Ácido 3-{1-[5-(3,5-Dimetil-isoxazol-4-il)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0505**), PM calculado 474.56, $[M+H^+]^+$ = 475.1,

Ácido 3-{5-Cloro-1-[5-(3,5-dimetil-isoxazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0506**), PM calculado 464.95, $[M+H^+]^+$ = 464.7,

Ácido 3-{1-[5-(3 ,5-Dimetil-isoxazol-4-il)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (P-0507), PM calculado 448.49, $[M+H^+]^+$ = 448.7,

Ácido 3-{1-[5-(4-Cloro-3-trifluorometil-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0508**), PM calculado 543.97, $[M+H^+]^+$ = 543.9,

Ácido 3-{1-[5-(4-Cloro-3-trifluorometil-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-05**09), PM calculado 558.00, $[M+H^+]^+$ = 558.0,

Ácido 3-{5-Cloro-1-[5-(4-cloro-3-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0510**), PM calculado 548.39, $[M-H^+]^+$ = 546.7,

Ácido 3-{1-[5-(4-Cloro-3-trifluorometilo-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0511**), PM calculado 531.93, $[M+H^+]^+$ = 531.9,

Ácido 3-{5-Metoxi-l-[5-(4-morfolin-4-il-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0512**), PM calculado 526.63, $[M+H^+]^+$ = 527.1,

Ácido 3-{5-Etoxi-1-[5-(4-morfolin-4-il-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (P-0513), PM calculado 540.66, $[M+H^+]^+$ = 541.1,

Ácido 3-{5-Cloro-1-[5-(4-morfolin-4-il-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0514**), PM calculado 531.05, $[M+H^+]^+$ = 531.1,

Ácido 3-{1-[5-(2-Cloro-4-trifluorometil-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico (**P-0515**), PM calculado 543.97, $[M+H^+]^+$ = 543.9,

Ácido 3-{1-[5-(2-Cloro-4-trifluorometil-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0516**), PM calculado 558.00, $[M+H^+]^+$ = 558.0,

Ácido 3-{5-Cloro-1-[5-(2-cloro-4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0517**), PM calculado 548.39, $[M+H^+]^+$ = 548.3,

Ácido 3-{1-[5-(2-Cloro-4-trifluorometil-fenil)-tiofen-2-sulfonil]-5-fluoro-1H-indol-3-il}-propiónico (**P-0518**), PM calculado 531.93, $[M+H^+]^+$ = 531.9,

Ácido 3-{5-Metoxi-l-[5-(1-propil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0519**), PM calculado 473.57, $[M+H^+]^+$ = 473.9,

Ácido 3-{5-Etoxi-1-[5-(1-propil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0520**), PM calculado 487.60, $[M+H^+]^+$ = 487.9,

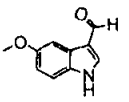
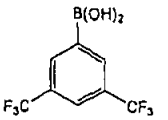
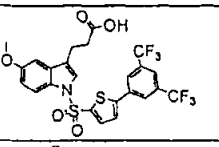
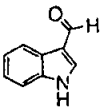
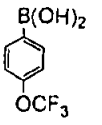
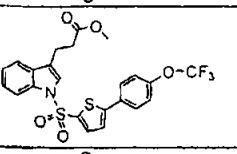
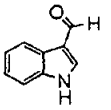
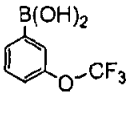
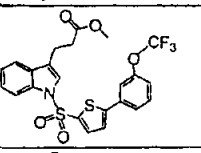
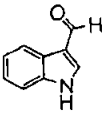
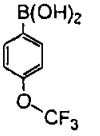
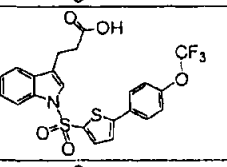
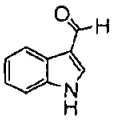
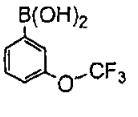
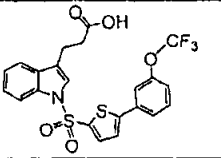
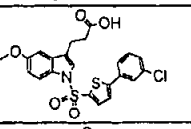
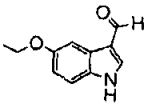
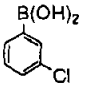
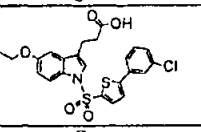
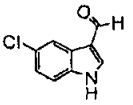
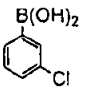
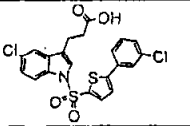
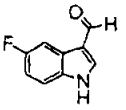
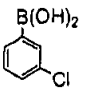
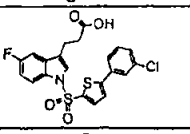
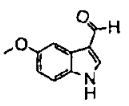
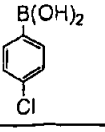
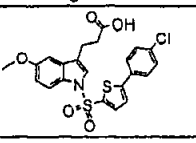
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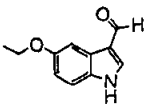
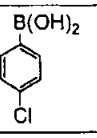
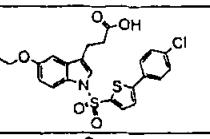
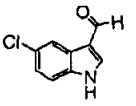
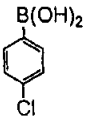
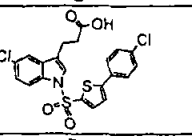
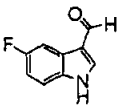
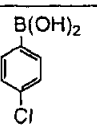
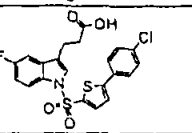
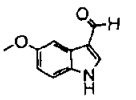
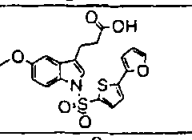
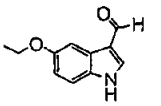
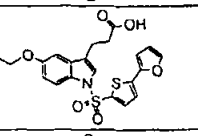
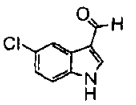
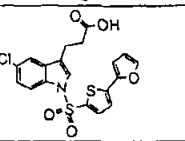
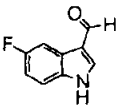
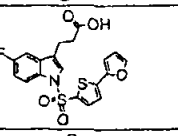
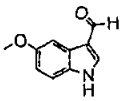
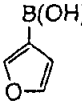
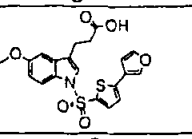
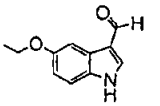
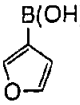
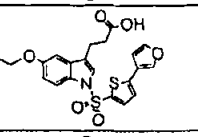
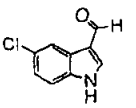
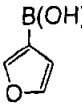
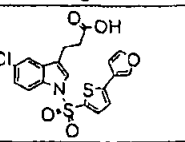
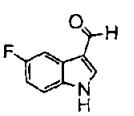
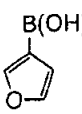
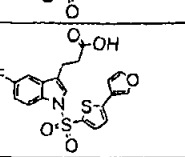
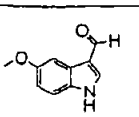
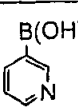
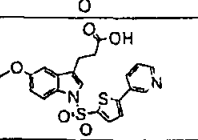
Ácido 3-{5-Fluoro-1-[5-(1-propil-1H-pirazol-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0522**), PM calculado 461.54, $[M+H^+]^+$ = 462.3, y

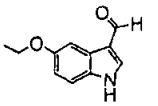
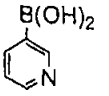
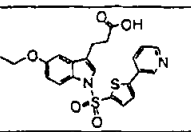
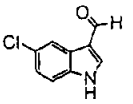
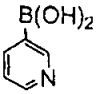
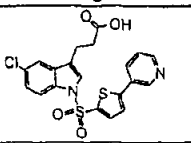
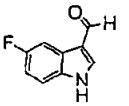
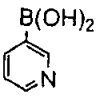
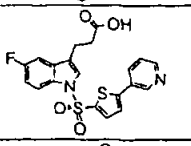
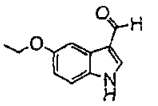
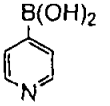
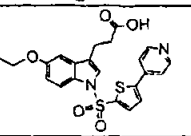
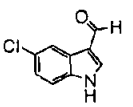
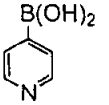
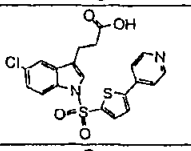
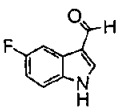
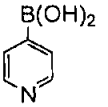
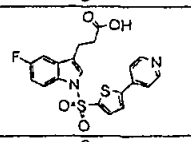
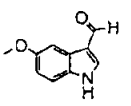
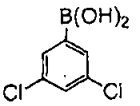
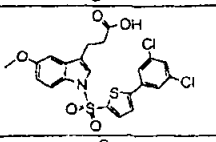
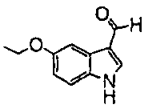
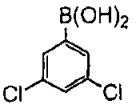
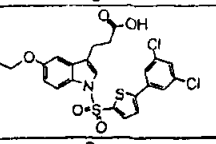
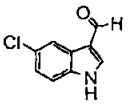
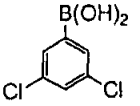
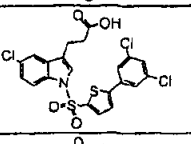
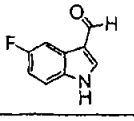
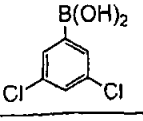
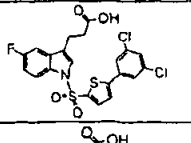
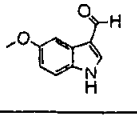
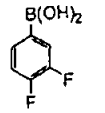
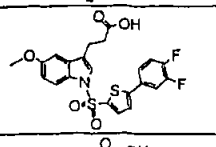
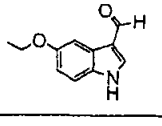
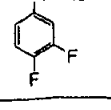
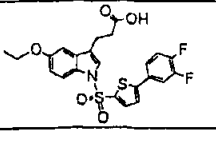
Ácido 3-(5-Metoxi-1-{5-[4-(2,2,2-trifluoro-etoxi)-fenil]-tiofen-2-sulfonil}-1H-indol-3-il)-propiónico (**P-0523**), PM calculado 539.55, $[M-H^+]^+$ = 538.06.

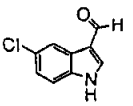
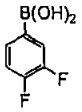
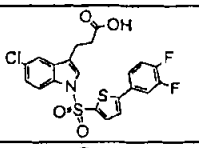
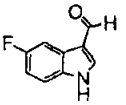
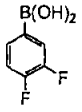
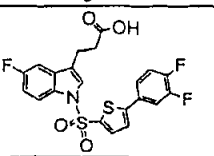
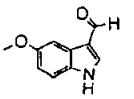
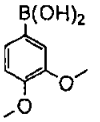
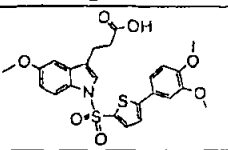
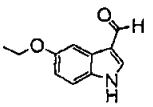
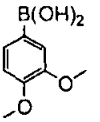
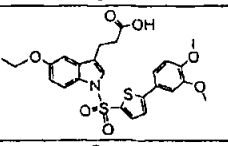
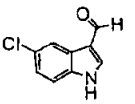
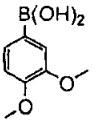
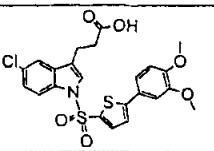
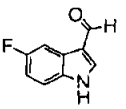
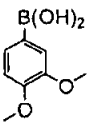
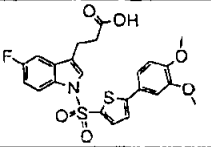
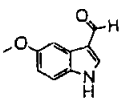
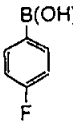
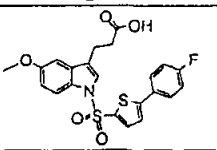
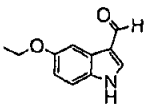
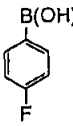
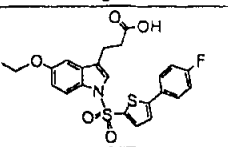
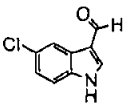
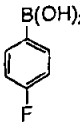
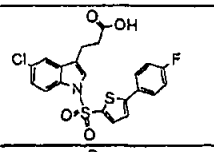
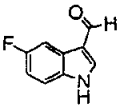
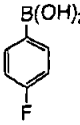
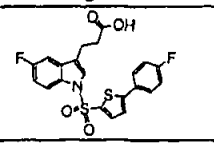
Estos Compuestos se muestran en la Tabla 3 siguiente, indicando el indol-3-carboxilaldehído usado en la Etapa 1 (Columna 2), el ácido borónico usado en la Etapa 4 (Columna 3), y la estructura del compuesto (Columna 4), con el número de compuesto proporcionado en la Columna 1.

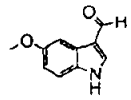
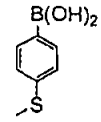
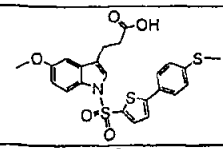
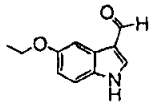
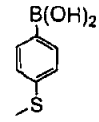
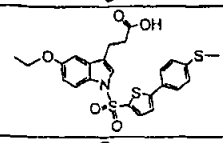
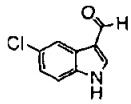
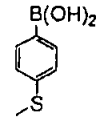
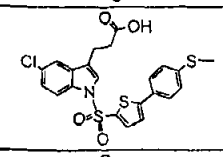
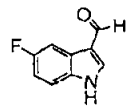
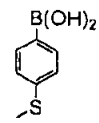
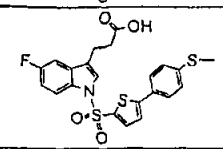
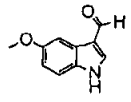
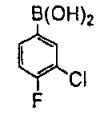
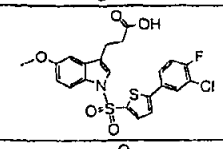
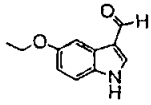
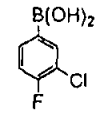
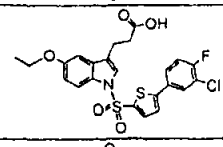
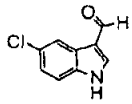
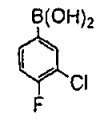
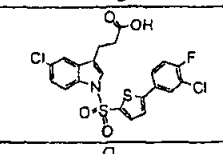
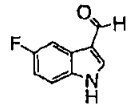
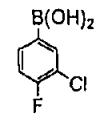
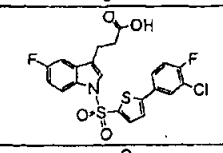
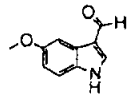
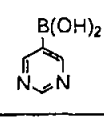
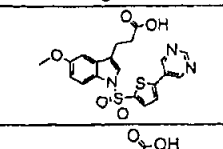
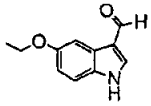
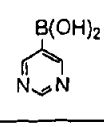
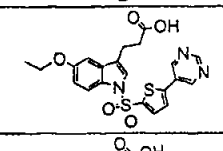
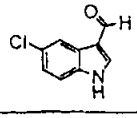
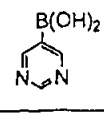
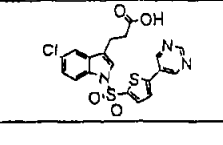
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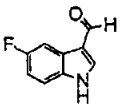
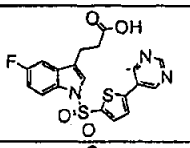
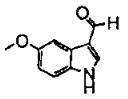
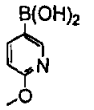
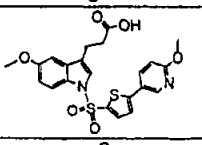
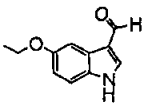
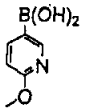
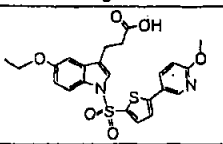
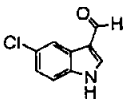
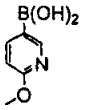
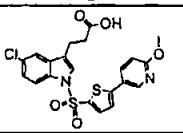
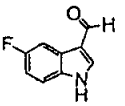
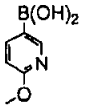
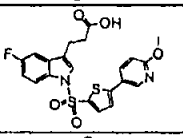
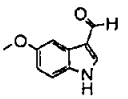
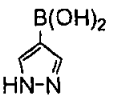
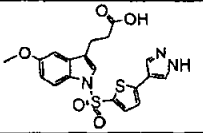
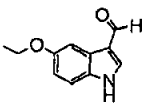
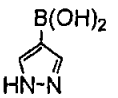
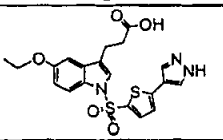
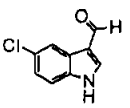
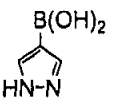
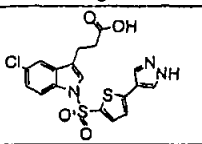
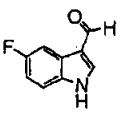
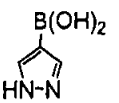
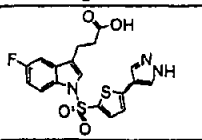
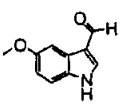
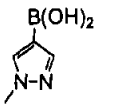
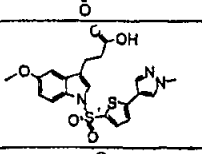
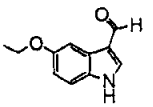
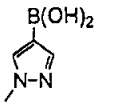
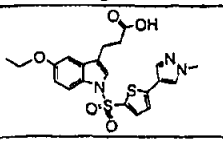
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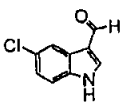
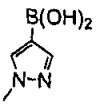
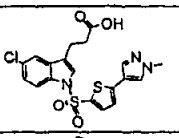
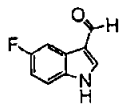
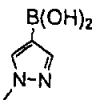
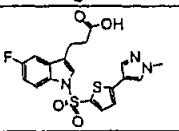
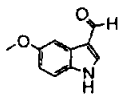
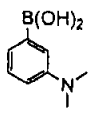
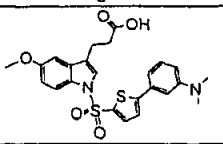
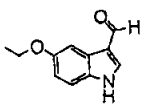
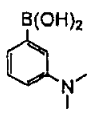
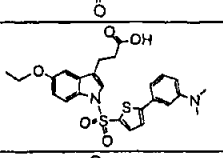
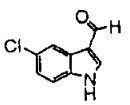
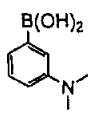
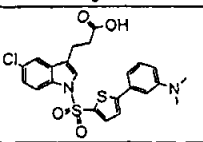
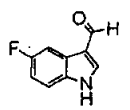
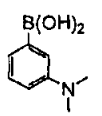
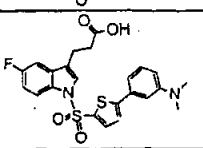
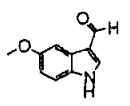
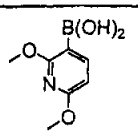
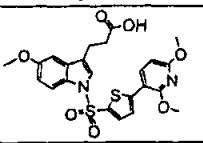
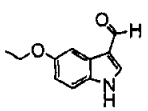
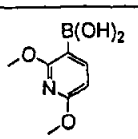
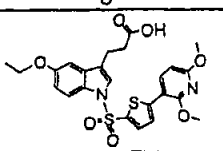
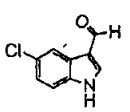
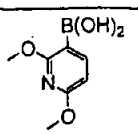
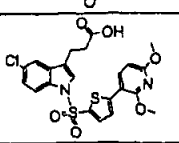
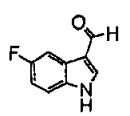
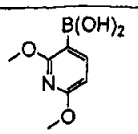
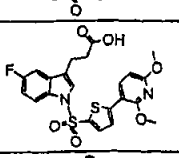
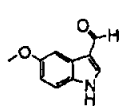
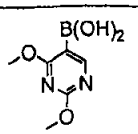
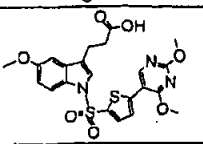
Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0400			
P-0401			
P-0402			
P-0403			
P-0404			
P-0405			
P-0406			
P-0407			
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P-0410			
P-0411			

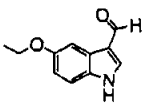
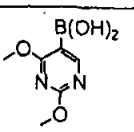
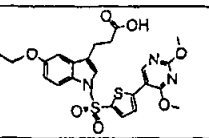
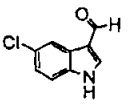
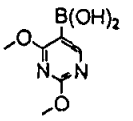
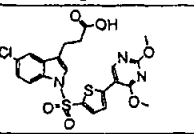
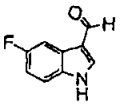
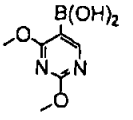
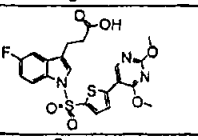
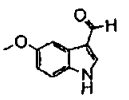
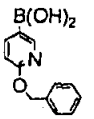
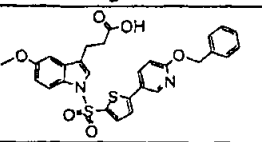
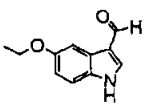
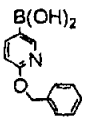
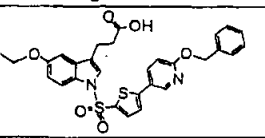
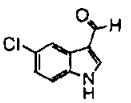
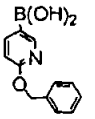
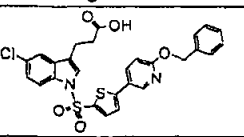
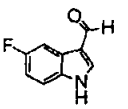
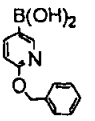
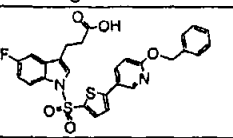
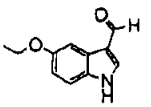
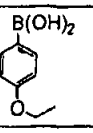
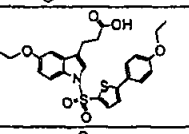
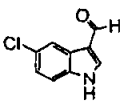
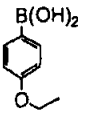
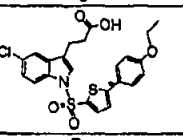
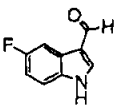
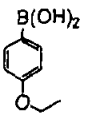
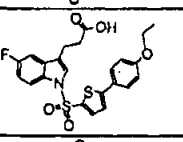
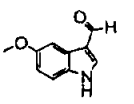
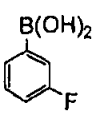
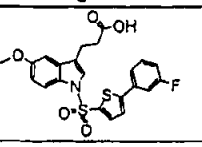
Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0412			
P-0413			
P-0414			
P-0415			
P-0416			
P-0417			
P-0418			
P-0419			
P-0420			
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P-0423			

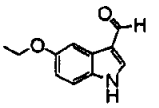
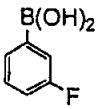
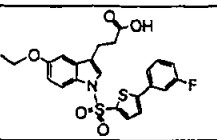
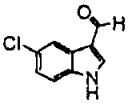
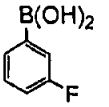
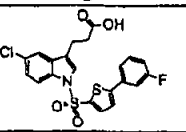
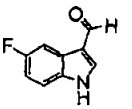
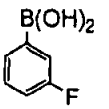
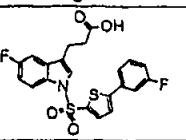
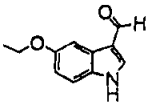
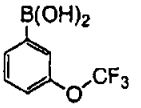
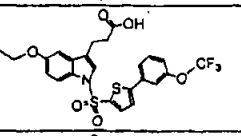
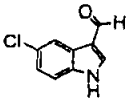
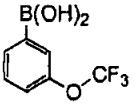
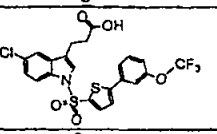
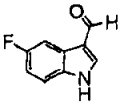
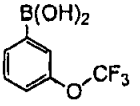
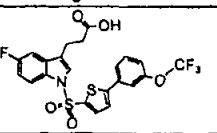
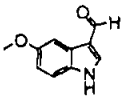
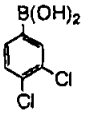
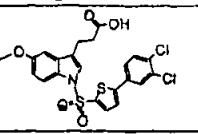
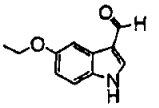
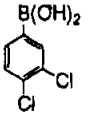
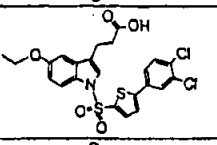
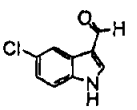
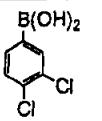
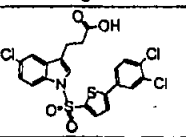
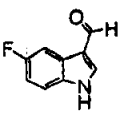
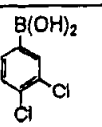
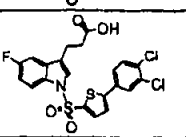
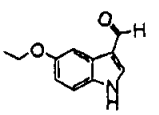
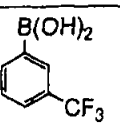
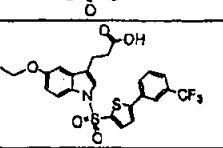
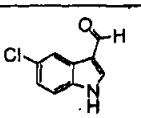
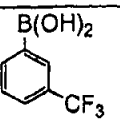
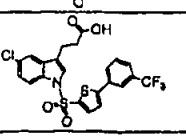
Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
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P-0426			
P-0427			
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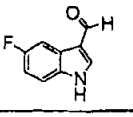
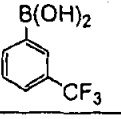
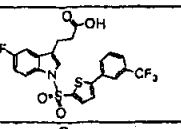
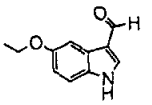
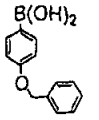
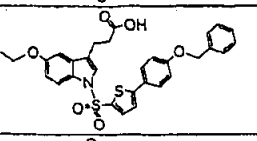
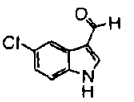
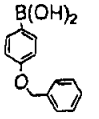
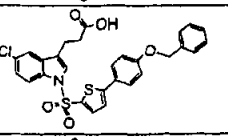
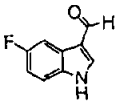
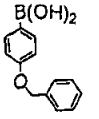
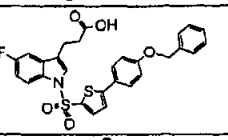
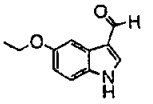
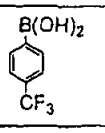
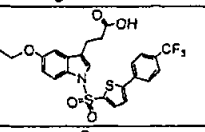
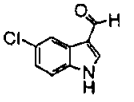
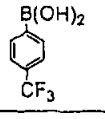
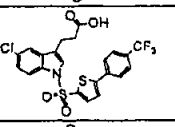
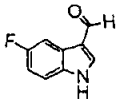
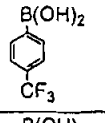
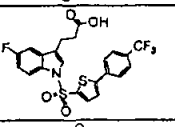
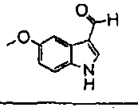
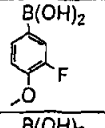
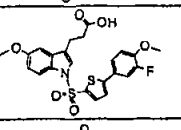
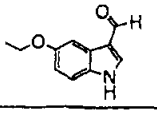
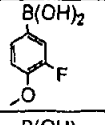
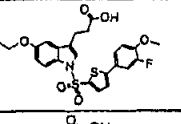
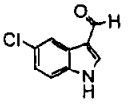
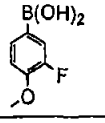
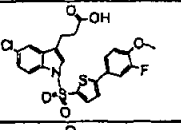
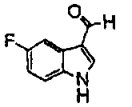
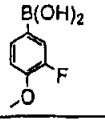
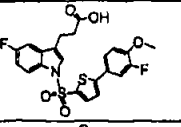
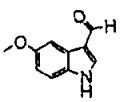
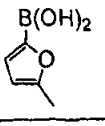
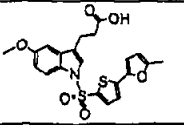
Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0434			
P-0435			
P-0436			
P-0437			
P-0438			
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P-0444			

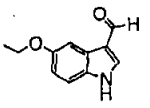
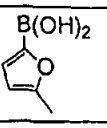
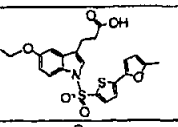
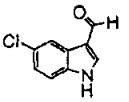
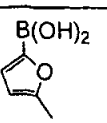
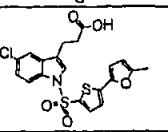
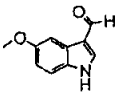
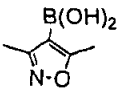
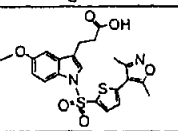
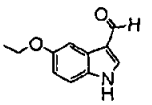
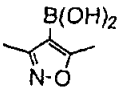
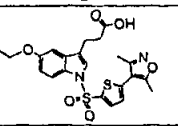
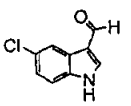
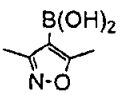
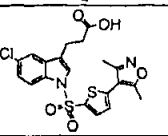
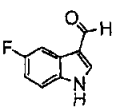
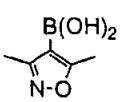
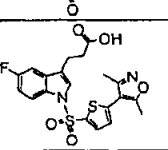
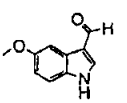
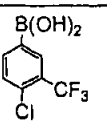
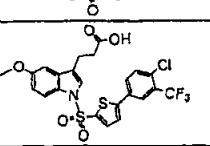
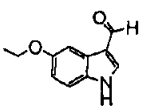
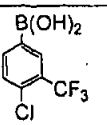
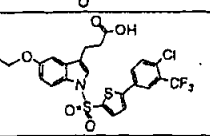
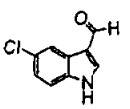
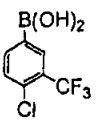
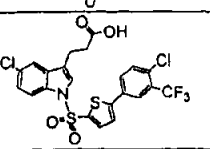
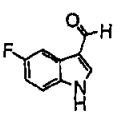
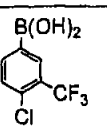
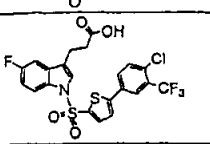
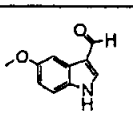
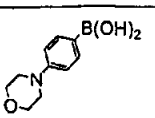
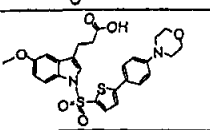
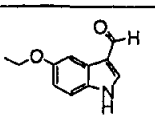
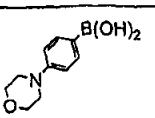
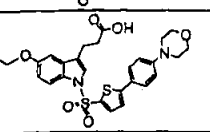
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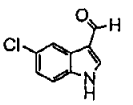
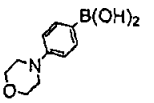
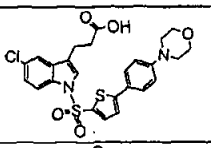
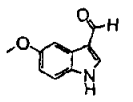
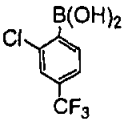
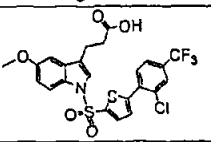
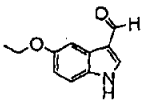
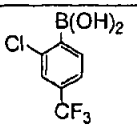
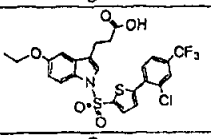
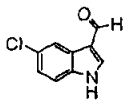
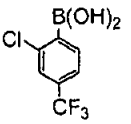
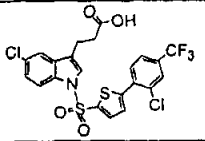
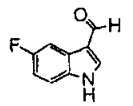
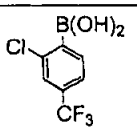
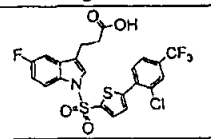
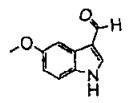
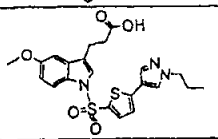
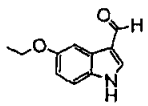
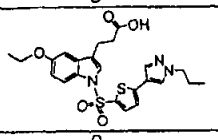
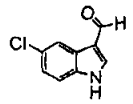
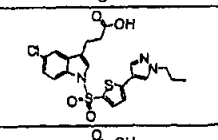
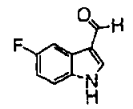
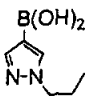
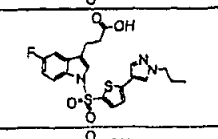
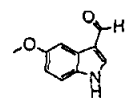
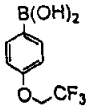
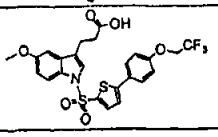
Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0456			
P-0457			
P-0458			
P-0459			
P-0460			
P-0461			
P-0462			
P-0463			
P-0464			
P-0465			
P-0466			

Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0467			
P-0468			
P-0469			
P-0470			
P-0471			
P-0472			
P-0473			
P-0474			
P-0475			
P-0476			
P-0477			

Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0478			
P-0479			
P-0480			
P-0481			
P-0482			
P-0483			
P-0484			
P-0485			
P-0486			
P-0487			
P-0488			
P-0489			

Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0490			
P-0491			
P-0492			
P-0493			
P-0494			
P-0495			
P-0496			
P-0497			
P-0498			
P-0499			
P-0500			
P-0501			

Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0502			
P-0503			
P-0504			
P-0505			
P-0506			
P-0507			
P-0508			
P-0509			
P-0510			
P-0511			
P-0512			
P-0513			

Comp. número	Indol-3-carboxialdehído	Ácido borónico	Estructura del compuesto
P-0514			
P-0515			
P-0516			
P-0517			
P-0518			
P-0519			
P-0520			
P-0521			
P-0522			
P-0523			

Los Compuestos Adicionales se prepararon en forma similar, reemplazando cloruro de 5-bromo tiofen-2-sulfonilo 7 con ya sea cloruro de 2-bromo-bencensulfonilo o cloruro de 3-bromo-5-metil-tiofen-2-sulfonilo en la Etapa 3 y reemplazando 5-metoxiindol-3-carboxilaldehído 4 con un 5-etoxiindol-5-carboxilaldehído apropiado en la Etapa 1, y haciendo reaccionar el producto de la

Etapa 3 con un ácido borónico apropiado mediante una Etapa 4 modificada, donde 10 mg del producto de la Etapa 3 se disuelve en 400 µL de acetonitrilo en un frasco para microondas de 2 mL. A esto se agregó 2 equivalentes del ácido borónico apropiado y 3 mg de tetraquis(trifenilfosfina)paladio(0), luego se agregó 400 µL del carbonato de potasio IM acuoso, el frasco se tapó, e irradió 10 minutos a 160 °C. La solución se neutralizó con ácido acético y los solventes se removieron bajo vacío. El material sin purificar se disolvió en dimetil sulfóxido y se purificó por fase inversa HPLC (columna CI 8), eluyendo con gradiente de agua/0.1% de ácido trifluoro acético y acetonitrilo/0.1% de ácido trifluoroacético, 20-100% acetonitrilo durante 16 minutos.

Los siguientes compuestos se prepararon utilizando 5-etoxiindol-3-carboxilaldehído en la Etapa 1, cloruro de 2-bromo-bencensulfonil o cloruro de 3-bromo-5-metil-tiofen-2-sulfonilo en la Etapa 3, y el ácido borónico apropiado en la Etapa 4, con el peso molecular calculado y masa medida (MS(ESI)) proporcionados después del compuesto:

Etiléster del ácido 3-[l-(2-Bromo-bencensulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0528**), PM calculado 480.38, $[M+H^+]^+$ = 480.1, 482.1,

Ácido 3-[l-(4'-Cloro-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0529**), PM calculado 483.97, $[M+H^+]^+$ = 484.3,

Ácido 3-[5-Etoxi-1-(4'-metoxi-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (P-0530), PM calculado 479.55, $[M+H^+]^+$ = 479.9,

Ácido 3-[5-Etoxi-1-(4'-isopropil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0531**), PM calculado 491.61, $[M+H^+]^+$ = 492.3,

ácido 3-[5-Etoxi-1-(4'-fluoro-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0532**), PM calculado 467.51, $[M+H^+]^+$ = 468.3,

Ácido 3-[l-(4'-Dimetilamino-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0533**), PM calculado 492.59, $[M+H^+]^+$ = 492.3,

Ácido 3-[l-(4'-Acetil-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0534**), PM calculado 491.56, $[M+H^+]^+$ = 492.3,

Ácido 3-[5-Etoxi-1-(4'-etoxi-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0535**), PM calculado 493.58, $[M+H^+]^+$ = 494.3,

Ácido 3-[5-Etoxi-1-(4'-trifluorometoxi-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0536**), PM calculado 533.52, $[M+H^+]^+$ = 533.9,

Ácido 3-[5-Etoxi-1-(4'-etilo-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0537**), PM calculado 477.58, $[M+H^+]^+$ = 477.9,

Ácido 3-[5-Etoxi-1-(4'-propil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0538**), PM calculado 491.61, $[M+H^+]^+$ = 492.3,

Ácido 3-[1-(4'-Amino-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0539**), PM calculado 464.54, $[M+H^+]^+$ = 465.1,

Ácido 3-[5-Etoxi-1-(4'-trifluorometil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0552**), PM calculado 517.52, $[M+H^+]^+$ = 517.9,

Ácido 3-[1-(3',4'-Difluoro-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0553**), PM calculado 517.52, $[M+H^+]^+$ = 517.9,

Ácido 3-{5-Etoxi-1-[2-(1H-indol-5-il)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0554**), PM calculado 488.56, $[M+H^+]^+$ = 489.1,

Ácido 3-[l-(3',4'-Dimetil-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico (**P-0555**), PM calculado 477.58, $[M+H^+]^+$ = 478.3,

Ácido 3-[5-Etoxi-1-(5-metil-3-p-tolil-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0524**),

Ácido 3-{1-[3-(4-Benciloxi-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0525**),

Ácido 3-{1-[3-(4-Amino-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0526**),

Ácido 3-{5-Etoxi-1-[3-(4-hidroxi-fenil)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0527**),

Ácido 3-{1-[3-(4-Cloro-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0540**),

Ácido 3-{5-Etoxi-1-[3-(4-metoxi-fenil)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0541**),

Ácido 3-{5-Etoxi-1-[3-(4-isopropil-fenil)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0542**),

Ácido 3-{5-Etoxi-1-[3-(4-fluoro-fenil)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0543**),

Ácido 3-{1-[3-(4-Dimetilamino-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0544**),

Ácido 3-{1-[3-(4-Acetil-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0545**),

Ácido 3-{5-Etoxi-1-[3-(4-etoxi-fenil)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0546**),

Ácido 3-{5-Etoxi-1-[5-metil-3-(4-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0547**),

Ácido 3-{5-Etoxi-1-[5-metil-3-(4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0548**),

Ácido 3-{5-Etoxi-1-[3-(4-etilo-fenil)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0549**),

Ácido 3-{5-Etoxi-1-[5-metil-3-(4-propyl-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0550**),

Ácido 3-{1-[3-(4-Aminometil-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0551**),

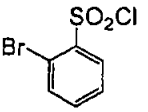
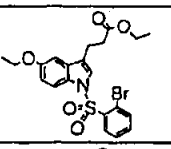
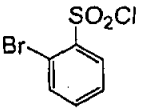
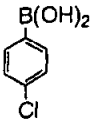
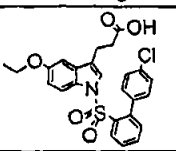
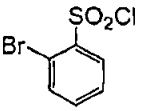
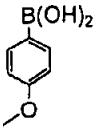
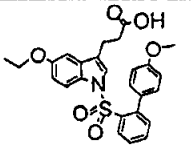
Ácido 3-{1-[3-(3,4-Difluoro-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0556**),

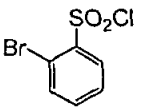
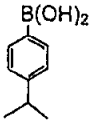
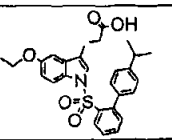
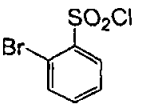
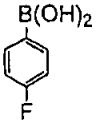
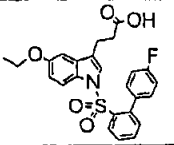
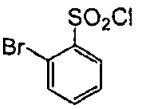
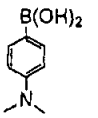
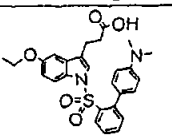
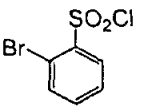
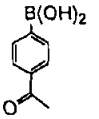
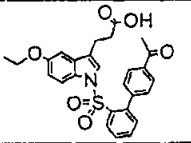
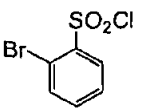
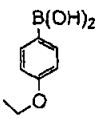
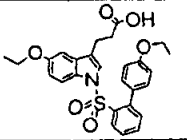
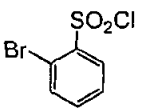
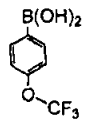
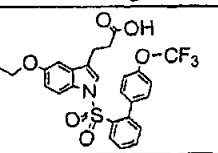
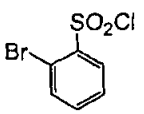
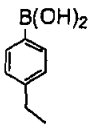
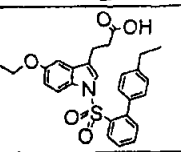
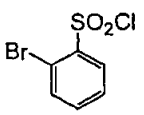
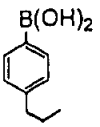
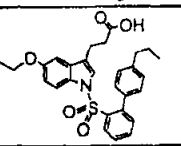
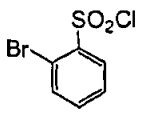
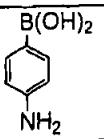
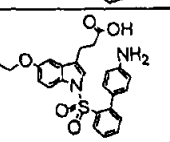
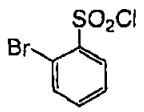
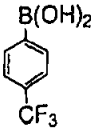
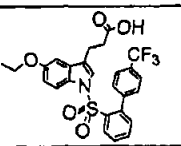
Ácido 3-{5-Etoxi-1-[3-(1H-indol-5-il)-5-metil-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0557**), y

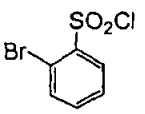
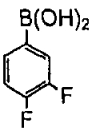
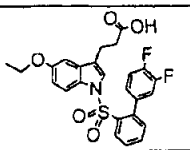
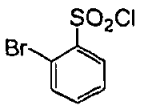
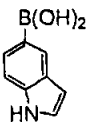
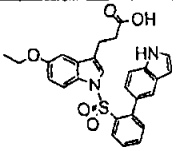
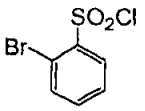
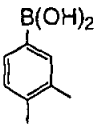
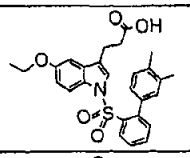
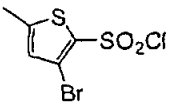
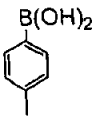
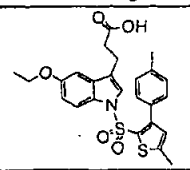
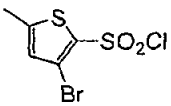
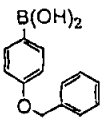
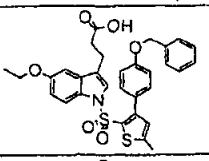
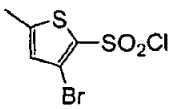
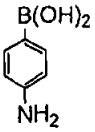
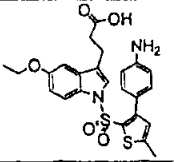
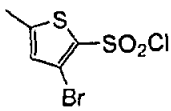
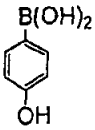
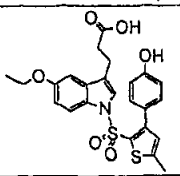
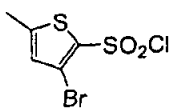
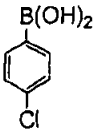
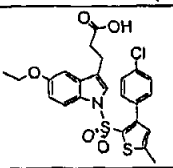
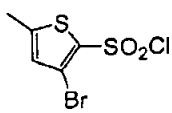
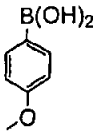
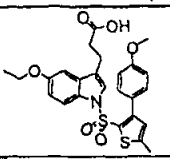
Ácido 3-{1-[3-(3,4-Dimetil-fenil)-5-metil-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico (**P-0558**).

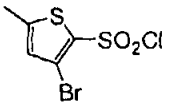
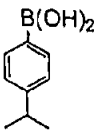
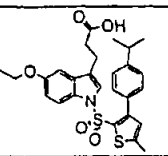
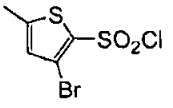
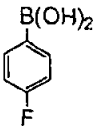
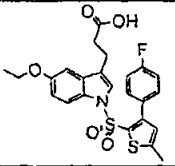
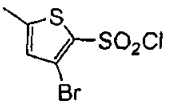
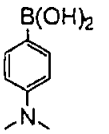
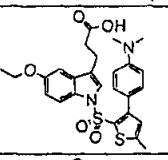
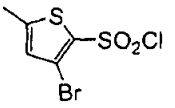
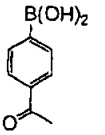
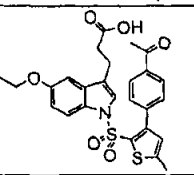
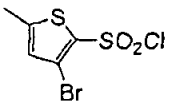
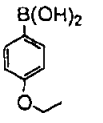
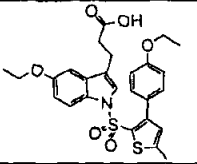
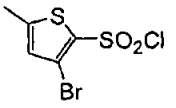
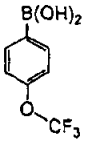
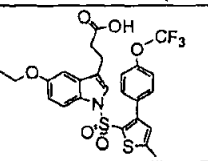
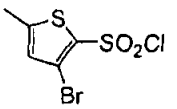
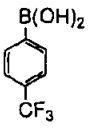
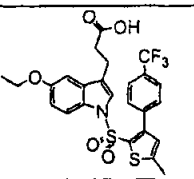
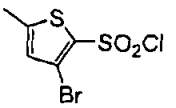
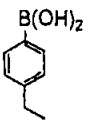
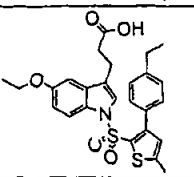
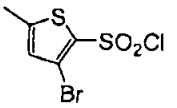
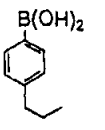
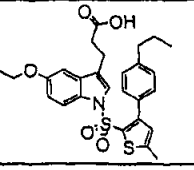
Estos Compuestos se muestran en la siguiente Tabla 4, indicando el cloruro de sulfonilo utilizado en la Etapa 3 (Columna 2), el ácido bórico utilizado en la Etapa 4 modificada (Columna 3), y la estructura del compuesto (Columna 4), con el número de compuesto proporcionado en la Columna 1.

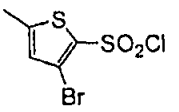
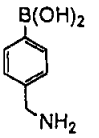
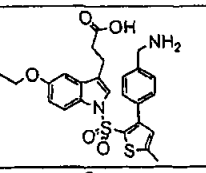
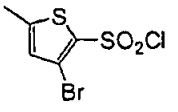
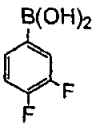
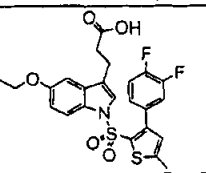
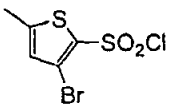
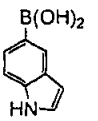
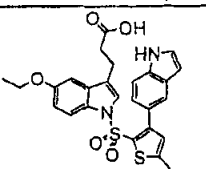
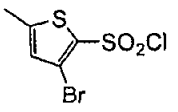
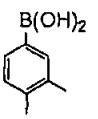
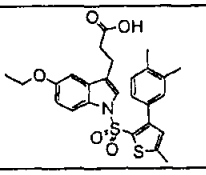
Tabla 4.

Comp. número	Cloruro de sulfonilo	Ácido borónico	Estructura del compuesto
P-0528 *		N/A	
P-0529			
P-0530			

Comp. número	Cloruro de sulfonilo	Ácido borónico	Estructura del compuesto
P-0531			
P-0532			
P-0533			
P-0534			
P-0535			
P-0536			
P-0537			
P-0538			
P-0539			
P-0552			

Comp. número	Cloruro de sulfonilo	Ácido borónico	Estructura del compuesto
P-0553			
P-0554			
P-0555			
P-0524			
P-0525			
P-0526			
P-0527			
P-0540			
P-0541			

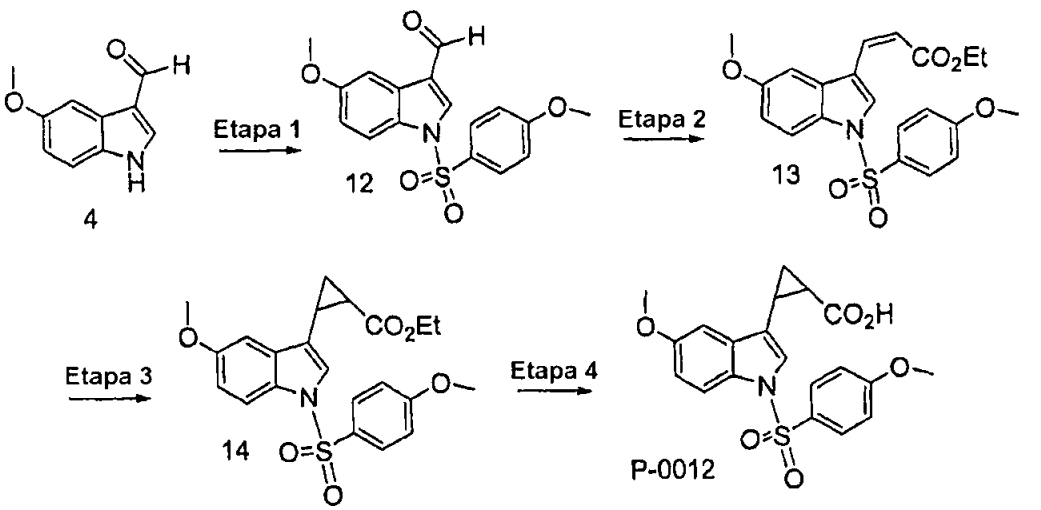
Comp. número	Cloruro de sulfonilo	Ácido borónico	Estructura del compuesto
P-0542			
P-0543			
P-0544			
P-0545			
P-0546			
P-0547			
P-0548			
P-0549			
P-0550			

Comp. número	Cloruro de sulfonilo	Ácido borónico	Estructura del compuesto
P-0551			
P-0556			
P-0557			
P-0558			

*Aislado después de la Etapa 3

Ejemplo 3: Síntesis del Ácido 2-[5-Metoxi-1-(4-metoxi-bencensulfonil)-1H-Indol-3-il)-ciclopropancarboxílico (P-0012).

El compuesto **P-0012** se sintetizó en las cuatro etapas como se muestra en el Esquema 3.



Etapa-1: Preparación de 5-metoxi-1-(4-metoxi bencensulfonil)-1H-indol-3-carbaldehído (12)

Se combinaron 5-metoxiindol-3-carboxilaldehído (4, 263 mg) y tolueno (15 mL) en un matraz de fondo redondo de 100 mL seco. La mezcla se agitó durante 5 minutos, después se agregó una solución acuosa de 50% de KOH (12 mL) seguida por sulfato ácido de tetrabutilamonio (8 mg). La solución se agitó a temperatura ambiente durante la noche, después de lo cual el sólido resultante se recolectó por filtración utilizando un embudo vitrificado de grado medio. El sólido se enjuagó con agua fría (10 mL) y etiléter (2 x 15 mL) para dar el compuesto deseado (**2**, 388 mg, 75%). 1H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa — 2: Preparación de etiléster del ácido (Z)-3-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-Indol-3-il)-acrílico (13)

Se enfrió a 0°C difenilfosfonoacetato de etilo (549 mg, 1.71 mmol) en tetrahidrofurano (2 mL) y se agregó hidruro de sodio (47.9 mg, 1.99 mmol). La mezcla se agitó a 0°C durante 15 minutos y la solución de difenilfosfonoacetato de etilo desprotonado se agregó por goteo a una solución en agitación de 5-metoxi-1-(4-metoxibencensulfonil)-1H-indol-3-carbaldehído (**12**, 493 mg, 1.43 mmol) en tetrahidrofurano (11 mL) a 0 °C. La mezcla de reacción se calentó lentamente a 25 °C durante la noche. Cuando la conversión de **12** fue incompleta, la mezcla de reacción se enfrió a 0°C y se agregó un equivalente adicional de difenilfosfonoacetato de etilo desprotonado. Después de calentar lentamente a 25°C durante la noche, se agregó acetato de etilo a la mezcla de reacción y la capa orgánica se lavó con bicarbonato de sodio saturado, se secó sobre sulfato de magnesio y se filtró. La concentración bajo presión reducida resultó en un sólido sin purificar que tuvo una relación de 2:1 de los isómeros Z y E. El isómero Z se aisló utilizando cromatografía (gradiente de hexanos a 20% de acetato de etilo en hexanos) (**13**, 251 mg, 42% de rendimiento). MS(ESI) [M + $H^+]^+$ = 438.2.

*Etapa — 3: Preparación de etiléster del ácido 2-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-Indol-3-il)-ciclopropano carboxílico (**14**)*

Se disolvió yoduro de trimetilsulfoxonio (116 mg, 0.053 mmol) en sulfóxido de dimetilo (0.75 mL) y se agregó hidruro de sodio (14 mg, 0.058 mmol). Después de 20 minutos de agitación a 25°C, se agregó etiléster del ácido (Z)-3-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-Indol-3-il)-acrílico (13, 200 mg, 0.048 mmol) en tetrahidrofurano (0.78 mL) y la solución se calentó a 60°C bajo una atmósfera de nitrógeno durante la noche. Se agregó agua a la mezcla de reacción seguida por la adición de acetato de etilo. La capa acuosa se lavó con acetato de etilo y las capas orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. La purificación del material sin purificar se llevó a cabo utilizando cromatografía preparatoria (30% acetato de etilo en hexanos) para obtener el compuesto deseado como un sólido blanquecino (**14**, 33 mg, 16% de producción). MS(ESI) $[M+H^+]^+$ = 430.4.

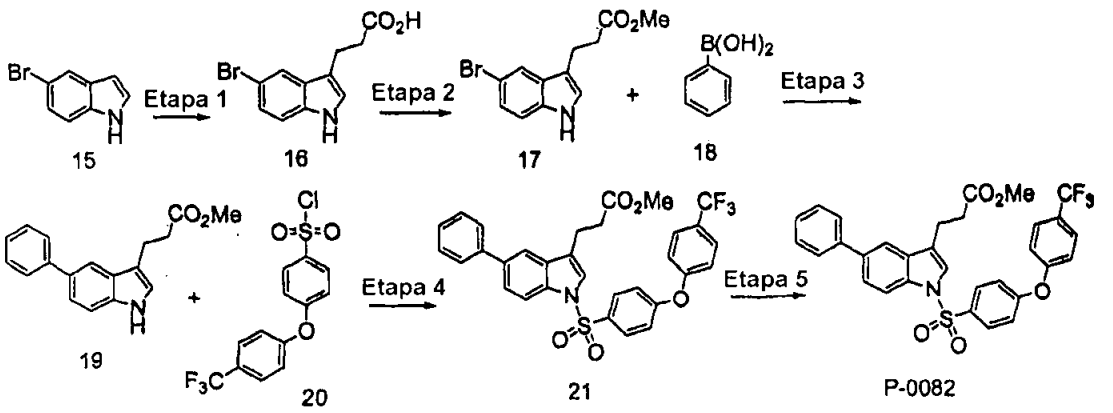
*Etapa — 4: Preparación de ácido 2-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-Indol-3-il)-ciclopropan carboxílico (**P-0012**)*

Se disolvió etiléster del ácido 2-[5-Metoxi-1-(4-metoxi-bencensulfonil)-1H-Indol-3-il)-ciclopropan carboxílico (**14**, 25 mg, 0.006 mmol) en tetrahidrofurano (1.0 mL) y se agregó hidróxido de litio 1M (0.25 mL). Después de agitar durante 4 días a 25°C, se agregó acetato de etilo y la mezcla se acidificó con ácido clorhídrico 1M. La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para producir un sólido rojo. El material sin purificar se trituró con *ter*-butilmetiléter para producir el compuesto deseado (**P-0012**, 2.6 mg, 11% de producción). Peso molecular calculado 401.43, MS(ESI) $[M-H^+]^+$ = 400.2.

Ejemplo 4: Síntesis del ácido 3-{5-fenil-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (P-0082).

El compuesto **P-0082** se sintetizó en cinco Etapas como se muestra en el Esquema 4.

Esquema 4



*Etapa 1: Preparación del ácido 5-bromoindol-3-propiónico (**16**)*

En un recipiente para microondas, se disolvieron en acetonitrilo (2 mL/minol) 5-bromo-indol (**15**, 1 equivalentes), paraformaldehído (1.1 equivalentes), 2,2-dimetil-l,3-dioxan-4,6-diona (1.1 equivalentes), y trietilamina (1.1 equivalentes). La reacción se calentó a 150°C durante 3 minutos en un reactor de microondas. La reacción se diluyó entonces con agua acidificada a pH ~ 5 con ácido acético y se extrajo la capa acuosa con acetato de etilo. La capa orgánica se lavó entonces con agua 2X, salmuera IX, y se secó sobre sulfato de magnesio. La evaporación de solvente produjo un sólido. El sólido sin purificar se purificó entonces mediante cromatografía instantánea con un gradiente en etapas de 2 a 4 a 6% de metanol en cloroformo sobre sílice para obtener el compuesto deseado como un sólido.

*Etapa 2: Preparación de metiléster del ácido de 5-bromoindol-3-propiónico (**17**)*

Se trató el ácido 5-bromo-indol-3-propiónico **16** con una solución acuosa de 4M HCl: metanol:dioxano (1:1:1) durante 1 hora. La reacción se volvió a evaporar entonces con xileno y se purificó mediante cromatografía instantánea en sílice (cloroformo) para obtener el compuesto deseado como un sólido blanquecino.

*Etapa 3: Preparación de metiléster del ácido 3-(5-fenil-1H-indol-3-il)-propiónico (**19**)*

En un tubo para microondas que contiene metiléster del ácido 5-bromo-indol-3-propiónico intermediario (**17**, 0.05mmol), ácido fenilborónico (**18**, 0.1 mmol), 0.2 mL K_2CO_3 1M (0.2 mmol), acetonitrilo (0.4 ml) y unos cuantos mg de tetrakis(trifenilfosfina)paladio(0) se combinaron y se

calentaron en el microondas a 160°C durante 400 segundos. El material sin purificar se purificó entonces mediante cromatografía instantánea con sílice, eluyendo con un gradiente en etapas de 2 a 4 a 6% de metanol en cloroformo para aislar el compuesto deseado como un sólido.

*Etapa 4: Preparación de metiléster del ácido 3-{5-fenil-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**21**)*

En un matraz que contiene metiléster del ácido 3-(5-fenil-1H-indol-3-il)-propiónico (**19**, 1mmol) disuelto en 5 mL tetrahidrofurano, BEMP (1.1 mmol), y cloruro de 4-(4-trifluorometil-fenoxi)-bencensulfonilo (**20**, 1.05 mmol) se combinaron y se mezclaron a temperatura ambiente durante 2 horas. La mezcla sin purificar se incorporó en la siguiente etapa.

Etapa 5: Preparación de ácido 3-{5-fenil-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0082**)

En un matraz, la mezcla sin purificar de la Etapa 4 se disolvió en una solución NaOH 1M, y se agitó durante 4 horas a temperatura ambiente. La hidrólisis se monitoreo mediante LC-MS. Con la transformación completa, la solución básica se neutralizó con ácido acético, seguida de la remoción del solvente bajo presión reducida para producir un sólido sin purificar. El material sin purificar se extrajo entonces en dimetilsulfóxido y se purificó mediante HPLC de fase inversa con un gradiente de 20-100% de acetonitrilo (gradiente de 12 minutos). El material purificado se analizó entonces mediante HPLC para identificar las fracciones puras. Las fracciones se combinaron entonces y se concentraron para producir el compuesto deseado como un sólido. Peso molecular calculado de 565.57, MS(ESI) $[M+H^+]^+$ = 566.4.

Se prepararon los compuestos adicionales siguiendo el protocolo del Esquema 4, opcionalmente reemplazando ácido fenilborónico **18** con ácido piridin-3-borónico o ácido tiofen-3-borónico en la Etapa 3, y/u opcionalmente reemplazando cloruro de 4-(4-trifluorometil-fenoxi)-bencensulfonilo **20** con un cloruro de sulfonilo apropiado en la Etapa 4. Los siguientes compuestos se prepararon por este método, con el peso molecular calculado y masa medida (MS(ESI)) proporcionados después del compuesto:

Ácido 3-[1-(5-Isoxazol-3-il-tiofen-2-sulfonil)-5-fenil-1H-indol-3-il]-propiónico (**P-0076**), PM calculado 478.55, $[M+H^+]^+$ = N/A,

Ácido 3-{1-[5-(2-Metil-tiazol-4-il)-tiofen-2-sulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0077**), PM calculado 508.64, $[M+H^+]^+$ = 509.1,

Ácido 3-{5-Fenil-1-[4-(piridin-2-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0078**), PM calculado 498.56, $[M+H^+]^+$= 499.1,

Ácido 3-{1-[4-(4-Metoxi-fenoxi)-bencensulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0079**), PM calculado 527.60, $[M+H^+]^+$ = 528.3,

Ácido 3-{1-[4-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0080**), PM calculado 566.46, $[M-H^+]$-= 566.4

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0081**), PM calculado 566.46, $[M-H^+]$-= 566.4,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0083**), PM calculado 601.01, $[M+H^+]^+$ = 601.2,

Ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0084**), PM calculado 566.46, $[M+H^+]^+$ = 566.8,

Ácido 3-[1-(4'-Metoxi-bifenil-4-sulfonil)-5-fenil-1H-indol-3-il]-propiónico (**P-0085**), PM calculado 511.60, $[M+H^+]^+$ = 512.3,

Ácido 3-[1-(6-Morfolin-4-il-piridin-3-sulfonil)-5-fenil-1H-indol-3-il]-propiónico (**P-0086**), PM calculado 491.57, $[M+H^+]^+$ = 492.3,

Ácido 3-[1-(6-Fenoxi-piridin-3-sulfonil)-5-fenil-1H-indol-3-il]-propiónico (**P-0087**), PM calculado 498.56, $[M+H^+]^+$ = 499.1,

Ácido 3-[5-Fenil-1-(5-piridin-2-il-tiofen-2-sulfonil]-1H-indol-3-il-propiónico (**P-0088**), PM calculado 488.59, $[M+H^+]^+$ = 489.1,

Ácido 3-(1-{4-[(Morfolin-4-carbonil)-amino]-bencensulfonil}-5-fenil-1H-indol-3-il)-propiónico ácido (**P-0089**), PM calculado 533.61, $[M+H^+]^+$ = 534.3,

Ácido 3-{1-[5-(1-Metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-5-fenil-1H-indol-3-il}-propiónico (**P-0091**), PM calculado 559.59, $[M+H^+]^+$ =560.4,

Ácido 3-{1-[5-(2-Metilsulfanil-pirimidin-4-il)-tiofen-2-sulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0095**), PM calculado 536.65, $[M+H^+]^+$ = 537.1,

Ácido 3-{5-Piridin-3-il-1-[4-(piridin-2-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0097**), PM calculado 499.55, $[M+H^+]^+$ = 500.3,

Ácido 3-{1-[4-(4-Metoxi-fenoxi)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0098**), PM calculado 528.59, $[M+H^+]^+$ = 529.1,

Ácido 3-{1-[4-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0099**), PM calculado 567.45, $[M-H^+]^+$ = 567.2,

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0100**), PM calculado 567.45, $[M-H^+]^+$ = 567.2,

Ácido 3-{5-Piridin-3-il-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico ácido (**P-0101**), PM calculado 566.56, $[M+H^+]^+$ = 567.2,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0102**), PM calculado 601.99, $[M+H^+]^+$ = 602.4,

Ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0103**), PM calculado 567.45, $[M-H^+]^+$ = 567.2,

Ácido 3-[1-(4'-Metoxi-bifenil-4-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0104**), PM calculado 512.59, $[M+H^+]^+$ = 513.5,

Ácido 3-[1-(6-Fenoxi-piridin-3-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0105**), PM calculado 499.55, $[M+H^+]^+$ = 500.3,

Ácido 3-[5-Piridin-3-il-1-(5-piridin-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0106**), PM calculado 489.58, $[M+H^+]^+$ = 490.3,

Ácido 3-{1-[5-(1-Metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0107**), PM calculado 560.58, $[M+H^+]^+$ = 561.2,

Ácido 3-[1-(5-Metil-1-fenil-1H-pirazol-4-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0113**), PM calculado 486.55, $[M+H^+]^+$ = 487.1,

Ácido 3-[1-(6-Morfolin-4-il-piridin-3-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0114**), PM calculado 492.56, $[M+H^+]^+$ = 493.5,

Ácido 3-(1-{4-[(Morfolin-4-carbonil)-amino]-bencensulfonil}-5-piridin-3-il-1H-indol-3-il)-propiónico (**P-0115**), PM calculado 534.60, $[MH-H^+]^+$ = 535.1,

Ácido 3-{5-Piridin-3-il-1-[4-(piridin-4-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0118**), PM calculado 499.55, $[M+H^+]^+$ = 500.3,

Ácido 3-{1-[3-(2-Metil-pirimidin-4-il)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0120**), PM calculado 498.56, $[M+H^+]^+$ = 499.1,

Ácido 3-[1-(Bifenil-2-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0125**), PM calculado 482.56, $[M+H^+]^+$ = 483.1,

Ácido 3-[1-(2-Fenoxi-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0128**), PM calculado 498.56, $[M+H^+]^+$ = 499.1,

Ácido 3-{1-[3-(Piridin-2-carbonil)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico (**P-0131**), PM calculado 511.56, $[M+H^+]^+$ = 512.3,

Ácido 3-[1-(4-Pirazol-1-il-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico (**P-0137**), PM calculado 472.53, $[M+H^+]$ = 473.1,

Ácido 3-{1-[5-(2-Metilsulfanil-pirimidin-4-il)-tiofen-2-sulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0573**), PM calculado 541.70,

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0574**), PM calculado 572.49,

Ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0575**), PM calculado 572.49,

Ácido 3-{1-[4-(Piridin-2-iloxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0581**), PM calculado 504.58,

Ácido 3-{1-[4-(Piridin-4-iloxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0582**), PM calculado 504.58,

Ácido 3-{1-[4-(4-Metoxi-fenoxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0583**), PM calculado 533.62,

Ácido 3-{1-[4-(3,4-Dicloro-fenoxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0584**), PM calculado 572.49,

Ácido 3-{5-Tiofen-3-il-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0585**), PM calculado 571.59,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0586**), PM calculado 607.03,

Ácido 3-[1-(4'-Metoxi-bifenil-4-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (**P-0587**), PM calculado 517.62,

Ácido 3-[1-(6-Morfolin-4-il-piridin-3-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (**P-0588**), PM calculado 497.59,

Ácido 3-[1-(6-Fenoxi-piridin-3-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (**P-0589**), PM calculado 504.58,

Ácido 3-[1-(5-Piridin-2-il-tiofen-2-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (P-0590), PM calculado 494.61,

Ácido 3-{1-[5-(1-Metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0592**), PM calculado 565.62,

Ácido 3-[1-(5-Metil-1-fenil-1H-pirazol-4-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (**P-0599**), PM calculado 491.59,

Ácido 3-{1-[3-(2-Metil-pirimidin-4-il)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (**P-0601**), PM calculado 503.60,

Ácido 3-{1-[3-(Piridin-2-carbonil)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico (P-0607), PM calculado 516.60,

Ácido 3-[1-(Bifenil-2-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (P-0608), PM calculado 487.60,

Ácido 3-[1-(4'-Metil-bifenil-2-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico (P-0617), PM calculado 501.62,

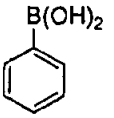
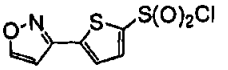
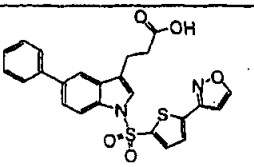
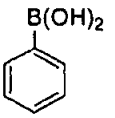
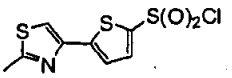
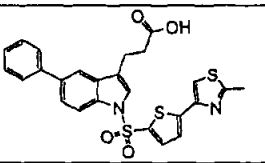
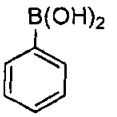
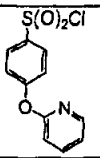
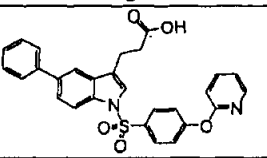
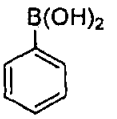
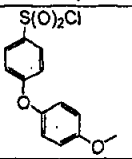
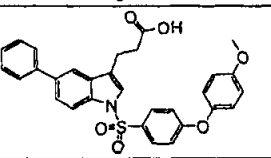
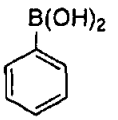
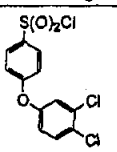
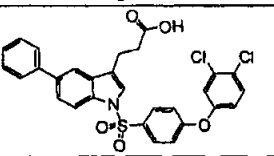
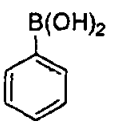
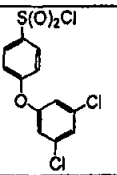
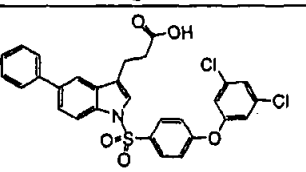
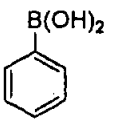
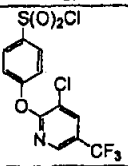
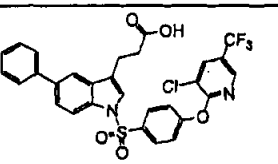
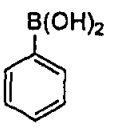
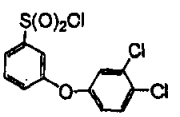
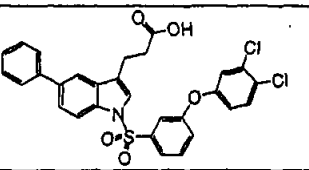
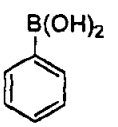
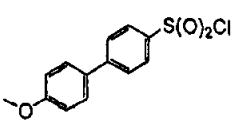
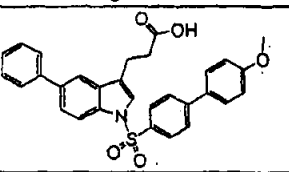
3-[1-(2-Fenoxi-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico ácido

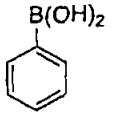
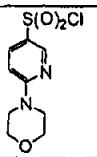
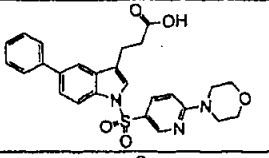
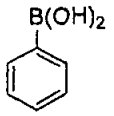
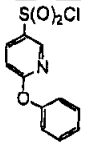
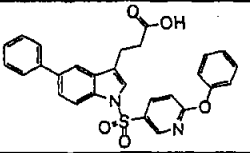
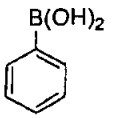
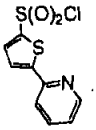
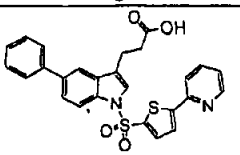
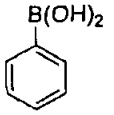
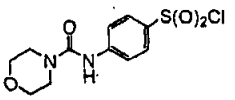
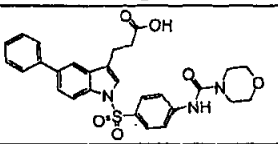
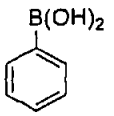
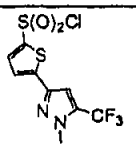
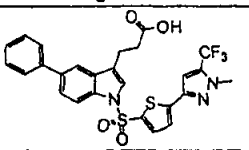
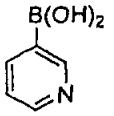
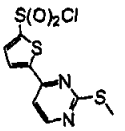
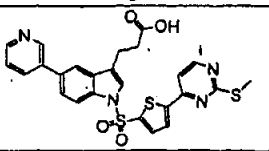
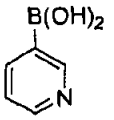
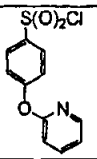
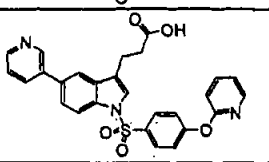
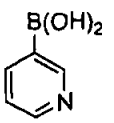
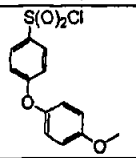
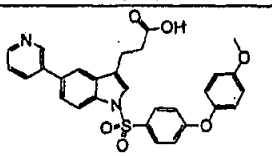
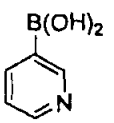
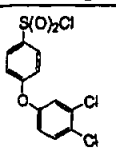
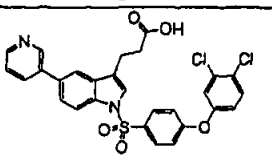
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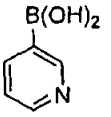
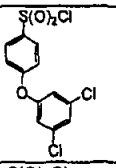
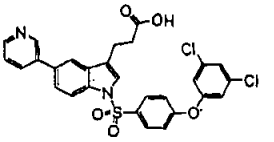
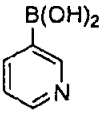
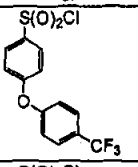
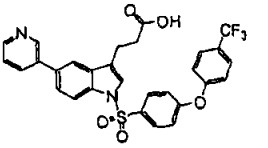
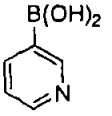
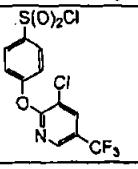
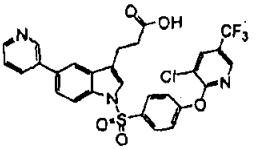
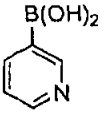
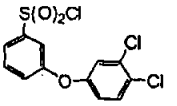
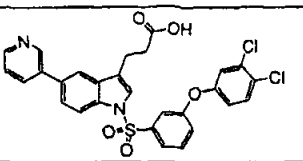
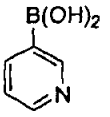
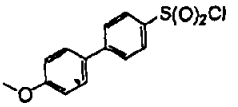
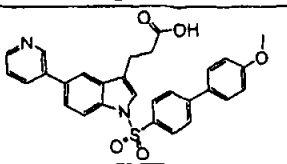
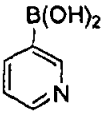
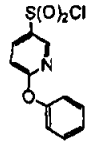
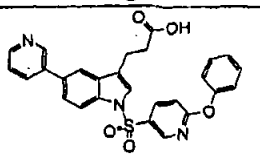
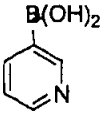
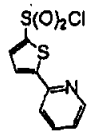
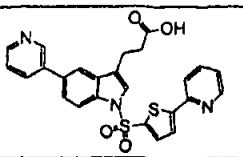
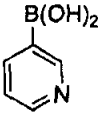
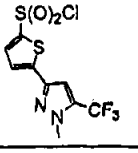
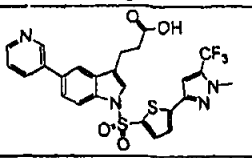
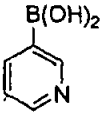
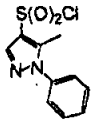
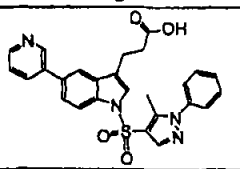
Estos compuestos se muestran en la siguiente Tabla 5, que indican el ácido borónico usado en la Etapa 3 (Columna 2), y el cloruro de sulfonilo utilizado en la Etapa 4 (Columna 3), con

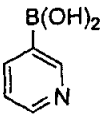
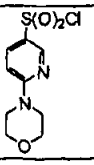
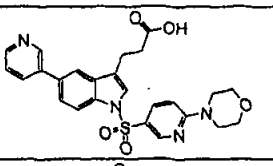
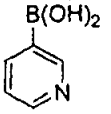
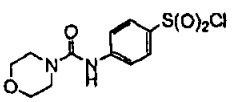
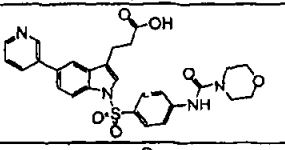
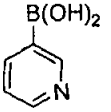
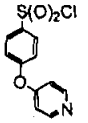
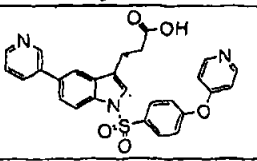
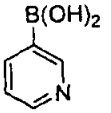
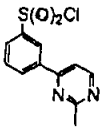
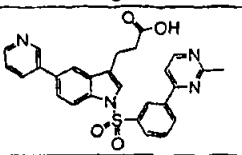
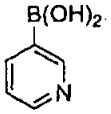
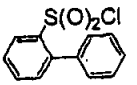
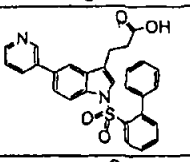
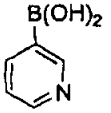
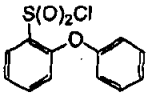
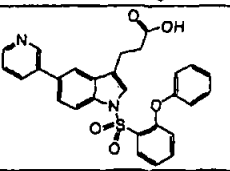
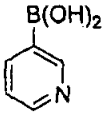
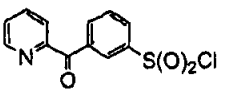
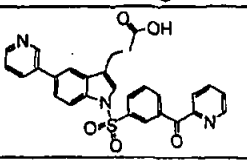
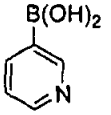
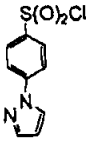
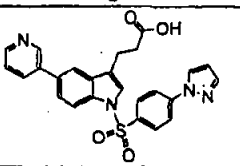
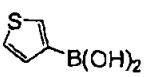
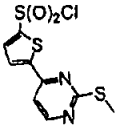
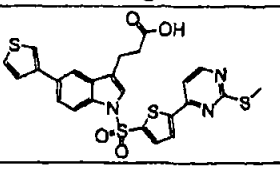
la estructura del compuesto proporcionada en la Columna 4 y el número del compuesto proporcionado en la Columna 1.

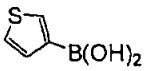
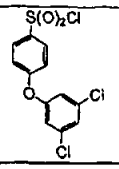
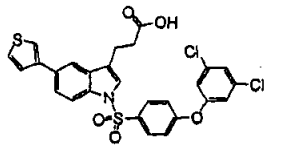
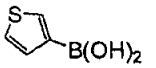
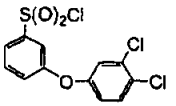
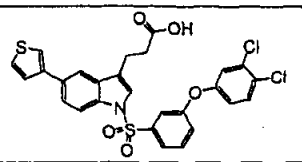
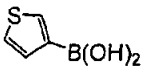
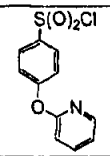
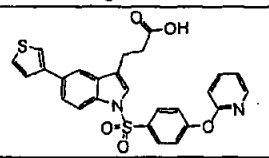
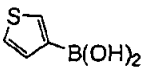
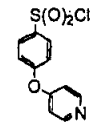
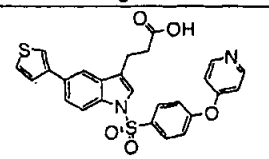
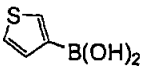
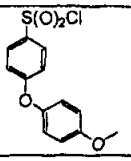
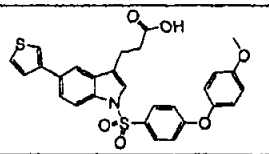
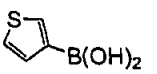
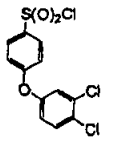
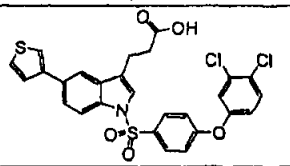
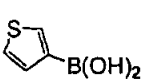
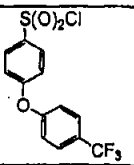
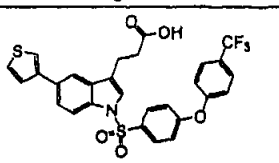
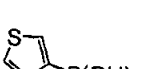
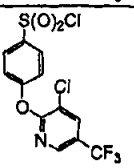
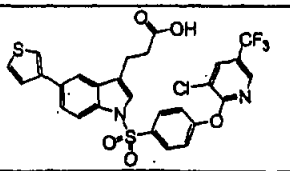
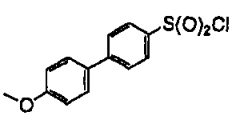
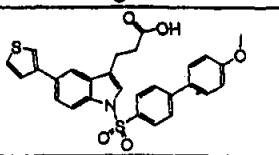
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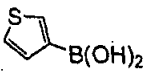
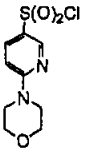
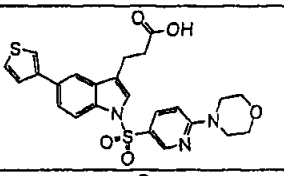
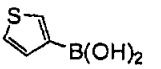
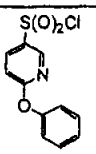
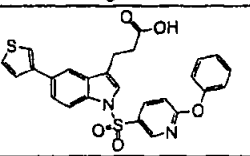
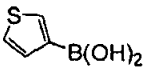
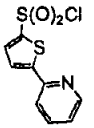
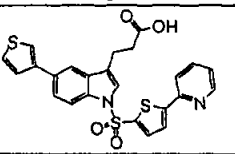
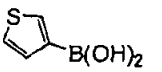
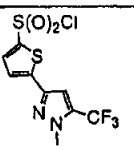
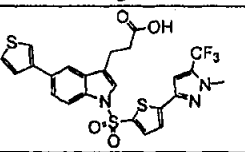
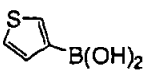
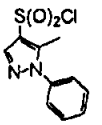
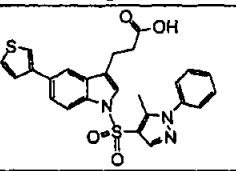
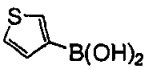
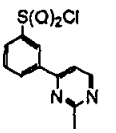
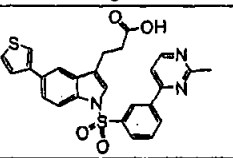
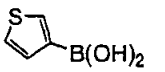
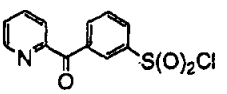
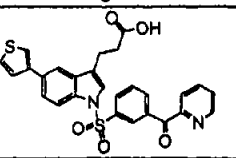
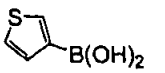
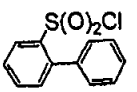
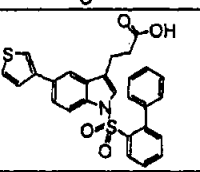
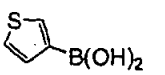
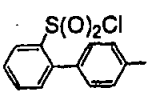
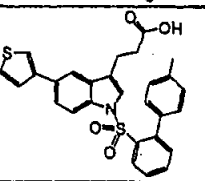
Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0076			
P-0077			
P-0078			
P-0079			
P-0080			
P-0081			
P-0083			
P-0084			
P-0085			

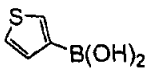
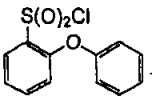
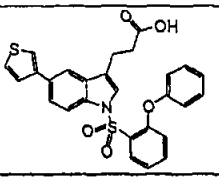
Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0086			
P-0087			
P-0088			
P-0089			
P-0091			
P-0095			
P-0097			
P-0098			
P-0099			

Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0100			
P-0101			
P-0102			
P-0103			
P-0104			
P-0105			
P-0106			
P-0107			
P-0113			

Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0114			
P-0115			
P-0118			
P-0120			
P-0125			
P-0128			
P-0131			
P-0137			
P-0573			

Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0574			
P-0575			
P-0581			
P-0582			
P-0583			
P-0584			
P-0585			
P-0586			
P-0587			

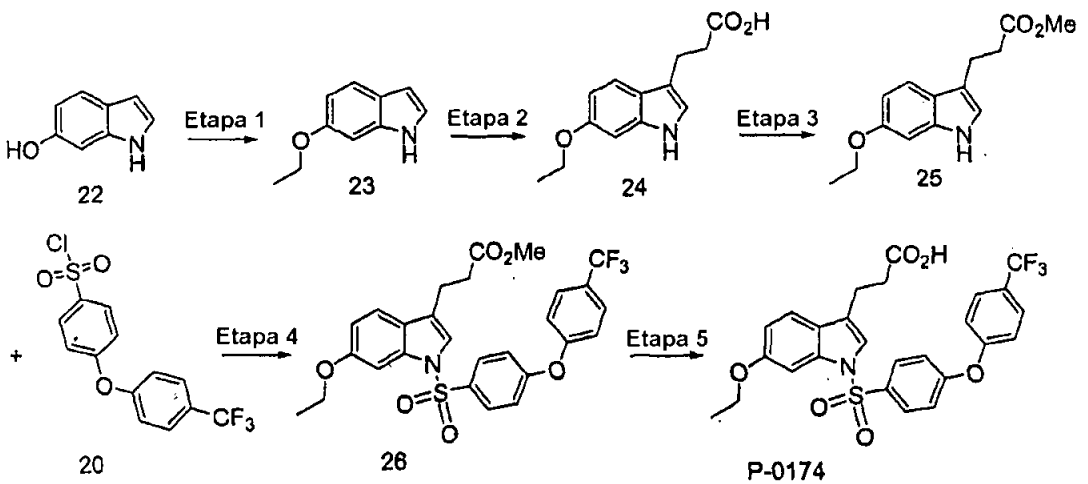
Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0588			
P-0589			
P-0590			
P-0592			
P-0599			
P-0601			
P-0607			
P-0608			
P-0617			

Comp. número	Ácido borónico	Cloruro de sulfonilo	Estructura del compuesto
P-0618			

Ejemplo 5: Síntesis de ácido 3-{6-Etoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (P-0174).

El compuesto **P-0174** se sintetizó en cinco Etapas como se muestra en el Esquema 5.

Esquema 5



Etapa 1: preparación de 6-etoxiindol (23)

En un matraz de fondo redondo 6-hidroxiindol (**22**, 2 g, 0.02 mol), carbonato de potasio (4 g, 0.03 mol), acetonitrilo (20 g, 0.5 mol), y yodoetano (4 g, 0.02 mol) se combinaron y se agitaron a temperatura ambiente durante 3-4 días. La reacción se filtró y se lavó con diclorometano. La capa orgánica se lavó entonces con agua dos veces, una vez con salmuera, y se secó sobre sulfato de sodio. La evaporación del solvente produjo un aceite. El aceite se absorbió entonces en sílice y se purificó por 80% hexano, 20% acetato de etilo para producir un sólido amarillo. ^{1}H NMR es consistente con la estructura del compuesto establecido en lo anterior.

Etapa 2: Preparación del ácido 6-etoxi-indol-3-propiónico (24)

En un recipiente para microondas, se disolvieron en acetonitrilo (2 mL/mmol) 6-etoxi indol (23.1 equivalentes), paraformaldehído (1.1 equivalentes), 2,2-dimetil-l,3-dioxan-4,6-diona (1.1 equivalentes), y trietilamina (1.1 equivalentes). La reacción se calentó a 150 °C durante 3 minutos en un reactor de microondas. La reacción se diluyó entonces con agua acidificada a pH ~ 5 con ácido acético y se extrajo la capa acuosa con acetato de etilo. La capa orgánica se lavó entonces con agua 2X, salmuera 1X, y se secó sobre sulfato de magnesio. La evaporación del solvente produjo un sólido. El sólido sin purificar se purificó entonces mediante cromatografía instantánea con gradiente en etapas de 2 a 4 a 6% de metanol en cloroformo sobre sílice para obtener el compuesto deseado como un aceite.

*Etapa 3: Preparación de metiléster del ácido 6-etoxi-indol-3-propiónico (**25**)*

En un matraz, el ácido 6-etoxi-indol-3-propiónico 24 se trató con metanol (4 mol equiv), N,N'-Diisopropilcarbodiimida (2 mol equiv), una cantidad catalítica de dimetilaminopiridina en diclorometano y se agitó durante 15 a 20 minutos en condiciones ambientales. El solvente se removió bajo presión reducida y la mezcla se purificó mediante cromatografía instantánea en sílice (cloroformo) para obtener el compuesto deseado como un sólido blanquecino.

Etapa 4: Preparación de metiléster del ácido 3-{6-etoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (26)

En un matraz que contiene metiléster del ácido 6-etoxi-indol-3-propiónico (25, 1mmol) disuelto en 5 mL de tetrahidrofurano, BEMP (1.1mmol), y cloruro de 4-(4-trifluorometil-fenoxi)-bencensulfonilo (20, 1.05 mmol) se combinaron y se mezclaron a temperatura ambiente durante 2 horas. La mezcla sin purificar se incorporó a la siguiente etapa.

Etapa 5: Preparación del ácido 3-{6-etoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (P-0174)

[0255] En un matraz, la mezcla sin purificar de la Etapa 4 se disolvió en una solución NaOH 1M, y se agita durante 4 horas a temperatura ambiente. La hidrólisis se monitoreo mediante LC-MS. Con la transformación completa, la solución básica se neutralizó con ácido acético, seguido de la remoción del solvente bajo presión reducida para producir un sólido sin purificar. El

material sin purificar se extrajo entonces en dimetilsulfóxido y se purificó mediante HPLC de fase inversa con un gradiente de 20-100% de acetonitrilo (gradiente de 12 minutos). El material purificado se analizó entonces mediante HPLC para identificar las fracciones puras. Las fracciones se combinaron entonces y se concentró para producir el compuesto deseado como un sólido. Peso molecular calculado de 533.53, MS (ESI) $[M+H^+]^+$ = 534.3.

Se prepararon los compuestos adicionales siguiendo el protocolo del Esquema 5, opcionalmente reemplazando yodoetano con 2- yodopropano en la Etapa 1, y/u opcionalmente reemplazando 4-(4-trifluorometil-fenoxi)-bencensulfonil cloruro 20 con un cloruro de sulfonilo apropiado en la Etapa 4. Los siguientes compuestos se prepararon por este método, con el peso molecular calculado y masa medida (MS(ESI)) proporcionados después del compuesto:

Ácido 3-{6-Etoxi-1-[4-(piridin-3-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0173**), PM calculado 466.52, $[M+H^+]^+$ = 467.1,

Ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencensulfonil]-6-etoxi-1H-indol-3-il}-propiónico (**P-0175**), PM calculado 534.42, $[M-H^+]$-= 533.9,

Ácido 3-[6-Etoxi-1-(6-morfolin-4-il-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (**P-0176**), PM calculado 459.53, $[M+H^+]^+$ = 460.3,

Ácido 3-[6-Etoxi-1-(6-phenoxy-piridin-3-sulfonil)-1H-indol-3-il]-propiónico (**P-0177**), PM calculado 466.52, $[M+H^+]^+$ = 467.1,

Ácido 3-{6-Etoxi-1-[3-(piridin-2-carbonil)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0182**), PM calculado 478.53, $[M+H^+]^+$ = 479.1,

Ácido 3-{6-Etoxi-1-[3-(piridin-4-carbonil)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0183**), PM calculado 478.53, $[M+H^+]^+$ = 479.1,

Ácido 3-[1-(Bifenil-2-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico (**P-0185**), PM calculado 449.53, $[M+H^+]^+$ = 449.9,

Ácido 3-[6-Etoxi-1-(2-fenoxi-bencensulfonil)-1H-indol-3-il]-propiónico (**P-0191**), PM calculado 465.53, $[M+H^+]^+$ = 466.3,

Ácido 3-{6-Etoxi-1-[4-(4-metoxi-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0195**), PM calculado 495.56, $[M+H^+]^+$ = 496.3,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-6-etoxi-1H-indol~3-il}-propiónico (**P-0196**), PM calculado 568.96, $[M+H^+]^+$ = 569.2,

Ácido 3-[6-Etoxi-1-(4'-metil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0201**), PM calculado 463.56, $[M+H^+]^+$ = 464.3,

Ácido 3-{6-Isopropoxi-1-[4-(4-metoxi-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0206**), PM calculado 509.58, $[M+H^+]^+$ = 510.3,

Ácido 3-{6-Isopropoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0207**), PM calculado 547.55, [M+H$^+$f = 548.3,

Ácido 3-{6-Isopropoxi-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0208**), PM calculado 541.57, $[M+H^+]^+$ = 543.1,

Ácido 3-[6-Isopropoxi-1-(5-metil-1-fenil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0232**), PM calculado 467.55, $[M+H^+]^+$ = 468.3,

Ácido 3-{1-[4-(3,4-Dicloro-fenoxi)-bencensulfonil]-6-isopropoxi-1H-indol-3-il}-propiónico (**P-0233**), PM calculado 548.45, $[M+H^+]^+$ = 550.3,

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-6-isopropoxi-1H-indol-3-il}-propiónico (**P-0234**), PM calculado 548.45, $[M-H^+]^+$ = 547.9,

Ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-6-isopropoxi-1H-indol-3-il}-propiónico (**P-0235**), PM calculado 582.99, $[M+H^+]^+$ = 583.2,

Ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencensulfonil]-6-isopropoxi-1H-indol-3-il}-propiónico (**P-0236**), PM calculado 548.45, $[M-H^+]^+$ = 548.3,

Ácido 3-[6-Isopropoxi-1-(4'-metoxi-bifenil-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0237**), PM calculado 493.58, $[M+H^+]^+$ = 494.3,

Ácido 3-[6-Etoxi-1-(5-metil-1-fenil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0346**), PM calculado 453.52, $[M+H^+]^+$-454.3,

Ácido 3-{6-Etoxi-1-[5-(2-metilsulfanil-pirimidin-4-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0347**), PM calculado 503.62, $[M+H^+]^+$ = 504.3,

3-{6-Etoxi-1-[4-(piridin-2-iloxi)-bencensulfonil]-1H-indol-3-il}-propiónico (**P-0350**), PM calculado 466.52, $[M+H^+]^+$ = 467.1,

3-{1-[4-(3,4-Dicloro-fenoxi)-bencensulfonil]-6-etoxi-1H-indol-3-il}-propiónico (**P-0351**), PM calculado 534.42, $[M-H^+]^+$ = 533.9,

Ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencensulfonil]-6-etoxi-1H-indol-3-il}-propiónico (**P-0352**), PM calculado 534.42, $[M-H^+]^+$ = 533.9,

Ácido 3-[6-Etoxi-1-(4'metoxi-bifenil-4-sulfonil)-1H-indol-3-il]-propiónico (**P-0353**), PM calculado 479.56, $[M+H^+]^+$ = 479.9,

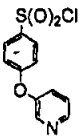
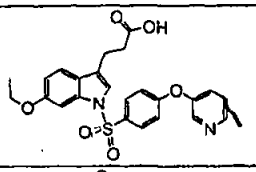
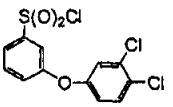
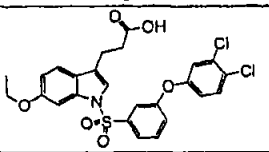
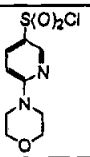
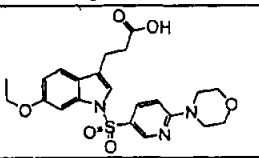
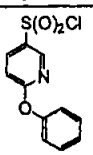
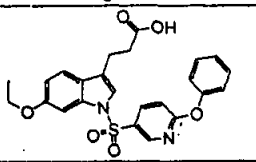
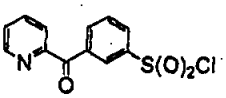
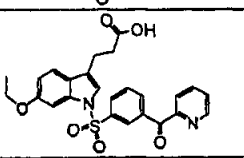
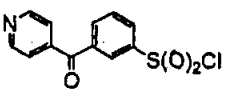
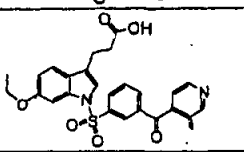
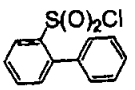
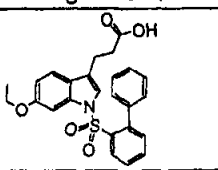
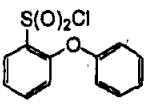
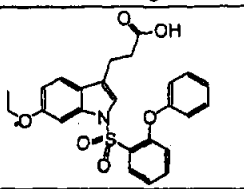
Ácido 3-[6-Etoxi-1-(5-piridin-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico (**P-0354**), PM calculado 456.54, $[M+H^+]^+$ = 457.1,

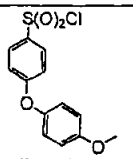
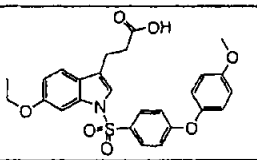
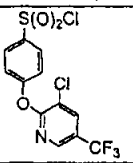
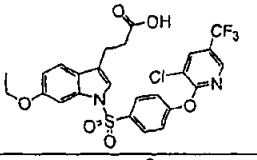
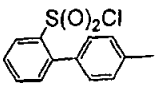
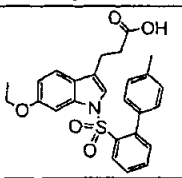
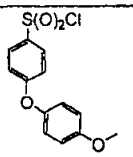
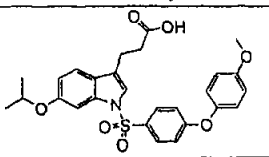
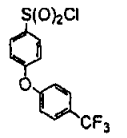
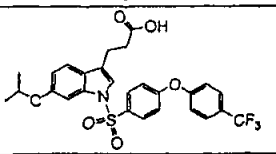
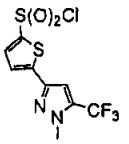
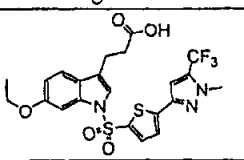
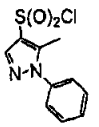
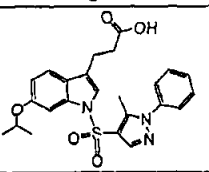
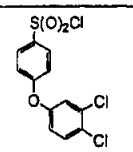
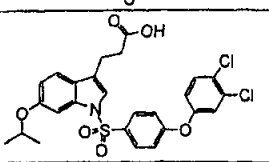
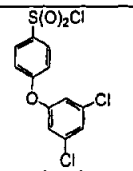
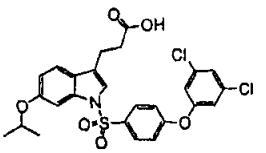
Ácido 3-(6-Etoxi-1-{4-[(morfolin-4-carbonil)-amino]-bencensulfonil}-1H-indol-3-il)-propiónico (**P-0355**), PM calculado 501.56, $[M+H^+]^+$ = 502.3, y

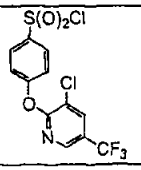
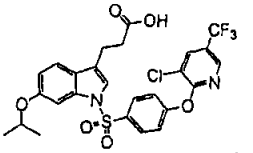
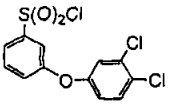
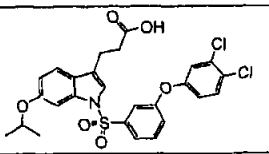
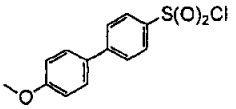
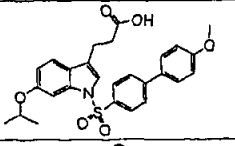
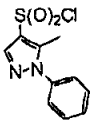
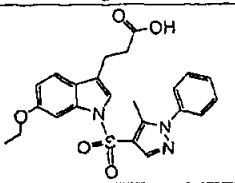
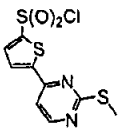
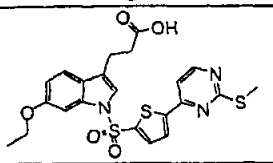
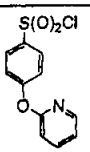
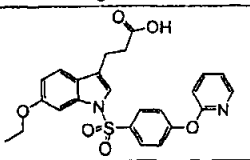
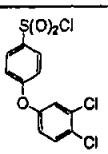
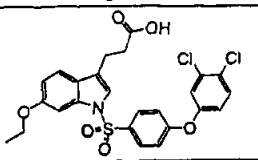
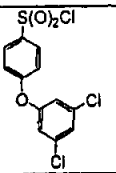
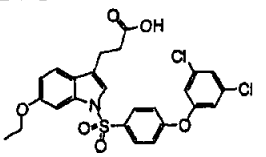
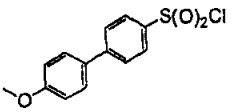
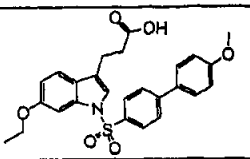
Ácido 3-{6-Etoxi-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico (**P-0356**), PM calculado 527.55, $[M+H^+]^+$ = 527.9

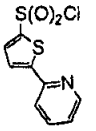
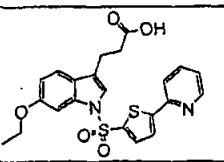
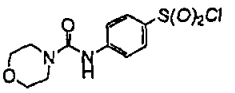
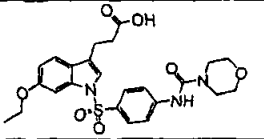
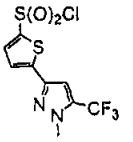
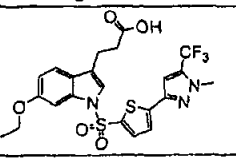
Estos compuestos se muestran en la siguiente Tabla 6, indicando el compuesto yodoalquilo utilizado en la Etapa 1 (Columna 2), y el cloruro de sulfonilo utilizado en la Etapa 4 (Columna 3), con la estructura del compuesto proporcionada en la Columna 4 y el número de compuesto proporcionado en la Columna 1.

Tabla 6.

Comp. número	Yodo-alquilo	Cloruro de sulfonilo	Estructura del compuesto
P-0173			
P-0175			
P-0176			
P-0177			
P-0182			
P-0183			
P-0185			
P-0191			

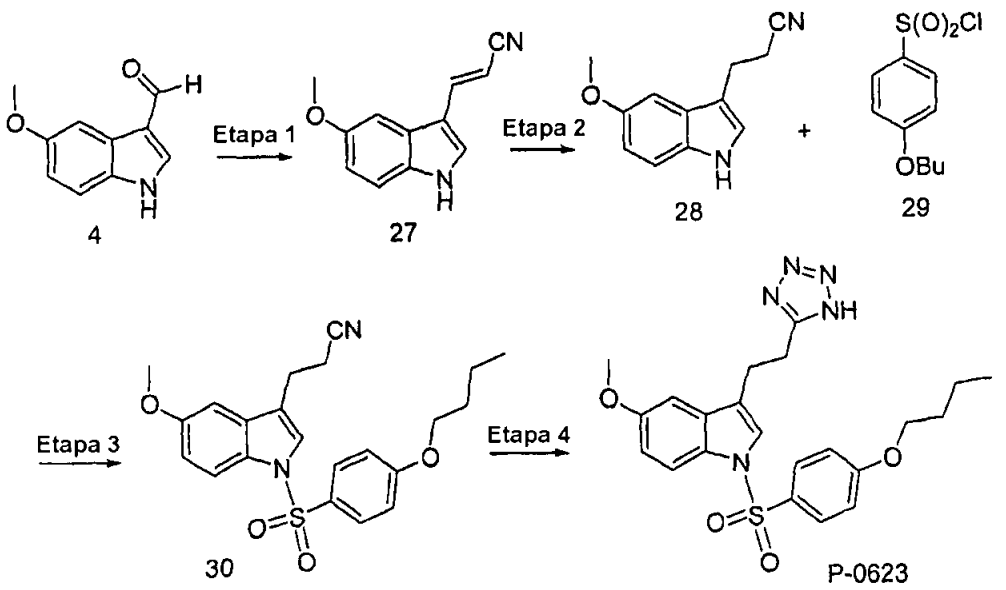
Comp. número	Yodo-alquilo	Cloruro de sulfonilo	Estructura del compuesto
P-0195			
P-0196			
P-0201			
P-0206			
P-0207			
P-0208			
P-0232			
P-0233			
P-0234			

Comp. número	Yodo-alquilo	Cloruro de sulfonilo	Estructura del compuesto
P-0235			
P-0236			
P-0237			
P-0346			
P-0347			
P-0350			
P-0351			
P-0352			
P-0353			

Comp. número	Yodo-alquilo	Cloruro de sulfonilo	Estructura del compuesto
P-0354			
P-0355			
P-0356			

Ejemplo 6: Síntesis de 1-(4-butoxi-bencensulfonil)-5-metoxi-3-[2-(1H-tetrazol-5-il)-etil]-1H-indol (P-0623).

El compuesto **P-0623** se sintetizó en cuatro etapas como se muestra en el Esquema 6.



*Etapa 1: Preparación de (E)-3-(5-metoxi-1H-indol-3-il)-acrilonitrilo (**27**)*

En un matraz de fondo redondo de 1 cuello, 5-metoxiindol-3-carboxaldehído (4, 0.500 g, 0.00280 mol) se disolvió en tetrahidrofurano (18 mL, 0.23 mol). En un matraz separado, se disolvió

cianometilfosfonato de dietilo (0.909 mL, 0.00559 mol) en 10 mL de tetrahidrofurano. El matraz se enfrió y se agregó el hidruro de sodio (224 mg, 0.00559 mol) al matraz bajo una atmósfera de argón. Después de que cesa la evolución de gas de hidrógeno, la solución se transfirió en una jeringa. La solución de tetrahidrofurano de fosfoacetato de sodio se agregó por goteo al matraz que contiene 5-metoxiindol-3-carboxilaldehído a temperatura ambiente durante 15 minutos. Después de la adición lenta de la solución de fosfoacetato, el matraz se calentó a 55 °C durante la noche bajo una atmósfera de argón. La mezcla se concentró, se diluyó después con diclorometano y se lavó con agua (100 mL) tres veces. Las capas orgánicas combinadas se lavaron con salmuera unas vez, y se secaron sobre sulfato de sodio. La capa orgánica seca se filtró entonces y el solvente se removió por rotovap para producir un aceite café. El aceite se purificó con cromatografía instantánea utilizando 10-20% de acetato de etilo en hexano. ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa 2: Preparación de 3-(5-metoxi-1H-indol~3-il)-propionitrilo (28)

En un matraz, (E)-3-(5-metoxi-1H-indol-3-il)-acrilonitrilo (27, 190 mg, 0.00096 mol) se disolvió en tetrahidrofurano (30 mL, 0.4 mol). 5% Pd/C (5:95, paladio:carbono, 2.0E2 mg) se agregó y la mezcla se agitó durante la noche en condiciones ambiente bajo una atmósfera de hidrógeno. El catalizador se filtró a través de celite, y el solvente se evaporó para producir un aceite ligeramente colorido. ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior.

Etapa 3: Preparación de 3-[1-(4-butoxi-bencensulfonil)-5-metoxi-1H-indol-3-il]-propionitrilo (30)

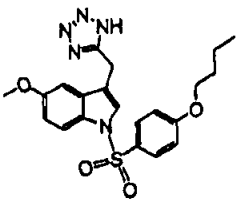
En un matraz de fondo redondo, se suspendió 3-(5-metoxi-1H-indol-3-il)-propionitrilo (28, 158 mg, 0.000789 mol) en tolueno (2 mL, 0.02 mol). Se agregaron hidróxido de potasio (1 mL, 0.02 mol) y sulfato ácido de tetrabutilamonio (7.5 mg, 0.000022 mol). A esto, se agregó cloruro de 4-butoxi-bencensulfonilo (29, 156 µL, 0.000968 mol) y la reacción se agitó a temperatura ambiente durante 5 horas. La reacción se diluyó con acetato de etilo y agua, las capas se separaron, y la capa acuosa se extrajo una vez con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua (3X), bicarbonato de sodio saturado solución (IX), y salmuera (IX). La porción orgánica se

secó sobre sulfato de sodio y se evaporó hasta sequedad bajo presión reducida. El producto se purificó utilizando cromatografía, eluyendo con acetato de etilo en hexanos. ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior.

*Etapa 4: Preparación ofl-(4-butoxi-bencensulfonil)-5-metoxi-3-[2-(1H-tetrazol-5-il)-ethil]-IH4ndole (**P-0623**)*

En una solución de 3-[1-(4-butoxi-bencensulfonil)-5-metoxi-1H-indol-3-il]-propionitrilo (30, 100 mg, 0.0002 mol) y azidotrimetilsilano (64.4 uL, 0.000485 mol) en tolueno (1 mL, 0.009 mol) se agregó dibutiloxoestaño (6.0 mg, 0.000024 mol) y la mezcla se calentó a 110 °C durante la noche. La mezcla de reacción se concentró al vacío. El residuo se disolvió en metanol y se volvió a concentrar. El residuo se dividió entre acetato de etilo y agua. La fase orgánica se secó sobre sulfato de sodio. El producto se aisló con dos purificaciones de placa TLC sucesiva con 100% acetato de etilo con algo de ácido acético como solvente para la primera corrida, seguida de otra placa de TLC con 30% de hexano, 70% de acetato de etilo con algo de ácido fórmico. ^{1}H NMR es consistente con la estructura del compuesto establecida en lo anterior. Peso molecular calculado 455.54, MS (ESI) $[M-H^+]^+$ = 454.2.

1-(4-Butoxi-bencensulfonil)-5-metoxi-3-(1H-tetrazol-5-ylmetil)-1H-indol P-0624,



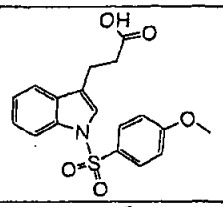
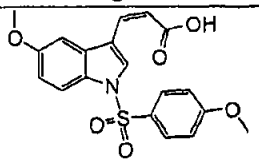
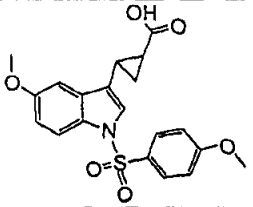
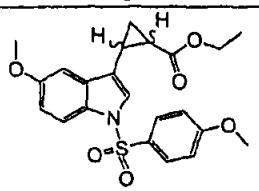
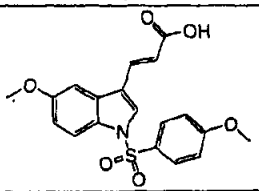
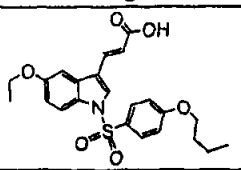
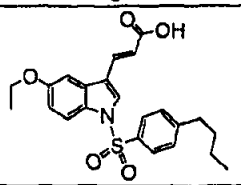
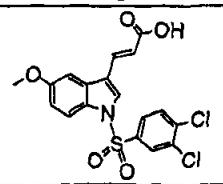
se preparó siguiendo las Etapas 3 y 4 del Esquema 6, reemplazando 3-(5-metoxi-1H-indol-3-il)-propionitrilo 28 con (5-metoxi-1H-indol-3-il)-acetonitrilo.

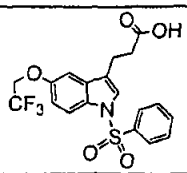
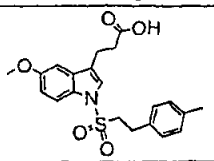
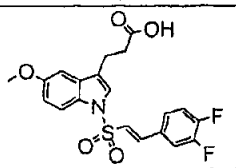
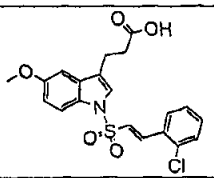
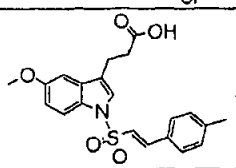
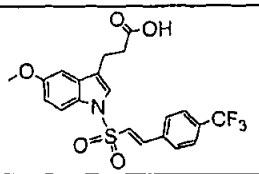
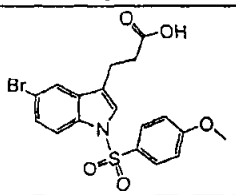
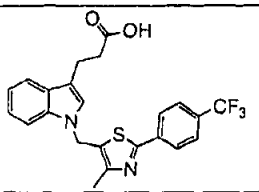
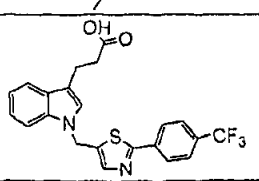
Ejemplo 7: Compuestos Adicionales

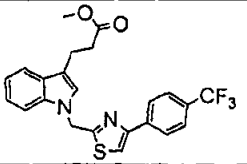
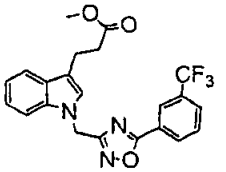
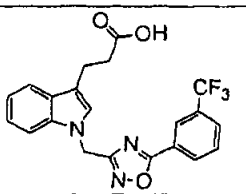
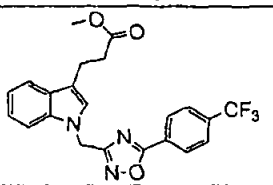
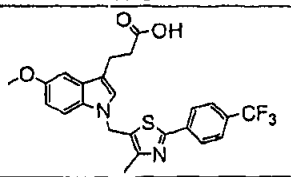
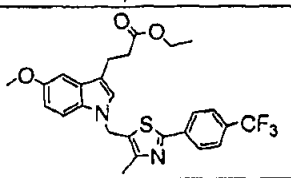
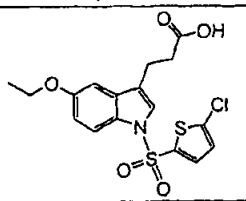
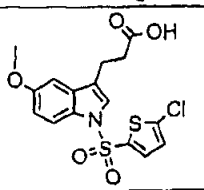
Los compuestos adicionales de la invención se sintetizaron siguiendo los métodos de los Ejemplos anteriores, o métodos similares conocidos por aquellos con experiencia en la técnica, y se muestran en la siguiente Tabla 7, con el número de compuesto en la Columna 1, estructura del

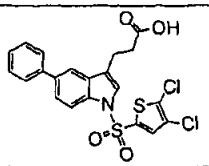
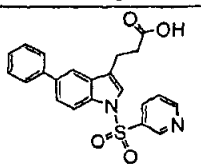
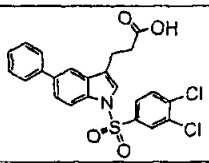
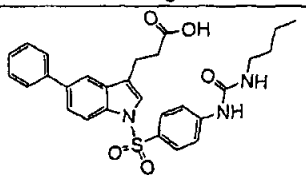
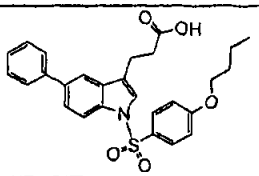
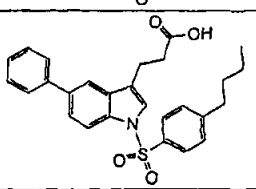
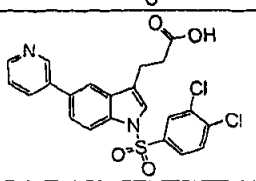
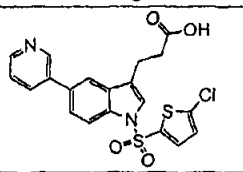
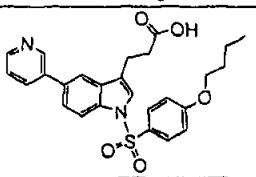
compuesto en la Columna 2, nombre del compuesto en la Columna 3, y el peso molecular calculado y el resultado de la espectroscopia de masa experimental en las Columnas 4 y 5.

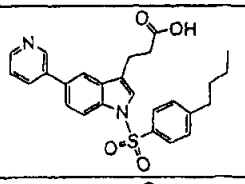
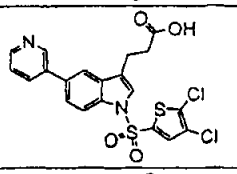
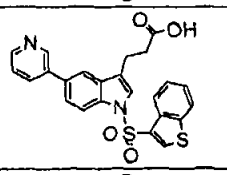
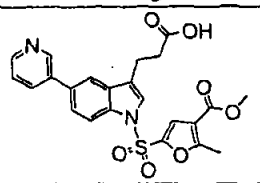
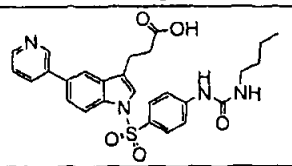
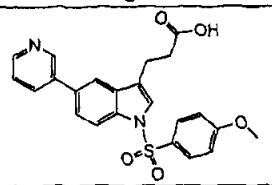
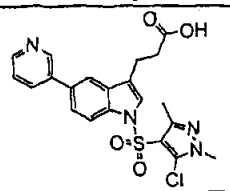
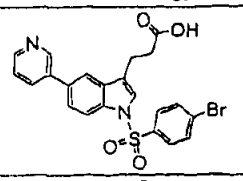
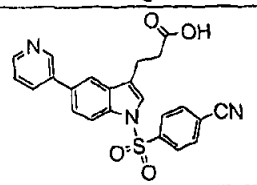
Tabla 7.

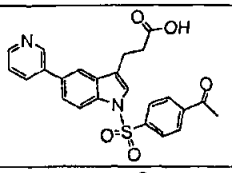
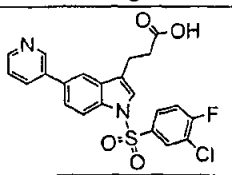
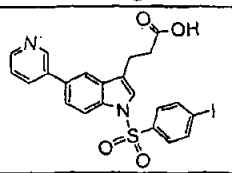
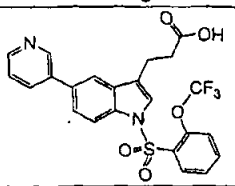
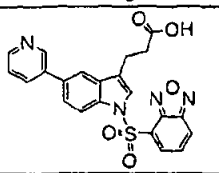
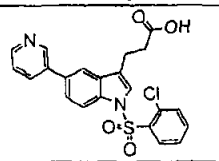
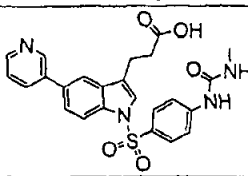
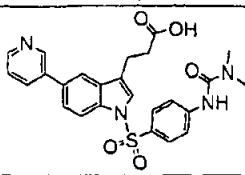
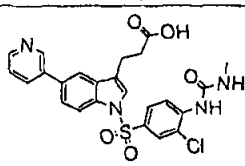
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0005		ácido 3-[1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	359.40	$[M - H^+]^-$ = 358.2
P-0010		ácido (Z)-3-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-acrílico	387.41	$[M - H^+]^-$ = 386.1
P-0011		ácido 2-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]- ciclopropan-carboxílico	401.43	$[M - H^+]^-$ = 400.2
P-0013		etiléster del ácido 2-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-ciclopropancarboxílico	429.49	$[M+H^+]^+$ = 430.4
P-0021		ácido (E)-3-[5-metoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-acrílico	387.41	$[M+ H^+]^+$ = 389.04
P-0022		ácido (E)-3-[l-(4-Butoxi-bencensulfonil)-5-etoxi-1H-indol-3-il]-acrílico	443.52	$[M - H^+]^-$ = 441.90
P-0023		ácido (E)-3-[1-(4-Butil-bencensulfonil)-5-etoxi-1H-indol-3-il]-acrílico	427.52	$[M - H^+]^-$ = 425.90
P-0024		ácido (E)-3-[1-(3,4-Dicloro-bencensulfonil)-5-metoxi-1H-indol-3-il]-acrílico	373.42	$[M+H^+]^+$ = 374.2

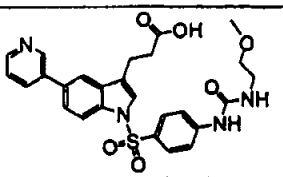
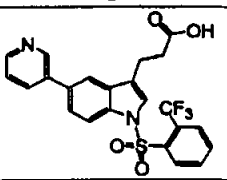
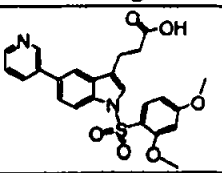
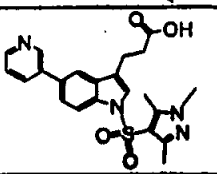
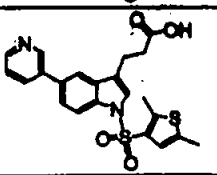
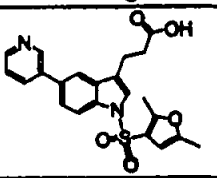
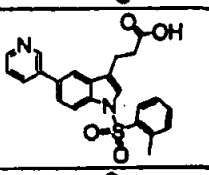
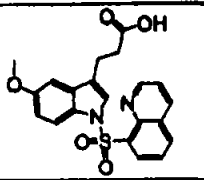
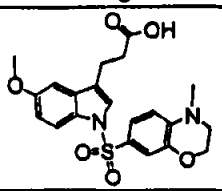
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0025		ácido 3-[1-Bencensulfonil-5-(2,2,2-trifluoro-etoxi)-1H-indol-3-il]-propiónico	444.47	$[M+H^+]^+$ = 445.3
P-0027		ácido 3-[5-metoxi-1-(2-p-tolil-etansulfonil)-1H-indol-3-il]-propiónico	401.48	$[M - H^+]^-$ = 400.1
P-0028		ácido 3-{1-[(E)-2-(3,4-Difluoro-fenil)-eten-sulfonil]-5-metoxi-1H-indol-3-il}- propiónico	421.42	$[M - H^+]^-$ = 420.0
P-0029		ácido 3-{1-[(E)-2-(2-Cloro-fenil)-etenesulfonil]-5-metoxi-1H-indol-3-il}-propiónico	419.88	$[M - H^+]^-$ = 418.0
P-0030		ácido 3-[5-metoxi-1-((E)-2-p-tolil-etenesulfonil)-1H-indol-3-il]-propiónico	399.46	$[M - H^+]^-$ = 398.1
P-0031		ácido 3-{5-metoxi-1-[(E)-2-(4-trifluorometil-fenil)-eten-sulfonil]-1H-indol-3-il}-propiónico	453.43	$[M - H^+]^-$ = 452.0
P-0032		ácido 3-[5-Bromo-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	436.99	$[M - H^+]^-$ = 436.11
P-0039		ácido 3-{1-[4-Metil-2-(4-trifluorometil-fenil)- tiazol-5-ilmetil]-1H-indol-3-il}-propiónico	444.48	$[M+H^+]^+$ = 445.3
P-0040		ácido 3-{1-[2-(4-Trifluoro-metil-fenil)-tiazol-5-ilmetil]-1H-indol-3-il}-propiónico	430.45	$[M+H^+]^+$ = 431.3

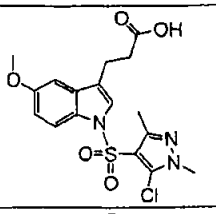
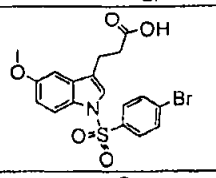
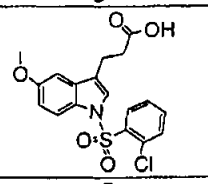
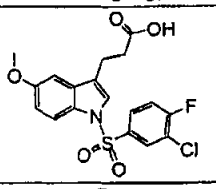
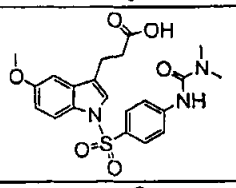
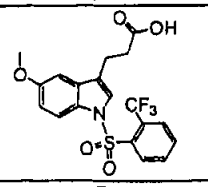
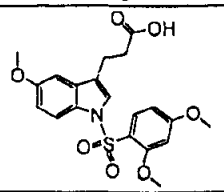
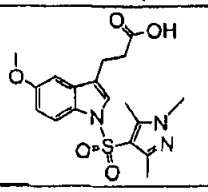
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0041		metiléster del ácido 3-{1-[4-(4-Trifluorometil-fenil)-tiazol-2-ilmetil]-1H-indol-3-il}-propiónico	444.48	$[M+H^+]^+$ = 445.3
P-0042		metiléster del ácido 3-{1-[5-(3-Trifluorometil-fenil)-[1,2,4]oxadiazol-3-ilmetil]-1H-indol-3-il}-propiónico	429.40	$[M+H^+]^+$ = 430.4
P-0043		ácido 3-{1-[5-(3-Trifluorometil-fenil)-[1,2,4]oxadiazol-3-ilmetil]-1H-indol-3-il}-propiónico	415.37	$[M+H^+]^+$ = 416.4
P-0044		metiléster del ácido 3-{1-[5-(4-Trifluorometil-fenil)-[1,2,4]oxadiazol-3-ilmetil]-1H-indol-3-il}-propiónico	429.40	$[M+H^+]^+$ = 430.3
P-0045		ácido 3-{5-metoxi-1-[4-metil-2-(4-trifluorometil-fenil)- tiazol-5-ilmetil]-1H-indol-3-il}-propiónico	474.50	$[M+H^+]^+$ = 475.2
P-0046		metiléster del ácido 3-{5-metoxi-1-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetil]-1H-indol-3-il}-propiónico	502.56	$[M+H^+]^+$ = 503.3
P-0054		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico	413.90	$[M+H^+]^+$ = 466.3
P-0070		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-5-metoxi-1H-indol-3-il-3-propiónico	399.87	$[M+H^+]^+$ = 400.3

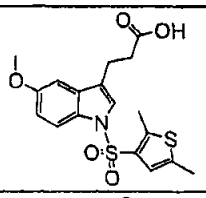
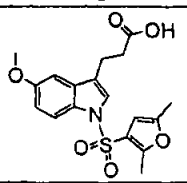
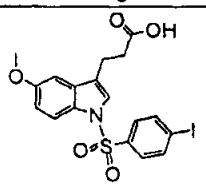
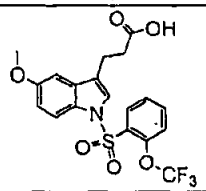
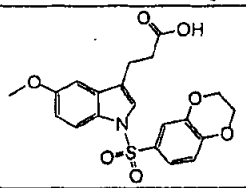
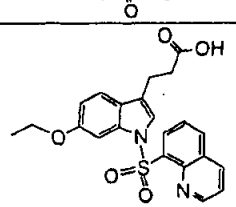
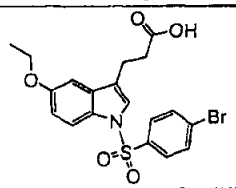
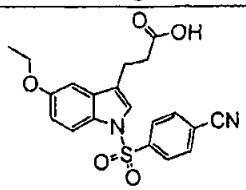
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0073		ácido 3-[1-(4,5-Dicloro-tiofen-2-sulfonil)-5-fenil-1H-indol-3-il]-propiónico	480.39	$[M+H^+]^+$ = 481.1
P-0074		ácido 3-[5-Fenil-1-(piridin-3-sulfonil)-1H-indol-3-il]-propiónico	406.46	$[M+H^+]^+$ = 407.1
P-0075		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-5-fenil-1H-indol-3-il]-propiónico	474.37	
P-0090		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5-fenil-1H-indol-3-il}-propiónico	519.62	$[M+H^+]^+$ = 520.3
P-0092		ácido 3-[1-(4-Butoxi-bencensulfonil)-5-fenil-1H-indol-3-il]-propiónico	477.58	$[M-H^+]^-$ = 478.3
P-0093		ácido 3-[1-(4-Butil-bencensulfonil)-5-fenil-1H-indol-3-il]-propiónico	461.58	$[M+H^+]^+$ = 462.3
P-0094		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-5-piridin-3-il-1H-indol-3-ill-propiónico	475.35	$[M-H^+]^-$ = 471.5
P-0096		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	446.93	$[M+H^+]^+$ = 447.1
P-0108		ácido 3-[1-(4-Butoxi-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	478.57	$[M+H^+]^+$ = 479.1

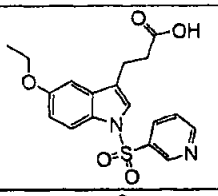
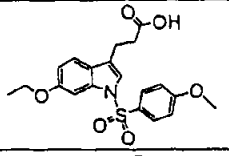
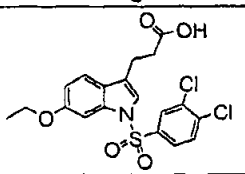
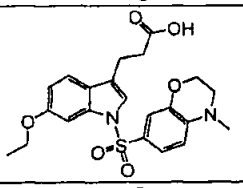
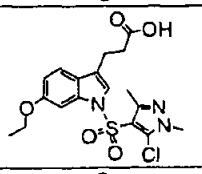
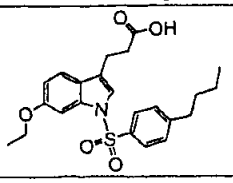
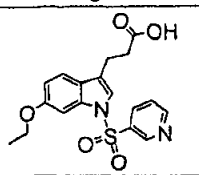
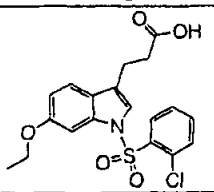
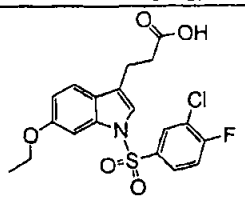
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0109		ácido 3-[1-(4-Butil-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	462.57	$[M+H^+]^+$ = 463.1
P-0110		ácido 3-[1-(4,5-Dicloro-tiofen-2-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	481.38	$[M-H^+]^-$ = 481.1
P-0111		ácido 3-[1-(Benzo[b]tiofen-3-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	462.55	$[M+H^+]^+$ = 463.1
P-0112		metiléster del ácido 5-[3-(2-carboxi-etil)-5-piridin-3-il-indol-1-sulfonil]-2-metil-furan-3-carboxílico	468.49	$[M+H^+]^+$ = 469.1
P-0116		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico	520.61	$[M+H^+]^+$ = 521.1
P-0117		ácido 3-[1-(4-metoxi-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	436.39	$[M+H^+]^+$ = 437.1
P-0119		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	458.93	$[M+H^+]^+$ = 459.1
P-0121		ácido 3-[1-(4-Bromo-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	485.36	$[M+H^+]^+$ = 487.1
P-0122		ácido 3-[1-(4-Ciano-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	431.47	$[M+H^+]^+$ = 432.3

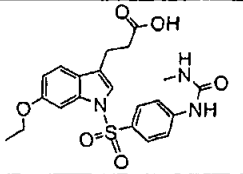
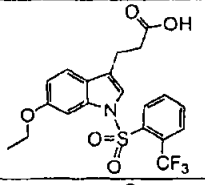
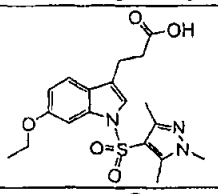
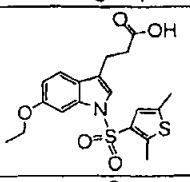
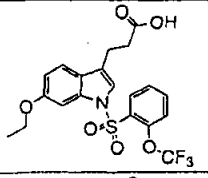
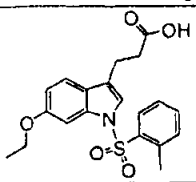
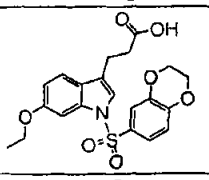
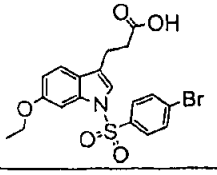
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0123		ácido 3-[1-(4-Acetil-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	448.50	$[M+H^+]^+$ = 449.1
P-0124		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	458.90	$[M+H^+]^+$ = 459.1
P-0126		ácido 3-[1-(4-yodo-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	532.36	$[M+H^+]^+$ = 533.1
P-0127		ácido 3-[5-Piridin-3-il-1-(2-trifluorometoxi-bencen-sulfonil)-1H-indol-3-il]-propiónico	490.46	$[M+H^+]^+$ = 491.1
P-0129		ácido 3-[1-(Benzo[1,2,5] oxadiazol-4-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	448.46	$[M+H^+]^+$ = 449.1
P-0130		ácido 3-[1-(2-Cloro-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	440.91	$[M+H^+]^+$ = 441.1
P-0132		ácido 3-{1-[4-(3-Metil-ureido)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico	478.53	$[M+H^+]^+$ = 479.1
P-0133		ácido 3-{1-[4-(3,3-Dimetil-ureido)-bencensulfonil]-5-piridin-3-il-1H-indol-3-il}-propiónico	492.56	$[M+H^+]^+$ = 493.1
P-0134		ácido 3-{1-[3-Cloro-4-(3-metil-ureido)-bencen sulfonil]-5-piridin-3-il-1H-indol-3-il}- propiónico	512.98	$[M+H^+]^+$ = 513.1

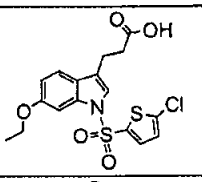
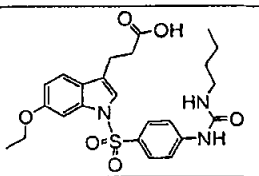
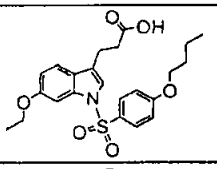
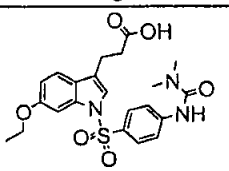
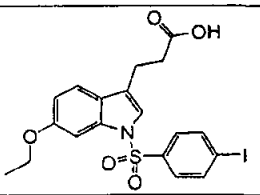
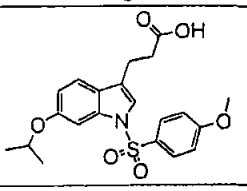
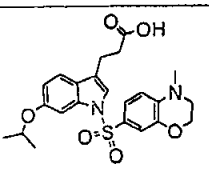
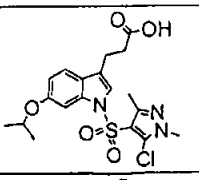
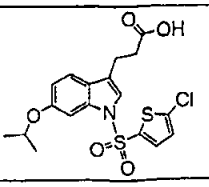
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0135		ácido 3-(1-{4-[3-(2-metoxi-etil)-ureido]-bencen-sulfonil}-5-piridin-3-il-1H-indol-3-il)-propiónico	522.98	$[M+H^+]^+$ = 523.5
P-0136		ácido 3-[5-Piridin-3-il-1-(2-trifluorometil-bencen-sulfonil)- 1H-indol-3-il]-propiónico	474.46	$[M+H^+]^+$ = 475.1
P-0138		ácido 3-[1-(2,4-Dimetoxi-bencensulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	466.52	$[M+H^+]^+$ = 467.1
P-0139		ácido 3-[5-Piridin-3-il-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	438.51	$[M+H^+]^+$ = 439.5
P-0140		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	440.54	$[M+H^+]^+$ = 441.1
P-0141		ácido 3-[1-(2,5-Dimetil-furan-3-sulfonil)-5-piridin-3-il-1H-indol-3-il]-propiónico	424.48	$[M+H^+]^+$ = 425.1
P-0142		ácido 3-[5-Piridin-3-il-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	420.49	$[M+H^+]^+$ = 521.1
P-0143		ácido 3-[5-metoxi-1-(quinolin-8-sulfonil)-1H-indol-3-il]- propiónico	410.45	$[M+H^+]^+$ = 411.1
P-0144		ácido 3-[5-metoxi-1-(4-metil-3,4-dihidro-2H-benzo [1,4]oxazin-7-sulfonil)-1H-indol-3-il]-propiónico	430.48	$[M+H^+]^+$ = 431.5

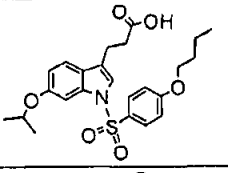
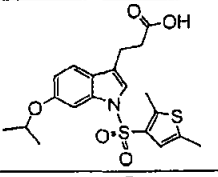
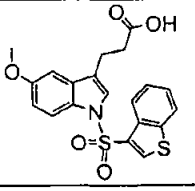
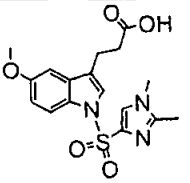
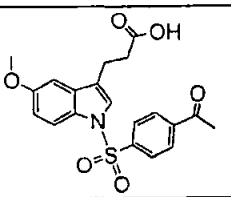
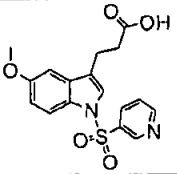
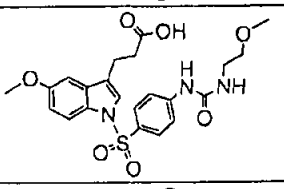
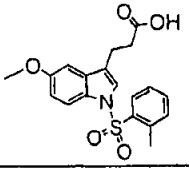
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0145		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico	411.87	$[M+H^+]^+$ = 412.3
P-0147		ácido 3-[1-(4-Bromo-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	438.30	$[M+H^+]^+$ = 437.9
P-0148		ácido 3-[1-(2-Cloro-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	393.85	$[M+H^+]^+$ = 394.3
P-0149		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	411.84	$[M+H^+]^+$ = 411.9
P-0153		ácido 3-{1-[4-(3,3-Dimetil-ureido)-bencen-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico	445.50	$[M+H^+]^+$ = 446.3
P-0154		ácido 3-[5-metoxi-1-(2-trifluorometil-bencen-sulfonil)-1H-indol-3-il]-propiónico	427.40	$[M+H^+]^+$ = 427.9
P-0156		ácido 3-[1-(2,4-Dimetoxi-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	419.46	$[M+H^+]^+$ = 429.9
P-0157		ácido 3-[5-metoxi-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	391.45	$[M+H^+]^+$ = 392.3

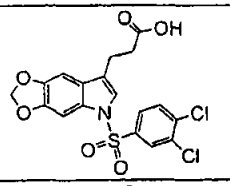
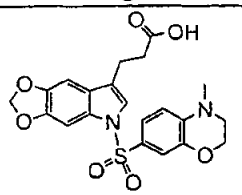
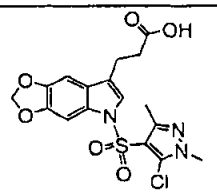
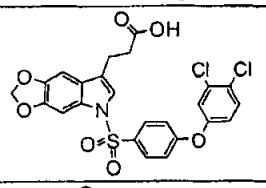
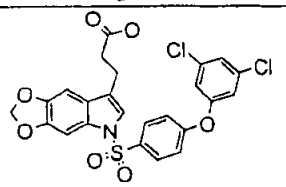
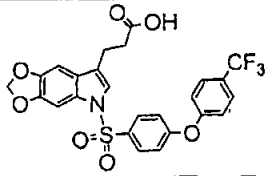
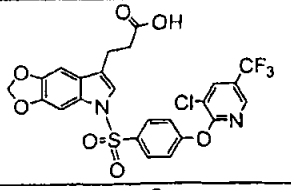
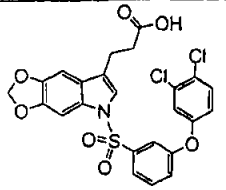
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0158		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico	393.48	$[M+H^+]^+$ = 394.3
P-0159		ácido 3-[1-(2,5-Dimetil-furan-3-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico	377.42	$[M+H^+]^+$ = 378.3
P-0160		ácido 3-[1-(4-yodo-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	485.30	$[M+H^+]^+$ = 486.3
P-0161		ácido 3-[5-metoxi-1-(2-trifluorometoxi-bencen-sulfonil)-1H-indol-3-il]-propiónico	443.40	$[M+H^+]^+$ = 444.3
P-0163		ácido 3-[1-(2,3-Dihidro-benzo[1,4]dioxin-6-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico	417.44	$[M+H^+]^+$ = 418.3
P-0164		ácido 3-[6-Etoxi-1-(quinolin-8-sulfonil)-1H-indol-3-il]-propiónico	424.48	$[M+H^+]^+$ = 425.1
P-0165		ácido 3-[1-(4-Bromo-bencensulfonil)-5-etoxi-1H-indol-3-il]-propiónico	452.33	$[M-H^+]^-$ = 451.9
P-0166		ácido 3-[1-(4-Ciano-bencensulfonil)-5-etoxi-1H-indol-3-il]-propiónico	398.44	$[M+H^+]^+$ = 399.1

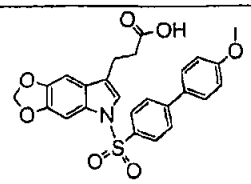
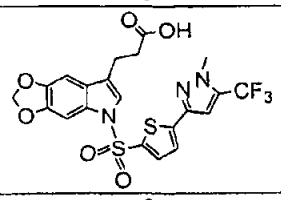
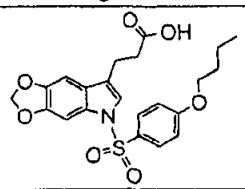
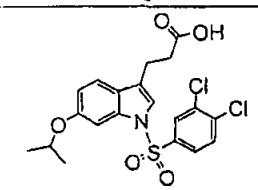
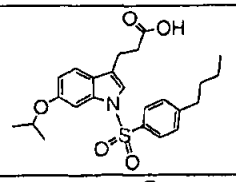
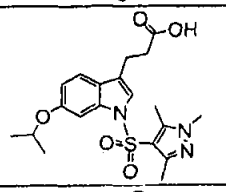
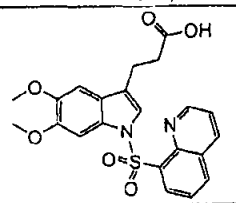
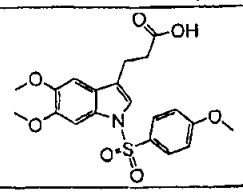
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0167		ácido 3-[5-Etoxi-1-(piridin-3-sulfonil)-1H-indol-3-il]-propiónico	374.42	$[M+H^+]^+$ = 375.1
P-0169		ácido 3-[6-Etoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	403.46	$[M+H^+]^+$ = 404.3
P-0170		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-6-etoxi-1H-indol-3-il]-propiónico	442.32	$[M-H^+]^-$ = 442.3
P-0171		ácido 3-[6-Etoxi-1-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-7-sulfonil)-1H-indol-3-il]- propiónico	444.51	$[M+H^+]^+$ = 445.1
P-0172		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)- 6-etoxi-1H-indol-3-il]-propiónico	425.89	$[M+H^+]^+$ = 425.9
P-0178		ácido 3-[1-(4-Butil-bencensulffinil)-6-etoxi-1H-indol-3-il]-propiónico	429.54	$[M+H^+]^+$ = 430.3
P-0179		ácido 3-[6-Etoxi-1-(piridin-3-sulfonil)-1H-indol-3-il]- propiónico	374.42	$[M+H^+]^+$ = 375.1
P-0180		ácido 3-[1-(2-Cloro-bencensulfonil)-6-etoxi-1H-indol-3-il]-propiónico	407.88	$[M+H^+]^+$ = 408.3
P-0181		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-6-etoxi-1H-indol-3-il]-propiónico	425.87	$[M+H^+]^+$ = 426.3

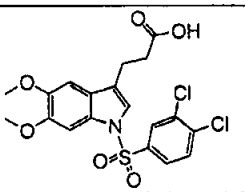
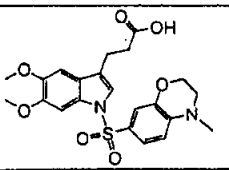
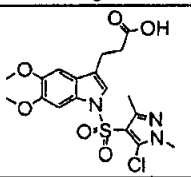
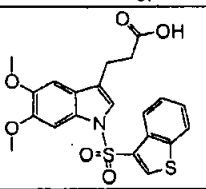
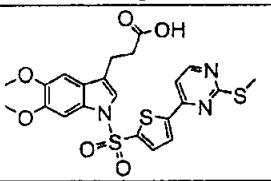
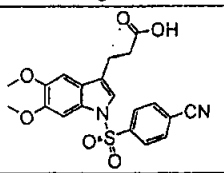
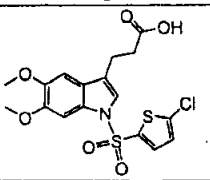
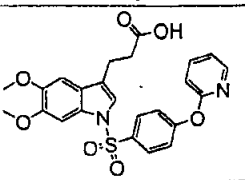
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0184		ácido 3-{6-Etoxi-1-[4-(3-metil-ureido)-bencen-sulfonil]-1H-indol-3-il}-propiónico	445.50	$[M+H^+]^+$ = 446.3
P-0186		ácido 3-[6-Etoxi-1-(2-trifluorometil-bencen-sulfonil)-1H-indol-3-il]-propiónico	441.43	$[M+H^+]^+$ = 442.3
P-0187		ácido 3-[6-Etoxi-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	405.48	$[M+H^+]^+$ = 406.3
P-0188		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	407.51	$[M+H^+]^+$ = 408.3
P-0189		ácido 3-[6-Etoxi-1-(2-trifluorometoxi-bencen-sulfonil)-1H-indol-3-il]-propiónico	457.43	$[M+H^+]^+$ = 458.3
P-0190		ácido 3-[6-Etoxi-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	387.46	$[M+H^+]^+$ = 388.3
P-0192		ácido 3-[1-(2,3-Dihidro-benzo[1,4]dioxin-6-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	431.67	$[M+H^+]^+$ = 432.3
P-0193		ácido 3-[1-(4-Bromo-bencensulfonil)-6-etoxi-1H-indol-3-il]-propiónico	452.33	$[M-H^+]^-$ = 451.9

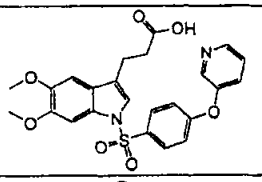
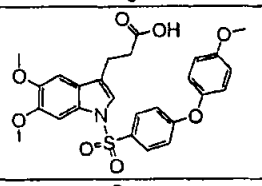
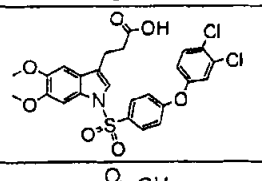
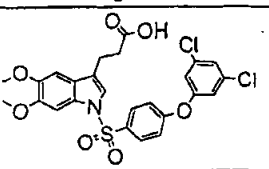
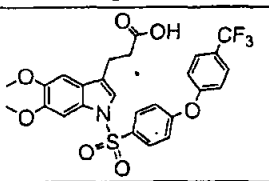
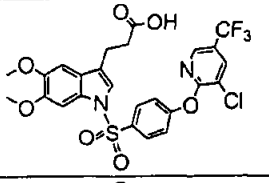
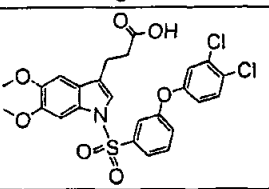
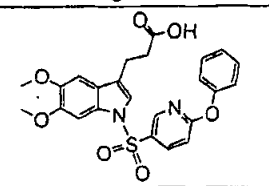
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0194		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	413.90	$[M-H^+]^-$ = 413.9
P-0197		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-6-etoxi-1H-indol-3-il}-propiónico	487.58	$[M+H^+]^+$ = 488.3
P-0198		ácido 3-[1-(4-Butoxi-bencensulfonil)-6-etoxi-1H-indol-3-il]-propiónico	445.54	$[M+H^+]^+$ = 446.3
P-0199		ácido 3-{1-[4-(3,3-Dimetil-ureido)-bencensulfonil]-6-etoxi-1H-indol-3-il}-propiónico	459.53	$[M+H^+]^+$ = 460.3
P-0200		ácido 3-[6-Etoxi-1-(4-yodo-bencensulfonil)-1H-indol-3-il)-propiónico	499.33	$[M+H^+]^+$ = 499.9
P-0202		ácido 3-[6-Isopropoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	417.48	$[M+H^+]^+$ = 418.3
P-0203		ácido 3-[6-Isopropoxi-1-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-7-sulfonil)-1H- indol-3-il]-propiónico	458.54	$[M+H^+]^+$ = 459.1
P-0204		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-6-isopropoxi-1H-indol-3-il]-propiónico	439.92	$[M+H^+]^+$ = 440.3
P-0205		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-6-isopropoxi-1H-indol-3-il]-propiónico	427.93	$[M+H^+]^+$ = 428.3

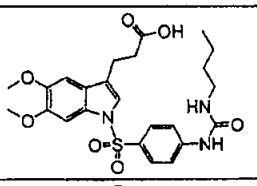
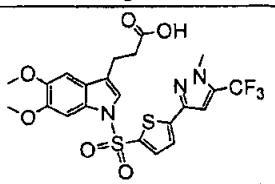
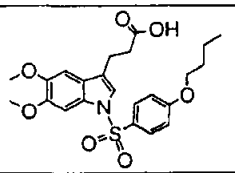
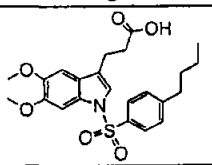
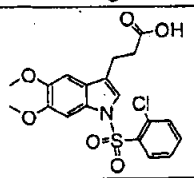
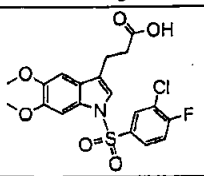
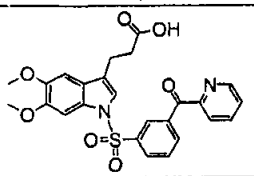
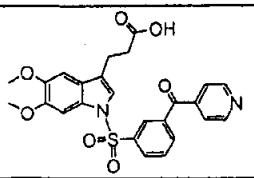
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0209		ácido 3-[1-(4-Butoxi-bencensulfonil)-6-isopropoxi-1H-indol-3-il]-propiónico	459.57	$[M+H^+]^+$ = 460.3
P-0210		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-6-isopropoxi-1H-indol-3-il]-propiónico	421.54	$[M+H^+]^+$ = 421.9
P-0211		ácido 3-[1-(Benzo[b] tiofen-3-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico	415.59	$[M-H^+]^-$ = 415.1
P-0212		ácido 3-[1-(1,2-Dimetil-1H-imidazol-4-sulfonil)-5-metoxi-1H-indol-3-il]-propiónico	377.42	$[M+H^+]^+$ = 378.3
P-0213		ácido 3-[1-(4-Acetil-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	401.44	$[M+H^+]^+$ = 401.9
P-0217		ácido 3-[5-metoxi-1-(piridin-3-sulfonil)-1H-indol-3-il]-propiónico	360.39	$[M+H^+]^+$ = 361.1
P-0218		ácido 3-(5-metoxi-1-{4-[3-(2-metoxi-etil)-ureido]-bencen-sulfonil}-1H-indol-3-il)-propiónico	475.52	$[M+H^+]^+$ = 475.9
P-0219		ácido 3-[5-metoxi-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	373.43	$[M+H^+]^+$ = 374.3

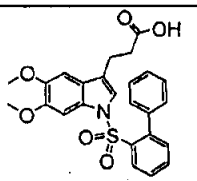
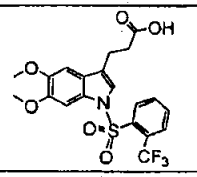
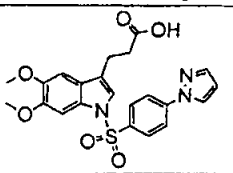
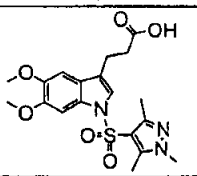
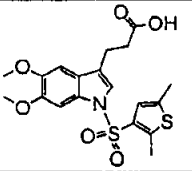
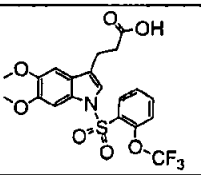
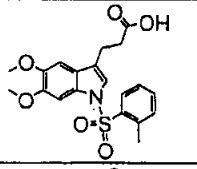
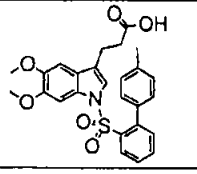
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0220		ácido 3-[5-(3,4-Dicloro-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	442.48	$[M-H^+]^-$ = 442.3
P-0221		ácido 3-[5-(4-Metil-3,4-dihidro-2H-benzo[1,4] oxazin-7-sulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	444.47	$[M+H^+]^+$ = 445.1
P-0222		ácido 3-[5-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-5H-[1,3]dioxolo [4,5-f]indol-7-il]-propiónico	425.85	$[M+H^+]^+$ = 425.9
P-0223		ácido 3-{5-[4-(3,4-Dicloro-fenoxi)-bencen-sulfonil]-5H-[1,3]dioxolo [4,5-f]indol-7-il}-propiónico	534.38	$[M-H^+]^-$ = 533.9
P-0224		ácido 3-{5-[4-(3,5-Dicloro-fenoxi)-bencen-sulfonil]-5H-[1,3]dioxolo [4,5-pindol-7-il}-propiónico	534.38	$[M-H^+]^-$ = 533.9
P-0225		ácido 3-{5-[4-(4-Trifluorometil-fenoxi)-bencensulfonil]-5H-[1,3] dioxolo[4,5-(indol-7-il}-propiónico	533.48	$[M+H^+]^+$ = 533.9
P-0226		ácido 3-{5-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5H-[1,3]dioxolo[4,5f] indol-7-il}-propiónico	568.92	$[M+H^+]^+$ = 569.2
P-0227		ácido 3-{5-[3-(3,4-Dicloro-fenoxi)-bencen-sulfonil]-5H-[1,3]dioxolo [4,5-f]indol-7-il}-propiónico	534.38	$[M-H^+]^-$ = 533.9

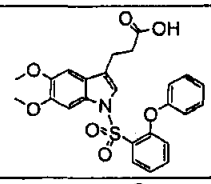
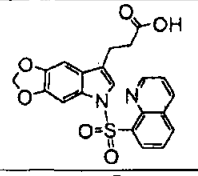
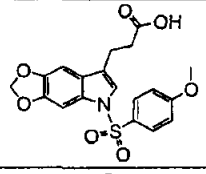
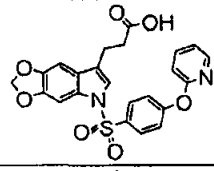
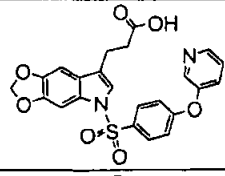
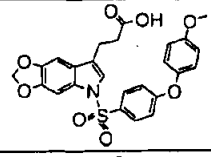
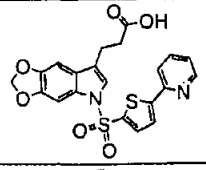
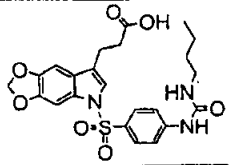
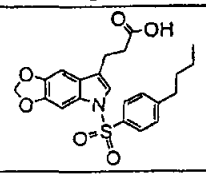
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0228		ácido 3-[5-(4'-metoxi-bifenil-4-sulfonil)-5H-[1,3]dioxolo[4,5f]indol-7-il]-propiónico	479.51	$[M+H^+]^+$ = 479.9
P-0229		ácido 3-{5-[5-(1-Metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-5H-[1,3]dioxolo [4,5-f]indol-7-il}-propiónico	527.50	$[M+H^+]^+$ = 527.9
P-0230		ácido 3-[5-(4-Butoxi-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	445.50	$[M+H^+]^+$ = 446.3
P-0231		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-6-isopropoxi-1H-indol-3-il]-propiónico	456.35	$[M-H^+]^-$ = 456.3
P-0238		ácido 3-[1-(4-Butil-bencen-sulfonil)-6-isopropoxi-1H-indol-3 -il]-propiónico	443.57	$[M+H^+]^+$ = 444.3
P-0239		ácido 3-[6-Isopropoxi-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	419.50	$[M+H^+]^+$ = 420.3
P-0240		ácido 3-[5,6-Dimetoxi-1-(quinolin-8-sulfonil)-1H-indol-3-il]-propiónico	440.48	$[M+H^+]^+$ = 441.1
P-0241		ácido 3-[5,6-Dimetoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	419.46	$[M+H^+]^+$ = 419.9

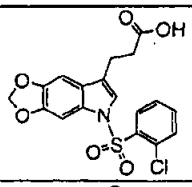
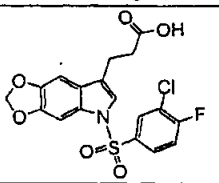
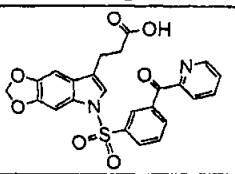
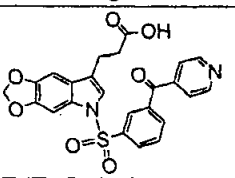
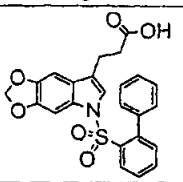
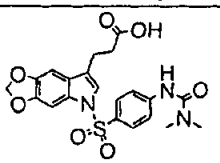
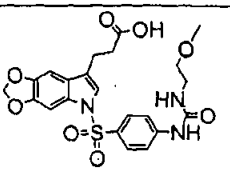
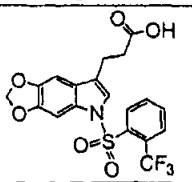
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0242		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	458.32	$[M-H^+]^-$ = 458.3
P-0243		ácido 3-[5,6-Dimetoxi-1-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-7-sulfonil)-1H-indol-3-il]-propiónico	460.51	$[M+H^+]^+$ = 461.1
P-0244		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	441.89	$[M+H^+]^+$ = 442.3
P-0245		ácido 3-[1(Benzo[b] tiofen-3-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	445.52	$[M+H^+]^+$ = 446.3
P-0246		ácido 3-{5,6-Dimetoxi-1-[5-(2-metilsulfanil-pirimidin-4-il)-tiofen-2-sulfinil]-1H-indol-3-il}-propiónico	519.62	$[M+H^+]^+$ = 520.3
P-0247		ácido 3-[1-(4-Ciano-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	414.44	$[M+H^+]^+$ = 415.1
P-0248		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	429.90	$[M+H^+]^+$ = 430.3
P-0249		ácido 3-{5,6-Dimetoxi-1-[4-(piridin-2-iloxi)-bencen-sulfonil]-1H-indol-3-il}-propiónico	482.52	$[M+H^+]^+$ = 483.1

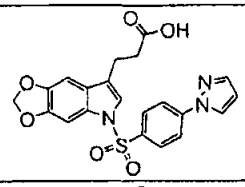
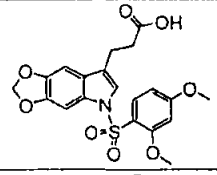
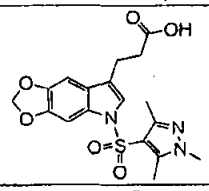
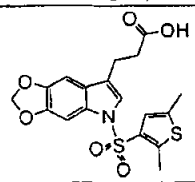
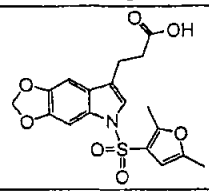
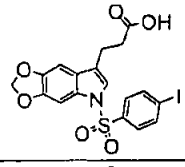
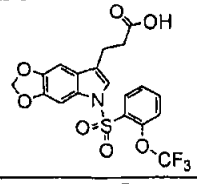
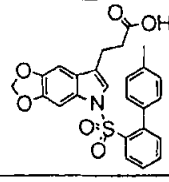
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0250		ácido 3-{5,6-Dimetoxi-1-[4-(piridin-3-iloxi)-bencen-sulfonil]-1H-indol-3-il}-propiónico	482.52	$[M+H^+]^+$ = 483.1
P-0251		ácido 3-{5,6-Dimetoxi-1-[4-(4-metoxi-fenoxi)-bencen-sulfonil]-1H-indol-3-il}-propiónico	511.56	$[M+H^+]^+$ = 512.3
P-0252		ácido 3-{1-[4-(3,4-Dicloro-fenoxi)-bencen-sulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	550.42	$[M-H^+]^-$ = 550.3
P-0253		ácido 3-{1-[4-(3,5-Dicloro-fenoxi)-bencen-sulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	550.42	$[M-H^+]^-$ = 550.3
P-0254		ácido 3-{5,6-Dimetoxi-1-[4-(4-trifluorometil-fenoxi)-bencensulfonil]-1H-indol-3-il}-propiónico	549.53	$[M+H^+]^+$ = 550.3
P-0255		ácido 3-{1-[4-(3-Cloro-5-trifluorometil-piridin-2-iloxi)-bencensulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	584.96	$[M+H^+]^+$ = 585.2
P-0256		ácido 3-{1-[3-(3,4-Dicloro-fenoxi)-bencen-sulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	550.42	$[M-H^+]^-$ = 550.3
P-0257		ácido 3-[5,6-Dimetoxi-1-(6-fenoxi-piridin-3-sulfonil)-1H-indol-3-il]-propiónico	482.52	$[M+H^+]^+$ = 483.1

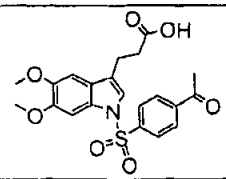
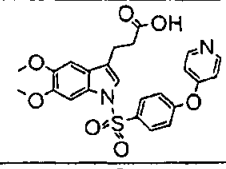
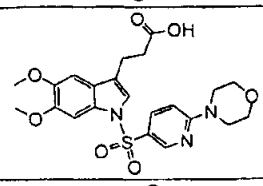
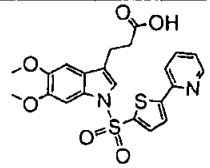
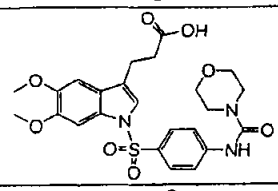
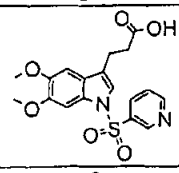
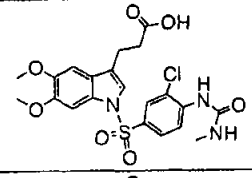
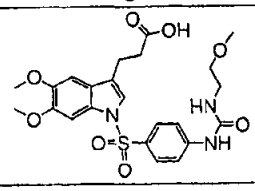
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0258		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	503.58	$[M+H^+]^+$ = 504.3
P-0259		ácido 3-{5,6-Dimetoxi-1-[5-(1-metil-5-trifluorometil-1H-pirazol-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico	543.54	$[M+H^+]^+$ = 544.3
P-0260		ácido 3-[1-(4-Butoxi-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	461.54	$[M+H^+]^+$ = 462.3
P-0261		ácido 3-[1-(4-Butil-bencen-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	445.54	$[M+H^+]^+$ = 446.3
P-0262		ácido 3-[1-(2-Cloro-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	423.88	$[M+H^+]^+$ = 423.9
P-0263		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	441.87	$[M+H^+]^+$ = 442.3
P-0264		ácido 3-{5,6-Dimetoxi-1-[3-(piridin-2-carbonil)-bencen-sulfonil]-1H-indol-3-il}-propiónico	494.53	$[M+H^+]^+$ = 495.1
P-0265		ácido 3-{5,6-Dimetoxi-1-[3-(piridin-4-carbonil) bencensulfonil]-1H-indol-3-il}-propiónico	494.53	$[M+H^+]^+$ = 495.1

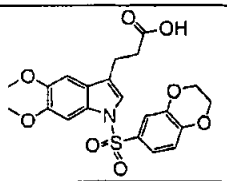
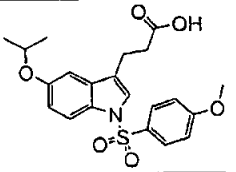
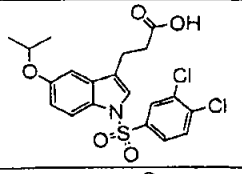
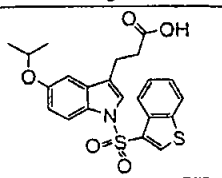
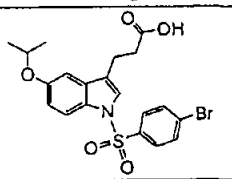
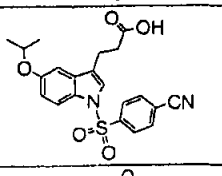
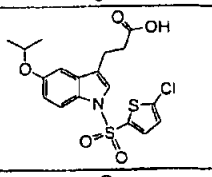
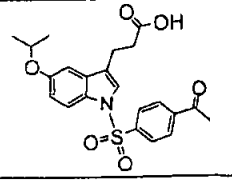
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0266		ácido 3-[1-(Bifenil-2-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	465.53	$[M+H^+]^+$ = 466.3
P-0267		ácido 3-[5,6-Dimetoxi-1-(2-trifluorometil-bencen-sulfonil)-1H-indol-3-il]-propiónico	457.43	$[M+H^+]^+$ = 458.3
P-0268		ácido 3-[5,6-Dimetoxi-1-(4-pirazol-1-il-bencen-sulfonil)-1H-indol-3-il]-propiónico	455.49	$[M+H^+]^+$ = 456.3
P-0269		ácido 3-[5,6-Dimetoxi-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	421.48	$[M+H^+]^+$ = 421.9
P-0270		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	423.51	$[M+H^+]^+$ = 423.9
P-0271		ácido 3-[5,6-Dimetoxi-1-(2-trifluorometoxi-bencen-sulfonil)-1H-indol-3-il]-propiónico	473.43	$[M+H^+]^+$ = 473.9
P-0272		ácido 3-[5,6-Dimetoxi-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	403.46	$[M+H^+]^+$ = 404.3
P-0273		ácido 3-[5,6-Dimetoxi-1-(4'-metil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico	479.56	$[M+H^+]^+$ = 479.9

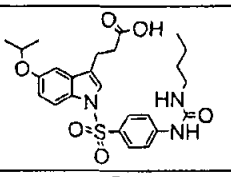
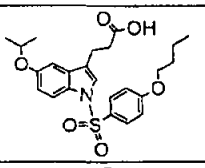
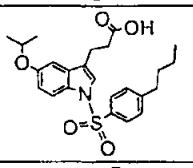
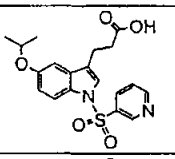
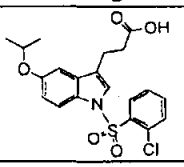
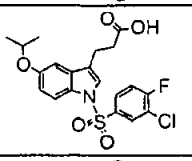
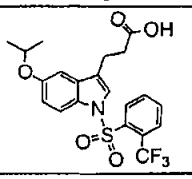
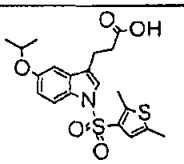
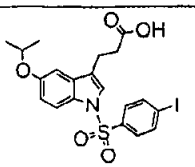
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0274		ácido 3-[5,6-Dimetoxi-1-(2-fenoxi-bencensulfonil)-1H-indol-3-il]-propiónico	481.53	$[M+H^+]^+$ = 482.3
P-0275		ácido 3-[5-(Quinolin-8-sulfonil)-5H-[1,3]dioxolo [4,5-f]indol-7-il]-propiónico	424.44	$[M+H^+]^+$ = 425.1
P-0276		ácido 3-[5-(4-metoxi-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	403.41	$[M+H^+]^+$ = 404.3
P-0277		ácido 3-{5-[4-(Piridin-2-iloxi)-bencensulfonil]-5H[1,3]dioxolo[4,5-f] indol-7-il}-propiónico	466.47	$[M+H^+]^+$ = 467.1
P-0278		ácido 3-{5-[4-(Piridin-3-iloxi)-bencensulfonil]-5H-[1,3]dioxolo[4,5-f] indol-7-il}-propiónico	466.47	$[M+H^+]^+$ = 467.1
P-0279		ácido 3-{5-[4-(4-metoxi-fenoxi)-bencensulfonil]-5H-[1,3]dioxolo[4,5-f]indol-7-il}-propiónico	495.51	$[M+H^+]^+$ = 495.9
P-0280		ácido 3-[5-(5-Piridin-2-il-tiofen-2-sulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	456.50	$[M+H^+]^+$ = 457.1
P-0281		ácido 3-{5-[4-(3-Butil-ureido)-bencensulfonil]-5H-[1,3]dioxolo[4,5-f] indol-7-il}-propiónico	487.54	$[M+H^+]^+$ = 488.3
P-0282		ácido 3-[5-(4-Butil-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico ácido	429.50	$[M+H^+]^+$ = 430.3

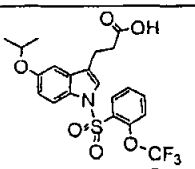
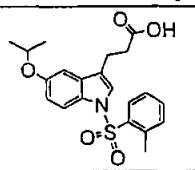
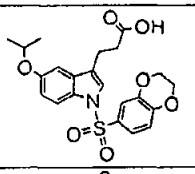
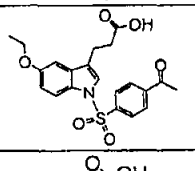
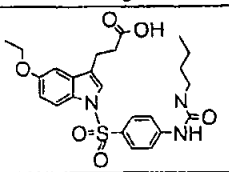
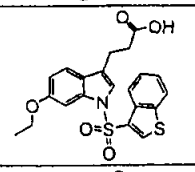
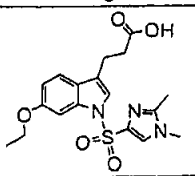
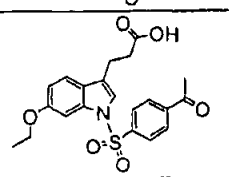
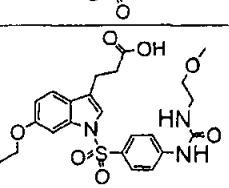
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0283		ácido 3-[5-(2-Cloro-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	407.83	$[M+H^+]^+$ = 408.3
P-0284		ácido 3-[5-(3-Cloro-4-fluoro-bencensulfonil)-5H-[1,3]dioxolo[4,5-f]indol-7-il]-propiónico	425.82	$[M+H^+]^+$ = 426.3
P-0285		ácido 3-{5-[3-(Piridin-2-carbonil)-bencensulfonil]-5H-[1,3]dioxolo[4,5-flindol-7-il}-propiónico	478.48	$[M+H^+]^+$ = 497.1
P-0286		ácido 3-{5-[3-(Piridin-4-carbonil)-bencensulfonil]-5H-[1,3]dioxolo[4,5-flindol-7-il}-propiónico	478.48	$[M+H^+]^+$ = 479.1
P-0287		ácido 3-[5-(Bifenil-2-sulfonil)-5H-[1,3]dioxolo [4,5-f]indol-7-il]-propiónico	449.49	$[M+H^+]^+$ = 450.3
P-0288		ácido 3-{5-[4-(3,3-Dimetil-ureido)-bencen-sulfonil]-5H-[1,3]dioxolo [4,5-flindol-7-il}-propiónico	459.48	$[M+H^+]^+$ = 460.3
P-0289		ácido 3-(5-{4-[3-(2-metoxi-etil)-ureido]-bencen-sulfonil}-5H-[1,3]dioxolo [4,5-f]indol-7-il)-propiónico	489.51	$[M+H^+]^+$ = 489.9
P-0290		ácido 3-[5-(2-Trifluorometil-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	441.39	$[M+H^+]^+$ = 442.3

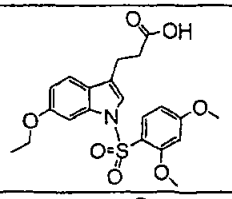
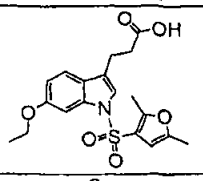
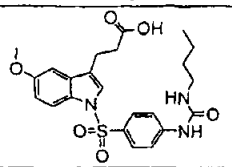
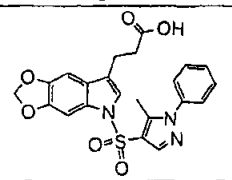
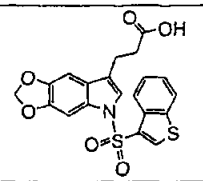
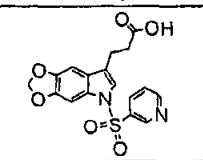
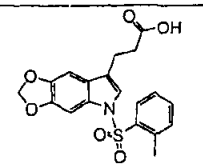
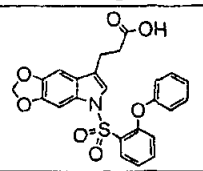
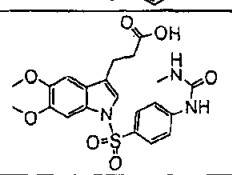
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0291		ácido 3-[5-(4-Pirazol-1-il-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	439.45	$[M+H^+]^+$ = 440.3
P-0292		ácido 3-[5-(2,4-Dimetoxi-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	433.44	$[M+H^+]^+$ = 434.3
P-0293		ácido 3-[5-(1,3,5-Trimetil-1H-pirazol-4-sulfonil)-5H-[1,3]dioxolo[4,5-f]indol-7-il]-propiónico	405.43	$[M+H^+]^+$ = 406.3
P-0294		ácido 3-[5-(2,5-Dimetil-tiofen-3-sulfonil)-5H-[1,3] dioxolo[4,5-]indol-7-il]-propiónico	407.47	$[M+H^+]^+$ = 407.9
P-0295		ácido 3-[5-(2,5-Dimetil-furan-3-sulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	391.40	$[M+H^+]^+$ = 391.9
P-0296		ácido 3-[5-(4-yodo-bencensulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	499.28	$[M+H^+]^+$ = 499.9
P-0297		ácido 3-[5-(2-Trifluoro-metoxi-bencensulfonil)-5H-[1,3]dioxolo[4,5-f]indol-7-il]- propiónico	457.39	$[M+H^+]^+$ = 458.3
P-0298		ácido 3-[5-(4'-Metil-bifenil-2-sulfonil)-5H-[1,3]dioxolo [4,5-f]indol-7-il]-propiónico	463.51	$[M+H^+]^+$ = 463.9

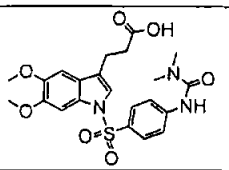
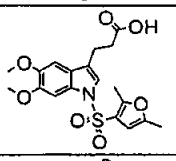
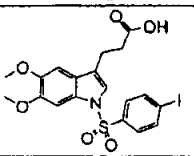
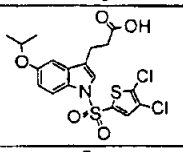
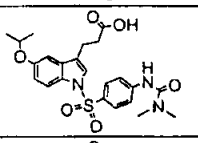
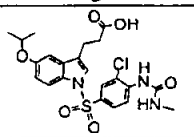
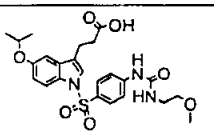
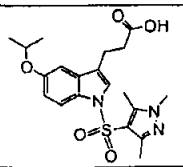
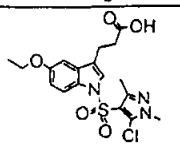
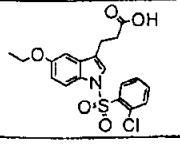
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0299		ácido 3-[1-(4-Acetil-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	431.47	$[M+H^+]^+$ = 432.3
P-0300		ácido 3-{5,6-Dimetoxi-1-[4-(piridin-4-iloxi)-bencen-sulfonil]-1H-indol-3-il}-propiónico	482.52	$[M+H^+]^+$ = 483.1
P-0301		ácido 3-[5,6-Dimetoxi-1-(6-morfolin-4-il-piridin-3-sulfonil)-1H-indol-3-il]-propiónico	475.52	
P-0302		ácido 3-[5,6-Dimetoxi-1-(5-piridin-2-il-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico	472.54	$[M+H^+]^+$ = 473.1
P-0303		ácido 3-(5,6-Dimetoxi-1-{4-[(morfolin-4-carbonil)-amino]-bencensulfonil}-1H-indol-3-il)-propiónico	517.56	$[M+H^+]^+$ = 518.3
P-0304		ácido 3-[5,6-Dimetoxi-1-(piridin-3-sulfonil)-1H-indol-3-il]-propiónico	390.42	$[M+H^+]^+$ = 391.1
P-0305		ácido 3-{1-[3-Cloro-4-(3-metil-ureido)-bencen-sulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	495.94	$[M+H^+]^+$ = 496.3
P-0306		ácido 3-(5,6-Dimetoxi-1-{4-[3-(2-metoxi-etil)-ureido]-bencensulfonil}-1H-indol-3-il)-propiónico	505.55	$[M+H^+]^+$ = 505.9

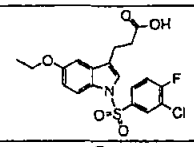
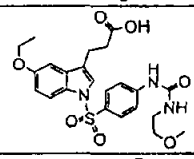
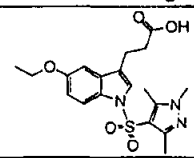
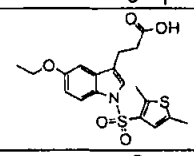
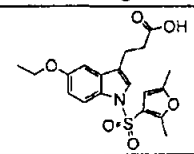
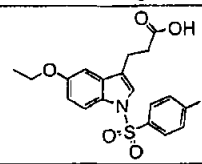
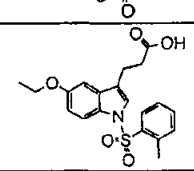
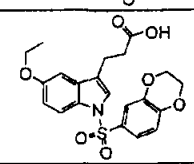
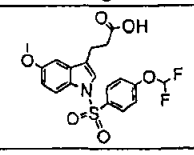
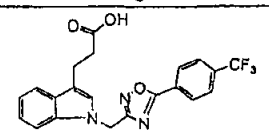
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0307		ácido 3-[1-(2,3-Dihidro-benzo[1,4]dioxin-6-sulfonil 5,6-dimetoxi-1H-indol-3-il]-propiónico	447.47	$[M+H^+]^+$ = 447.9
P-0308		ácido 3-[5-Isopropoxi-1-(4-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	417.48	$[M+H^+]^+$ = 418.3
P-0309		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	456.35	$[M+H^+]^+$ = 456.3
P-0310		ácido 3-[1-(Benzo[b]tiofen-3-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	443.54	$[M+H^+]^+$ = 444.3
P-0312		ácido 3-[1-(4-Bromo-bencen-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	466.35	$[M+H^+]^+$ = 468.3
P-0313		ácido 3-[1-(4-Ciano-bencen-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	412.47	$[M+H^+]^+$ = 413.1
P-0314		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	427.93	$[M-H^+]^-$ = 427.9
P-0315		ácido 3-[1-(4-Acetil-bencen-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	429.50	$[M+H^+]^+$ = 430.3

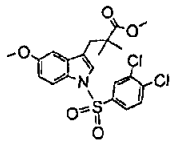
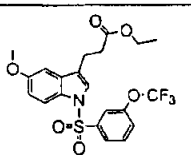
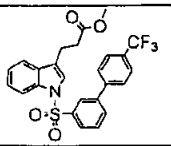
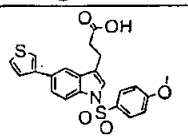
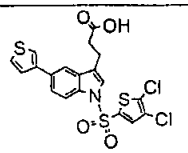
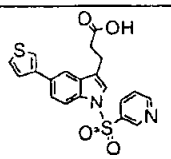
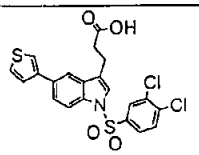
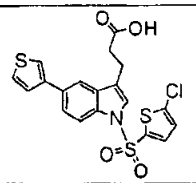
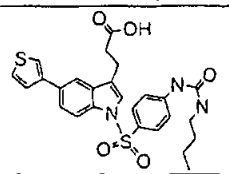
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0325		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5-isopropoxi-1H-indol-3-il}-propiónico	501.61	$[M+H^+]^+$ = 502.3
P-0327		ácido 3-[1-(4-Butoxi-bencensulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	459.57	$[M+H^+]^+$ = 460.3
P-0328		ácido 3-[1-(4-Butil-bencen-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	443.57	$[M+H^+]^+$ = 444.3
P-0329		ácido 3-[5-Isopropoxi-1-(piridin-3-sulfonil)-1H-indol-3-il]-propiónico	388.45	$[M+H^+]^+$ = 389.1
P-0330		ácido 3-[1-(2-Cloro-bencen-sulfonil)-5-isopropoxi-1H-indol-3-il]- propiónico	421.90	$[M+H^+]^+$ = 421.9
P-0331		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	439.59	$[M+H^+]^+$ = 440.3
P-0333		ácido 3-[5-Isopropoxi-1-(2-trifluorometil-bencen-sulfonil)-1H-indol-3-il]-propiónico	455.46	$[M+H^+]^+$ = 456.3
P-0334		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	421.54	$[M+H^+]^+$ = 421.9
P-0335		ácido 3-[1-(4-yodo-bencensulfonil)-5-isopropoxi-1H-indol-3- il]-propiónico	513.35	$[M+H^+]^+$ = 514.3

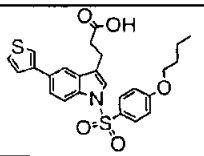
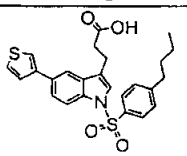
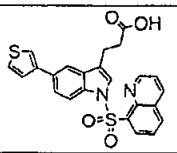
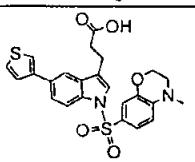
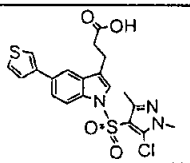
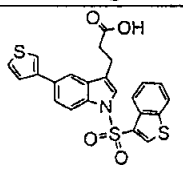
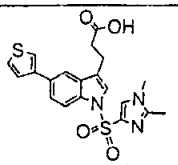
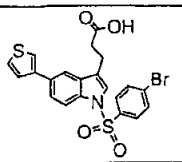
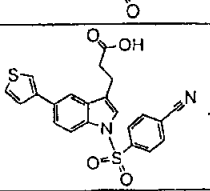
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0336		ácido 3-[5-Isopropoxi-1-(2-trifluorometoxi-bencen-sulfonil)-1H-indol-3-il]-propiónico	471.46	$[M+H^+]^+$ = 472.3
P-0337		ácido 3-[5-Isopropoxi-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	401.49	$[M+H^+]^+$ = 402.3
P-0340		ácido 3-[1-(2,3-Dihidro-benzo[1,4]dioxin-6-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	445.50	$[M+H^+]^+$ = 446.3
P-0341		ácido 3-[1-(4-Acetil-bencen-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico	415.47	$[M+H^+]^+$ = 416.3
P-0343		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5-etoxi-1H-indol-3-il}-propiónico	487.58	$[M+H^+]^+$ = 488.3
P-0345		ácido 3-[1-(Benzo[b] tiofen-3-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	429.52	$[M+H^+]^+$ = 430.3
P-0348		ácido 3-[1-(1,2-Dimetil-1H-imidazol-4-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	391.45	$[M+H^+]^+$ = 392.3
P-0349		ácido 3-[1-(4-Acetil-bencen-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	415.47	$[M+H^+]^+$ = 416.3
P-0357		ácido 3-(6-Etoxi-1-{4-[3-(2-metoxi-etil)-ureido]-bencensulfonil}-1H-indol-3-il)-propiónico	489.55	$[M+H^+]^+$ = 490.3

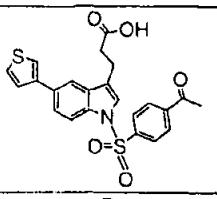
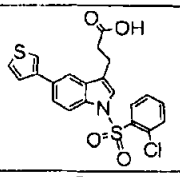
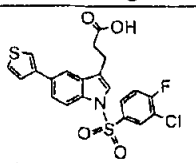
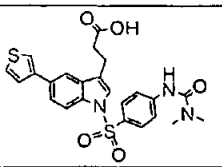
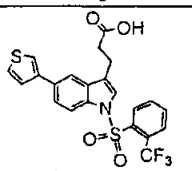
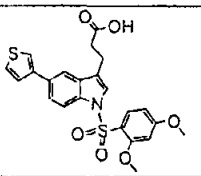
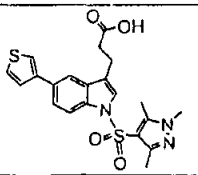
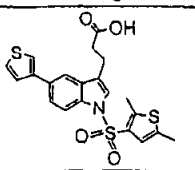
Comp. número	Estructura	Nombre	Peso molecular Calc.	Peso molecular Medido MS(ESI)
P-0358		ácido 3-[1-(2,4-Dimetoxi-bencensulfonil)-6-etoxi-1H-indol-3-il]-propiónico	433.48	$[M+H^+]^+$ = 434.3
P-0359		ácido 3-[1-(2,5-Dimetil-furan-3-sulfonil)-6-etoxi-1H-indol-3-il]-propiónico	391.45	$[M+H^+]^+$ = 392.3
P-0360		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5-metoxi-1H-indol-3-il}-propiónico	473.55	$[M+H^+]^+$ = 473.9
P-0361		ácido 3-[5-(5-Metil-1-fenil-1H-pirazol-4-sulfonil)-5H-[1,3]dioxolo[4,5-f]indol-7-il]-propiónico	453.48	$[M+H^+]^+$ = 453.9
P-0362		ácido 3-[5-(Benzo[b] tiofen-3-sulfonil)-5H-[1,3] dioxolo[4,5-f]indol-7-il]-propiónico	429.47	$[M+H^+]^+$ = 430.3
P-0363		ácido 3-[5-(Piridin-3-sulfonil)-5H-[1,3]-dioxolo [4,5-f]indol-7-il]-propiónico	374.37	$[M+H^+]^+$ = 375.1
P-0364		ácido 3-[5-(Toluen-2-sulfonil)-5H-[1,3]dioxolo [4,5-f]indol-7-il]-propiónico	387.41	$[M+H^+]^+$ = 387.9
P-0365		ácido 3-[5-(2-Fenoxi-bencen-sulfonil)-5H-[1,3]dioxolo[4,5-f] indol-7-il]-propiónico	465.49	$[M+H^+]^+$ = 466.3
P-0366		ácido 3-{5,6-Dimetoxi-1-[4-(3-metil-ureido)-bencen-sulfonil]-1H-indol-3-il}-propiónico	461.50	$[M+H^+]^+$ = 462.3

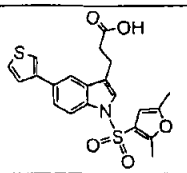
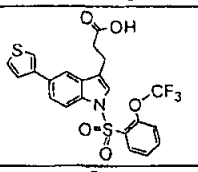
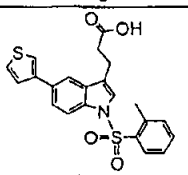
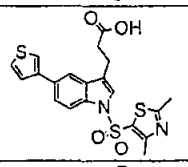
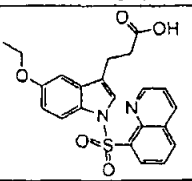
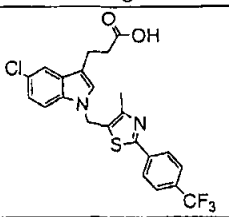
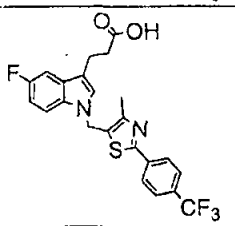
Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0367		ácido 3-{1-[4-(3,3-Dimetil-ureido)-bencensulfonil]-5,6-dimetoxi-1H-indol-3-il}-propiónico	475.52	$[M+H^+]^+$ = 475.9
P-0368		ácido 3-[1-(2,5-Dimetil-furan-3-sulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	407.45	$[M+H^+]^+$ = 408.3
P-0369		ácido 3-[1-(4-yodo-bencensulfonil)-5,6-dimetoxi-1H-indol-3-il]-propiónico	515.33	$[M+H^+]^+$ = 516.3
P-0370		ácido 3-[1-(4,5-Dicloro-tiofen-2-sulfonil)-5-isopropoxi-1H-indol-3-il]-propiónico	462.37	$[M-H^+]^-$ = 461.9
P-0372		ácido 3-{1-[4-(3,3-Dimetil-ureido)-bencen-sulfonil]-5-isopropoxi-1H-indol-3-il}-propiónico	473.55	$[M+H^+]^+$ = 474.3
P-0373		ácido 3-{1-[3-Cloro-4-(3-metil-ureido)-bencen-sulfonil]-5-isopropoxi-1H-indol-3-il}-propiónico	493.97	$[M+H^+]^+$ = 494.3
P-0374		ácido 3-(5-Isopropoxi-1-{4-[3-(2-metoxi-etil)-ureido]-bencensulfonil}-1H-indol-3-il)-propiónico	503.58	$[M+H^+]^+$ = 504.3
P-0376		ácido 3-[5-Isopropoxi-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	419.50	$[M+H^+]^+$ = 420.3
P-0377		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico	425.89	$[M+H^+]^+$ = 426.3
P-0378		ácido 3-[1-(2-Cloro-bencensulfonil)-5-etoxi-1H-indol-3-il]-propiónico	407.87	$[M+H^+]^+$ = 408.3

Comp. número	Estructura	Nombre	Peso molecular Calc.	Medido MS(ESI)
P-0379		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-5-etoxi-1H-indol-3-il]-propiónico	425.86	$[M+H^+]^+$ = 425.9
P-0380		ácido 3-(5-Etoxi-1-{4-[3-(2-metoxi-etil)-ureido]-bencensulfonil}-1H-indol-3-il)-propiónico	489.56	$[M+H^+]^+$ = 490.3
P-0381		ácido 3-[5-Etoxi-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	405.47	$[M+H^+]^+$ = 406.3
P-0382		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico	407.51	$[M+H^+]^+$ = 408.3
P-0383		ácido 3-[1-(2,5-Dimetil-furan-3-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico	391.44	$[M+H^+]^+$ = 392.3
P-0384		ácido 3-[5-Etoxi-1-(4-yodo-bencensulfonil)-1H-indol-3-il]-propiónico	499.32	$[M+H^+]^+$ = 500
P-0385		ácido 3-[5-Etoxi-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	387.45	$[M+H^+]^+$ = 388.3
P-0387		ácido 3-[1-(2,3-Dihidro-benzo[1,4]dioxin-6-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico	431.46	$[M+H^+]^+$ = 432.3
P-0389		ácido 3-[1-(4-Difluoro-metoxi-bencensulfonil)-5-metoxi-1H-indol-3-il]-propiónico	425.1	$[M-H^+]^-$ = 442
P-0390		ácido 3-{1-[5-(4-Trifluoro-metil-fenil)-[1,2,4]oxadiazol-3-ilmetil]-1H-indol- 3-il}-propiónico	415.37	$[M+H^+]^+$ = 416.4

Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0559		metiléster del ácido 3-[1-(3,4-Dicloro-bencen-sulfonil)-5-metoxi-1H-indol-3-il]-2,2-dimetil-propiónico	470.37	$[M+H^+]^+$ = 470.1; 472.1
P-0569		etiléster del ácido 3-[5-metoxi-1-(3-trifluoro-metoxi-bencensulfonil)-1H-indol-3-il]-propiónico	471.45	
P-0571		metiléster del ácido 3-[1-(4'-Trifluorometil-bifenil-3-sulfonil)-1H-indol-3-il]-propiónico	487.50	
P-0576		ácido 3-[1-(4-metoxi-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	441.53	
P-0577		ácido 3-[1-(4,5-Dicloro-tiofen-2-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	486.42	
P-0578		ácido 3-[1-(Piridin-3-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	412.49	
P-0579		ácido 3-[1-(3,4-Dicloro-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	480.39	
P-0580		ácido 3-[1-(5-Cloro-tiofen-2-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	451.97	
P-0591		ácido 3-{1-[4-(3-Butil-ureido)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico	525.65	

Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0593		ácido 3-[1-(4-Butoxi-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	483.61	
P-0594		ácido 3-[1-(4-Butil-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	467.61	
P-0595		ácido 3-[1-(Quinolin-8-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	462.55	
P-0596		ácido 3-[1-(4-Metil-3,4-dihidro-2H-benzo[1,4] oxazin-7-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	482.58	
P-0597		ácido 3-[1-(5-Cloro-1,3-dimetil-1H-pirazol-4-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	463.96	
P-0598		ácido 3-[1-(Benzo[b] tiofen-3-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	467.59	
P-0600		ácido 3-[1-(1,2-Dimetil-1H-imidazol-4-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	429.52	
P-0602		ácido 3-[1-(4-Bromo-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	490.40	
P-0603		ácido 3-[1-(4-Ciano-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	436.51	

Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0604		ácido 3-[1-(4-Acetil-bencen-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	453.54	
P-0605		ácido 3-[1-(2-Cloro-bencen-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	445.95	
P-0606		ácido 3-[1-(3-Cloro-4-fluoro-bencensulfonil)-5 tiofen-3-il-1H-indol-3-il]-propiónico	463.94	
P-0609		ácido 3-[1-[4-(3,3-Dimetil-ureido)-bencensulfonil]-5-tiofen-3-il-1H-indol-3-il}-propiónico	497.59	
P-0610		ácido 3-[5-Tiofen-3-il-1-(2-trifluorometil-bencen-sulfonil)-1H-indol-3-il]-propiónico	479.50	
P-0611		ácido 3-[1-(2,4-Dimetoxi-bencensulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	471.55	
P-0612		ácido 3-[5-Tiofen-3-il-1-(1,3,5-trimetil-1H-pirazol-4-sulfonil)-1H-indol-3-il]-propiónico	443.55	
P-0613		ácido 3-[1-(2,5-Dimetil-tiofen-3-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	445.58	

Comp. número	Estructura	Nombre	Peso molecular	
			Calc.	Medido MS(ESI)
P-0614		ácido 3-[1-(2,5-Dimetil-furan-3-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	429.52	
P-0615		ácido 3-[5-Tiofen-3-il-1-(2-trifluorometoxi-bencen-sulfonil)-1H-indol3-il]-propiónico	495.50	
P-0616		ácido 3-[5-Tiofen-3-il-1-(toluen-2-sulfonil)-1H-indol-3-il]-propiónico	425.53	
P-0619		ácido 3-[1-(2,4-Dimetil-tiazol-5-sulfonil)-5-tiofen-3-il-1H-indol-3-il]-propiónico	446.57	
P-0620		ácido 3-[5-Etoxi-1-(quinolin-8-sulfonil)-1H-indol-3-il]-propiónico	424.48	
P-0621		ácido 3-{5-Cloro-1-[4-metil-2(4-trifluorometil-fenil)tiazol-5-ilmetil]-1H-indol-3-il}-propiónico	478.92	
P-0622		ácido 3-{5-Fluoro-1-[4-metil-2-(4-trifluorometil-fenil)tiazol-5-ilmetil]-1H-indol-3-il}-propiónico	462.47	

Ejemplo 8: Expresión y purificación de PPARs para su uso en ensayos bioquímicos y celulares.

Ingeniería genética:

Los plásmidos que codifican los Dominios de unión a ligando (LBDs) de PPARα, PPARγ y PPARδ se diseñaron usando métodos comunes de reacción en cadena de la polimerasa (PCR) (pGal4-PPARα-LBD, pGal4-PPARγ-LBD, pGal4-PPARδ-LBD). Las secuencias relevantes de ADN y secuencias codificadas de proteínas usadas en el ensayo se muestran para cada una (véase en lo siguiente). El ADN complementario, clonado a partir de diversos tejidos humanos se adquirió de Invitrogen, y se usó como sustrato en las reacciones de PCR. Se diseñaron iniciadores cebadores de oligonucleótidos habituales específicos (Invitrogen, véase en lo siguiente) para iniciar el producto de PCR, y también para proporcionar los sitios de escisión apropiados para enzimas de restricción, para la ligación con los plásmidos.

Los plásmidos usados para la ligación con los insertos que codifican receptores fueron pET28 (Novagen) o un derivado de pET28, pET-BAM6, para su expresión usando *E. coli*. En cada uno de estos casos, el receptor LBD se diseñó para que incluyera una etiqueta de Histidinas para su purificación usando cromatografía de afinidad a metal.

Expresión y Purificación de Proteínas de los PPAR:

Para la expresión de proteínas, los plásmidos que contienen genes de interés se transformaron en la cepa BL21 (DE3)RIL de *E. Coli* (Invitrogen) y las transformantes se seleccionaron por su crecimiento en placas de agar LB que contenían antibióticos apropiados. Se hicieron crecer colonias individuales durante 4 horas a 37°C en 200ml de medio LB. Para PPARα y PPARγ toda la expresión de proteinas se realizó por fermentación a gran escala usando un biorreactor de 30L. Se agregaron 400ml de cultivo de inicio a 30L de cultivo en TB y se dejó crecer a 37°C hasta que se obtuvo una OD600mm de 2-5. El cultivo se enfrió a 20°C y se agregó IPTG 0.5mM, el cultivo se dejó crecer durante 18 horas adicionales.

Para la expresión de proteínas de PPARδ, se hicieron crecer colonias individuales durante 4 horas a 37°C en 200ml de medio LB. 16x1L de medios TB recién preparados en

matraces de 2.8L se inocularon con 10ml de cultivo de inicio y se hicieron crecer con agitación constante a 37°C. Una vez que los cultivos alcanzaron una absorbancia de 1.0 a 600nm, se agregó al cultivo un aditivo para mejorar la solubilidad del PPARδ y, 30 minutos más tarde, se agregó IPTG 0.5mM y los cultivos se dejaron crecer durante 12 a 18 horas adicionales a 20°C. Las células se cosecharon por centrifugación y los gránulos se congelaron a -80°C hasta que estuvieron listos para lisis/purificación.

Para purificación de proteínas; todas las operaciones se llevaron a cabo a 4°C. Los gránulos congelados de células de *E. Coli* se resuspendieron en tampón de lisis y se lisaron usando métodos mecánicos estándar. Las proteínas solubles se purificaron mediante etiquetas de poli-Histidina usando purificación de afinidad a metal inmovilizada (IMAC). Para cada uno de los PPAR descritos, todos se han purificado usando un proceso de purificación de 3 etapas usando IMAC, cromatografía por exclusión de tamaños y cromatografía de intercambio iónico. Para el PPARα, la etiqueta de poli-Histidina se removió opcionalmente usando Trombina (Calbiochem). En el caso del PPARδ, durante la purificación de proteínas, el aditivo que mejora la solubilidad se presentó con el fin de mantener la estabilidad de la proteína. Durante la etapa final de purificación, los aditivos que mejoran la solubilidad se retiraron por desalado antes de la concentración.

Información de secuencias de plásmidos y cebadores de PCR:

PPARα: (**Ácido nucleico** SEQ ID NO:___) (**Proteína** SEQ ID NO:___)

P332. pET28 PPARA E199-Y468-X

```
                                                    taatacgactcactatagggaattgt
gagcggataacaattcccctctagaaataattttgtttaactttaagaaggagatatacc
atgggcagcagccatcatcatcatcatcacagcagcggcctggtgccgcgcggcagccat
 M  G  S  S  H  H  H  H  H  H  S  S  G  L  V  P  R  G  S  H
atggaaactgcagatctcaaatctctggccaagagaatctacgaggcctacttgaagaac
 M  E  T  A  D  L  K  S  L  A  K  R  I  Y  E  A  Y  L  K  N
ttcaacatgaacaaggtcaaagcccgggtcatcctctcaggaaaggccagtaacaatcca
 F  N  M  N  K  V  K  A  R  V  I  L  S  G  K  A  S  N  N  P
ccttttgtcatacatgatatggagacactgtgtatggctgagaagacgctggtggccaag
 P  F  V  I  H  D  M  E  T  L  C  M  A  E  K  T  L  V  A  K
ctggtggccaatggcatccagaacaaggaggcggaggtccgcatctttcactgctgccag
 L  V  A  N  G  I  Q  N  K  E  A  E  V  R  I  F  H  C  C  Q
tgcacgtcagtggagaccgtcacggagctcacggaattcgccaaggccatcccaggcttc
 C  T  S  V  E  T  V  T  E  L  T  E  F  A  K  A  I  P  G  F
gcaaacttggacctgaacgatcaagtgacattgctaaaatacggagtttatgaggccata
 A  N  L  D  L  N  D  Q  V  T  L  L  K  Y  G  V  Y  E  A  I
ttcgccatgctgtcttctgtgatgaacaaagacgggatgctggtagcgtatggaaatggg
 F  A  M  L  S  S  V  M  N  K  D  G  M  L  V  A  Y  G  N  G
tttataactcgtgaattcctaaaaagcctaaggaaaccgttctgtgatatcatggaaccc
 F  I  T  R  E  F  L  K  S  L  R  K  P  F  C  D  I  M  E  P
aagtttgattttgccatgaagttcaatgcactggaactggatgacagtgatatctccctt
 K  F  D  F  A  M  K  F  N  A  L  E  L  D  D  S  D  I  S  L
tttgtggctgctatcatttgctgtggagatcgtcctggccttctaaacgtaggacacatt
 F  V  A  A  I  I  C  C  G  D  R  P  G  L  L  N  V  G  H  I
gaaaaaatgcaggagggtattgtacatgtgctcagactccacctgcagagcaaccacccg
 E  K  M  Q  E  G  I  V  H  V  L  R  L  H  L  Q  S  N  H  P
gacgatatctttctcttcccaaaacttcttcaaaaaatggcagacctccggcagctggtg
 D  D  I  F  L  F  P  K  L  L  Q  K  M  A  D  L  R  Q  L  V
acggagcatgcgcagctggtgcagatcatcaagaagacggagtcggatgctgcgctgcac
 T  E  H  A  Q  L  V  Q  I  I  K  K  T  E  S  D  A  A  L  H
ccgctactgcaggagatctacagggacatgtactgagtcgacaagcttgcggccgcactc
 P  L  L  Q  E  I  Y  R  D  M  Y  -
gagcaccaccaccaccaccactgagat
```

Cebadores de PCR

PPARA	PPARA-S	GCTGACACATATGGAAACTGCAGATCTCAAATC	(SEQ ID NO:___)
	PPARA-A	GTGACTGTCGACTCAGTACATGTCCCTGTAGA	(SEQ ID NO:___)

PPARγ: (Ácido nucleico SEQ ID NO:___) (Proteína SEQ ID NO:___)

P333. pET28 PPARG E205-Y475-X

```
                                                    taatacgactcactatagggaattgt
gagcggataacaattcccctctagaaataattttgtttaactttaagaaggagatatacc
atgggcagcagccatcatcatcatcatcacagcagcggcctggtgccgcgcggcagccat
 M  G  S  S  H  H  H  H  H  H  S  S  G  L  V  P  R  G  S  H
atggagtccgctgacctccgggccctggcaaaacatttgtatgactcatacataaagtcc
 M  E  S  A  D  L  R  A  L  A  K  H  L  Y  D  S  Y  I  K  S
ttcccgctgaccaaagcaaaggcgagggcgatcttgacaggaaagacaacagacaaatca
 F  P  L  T  K  A  K  A  R  A  I  L  T  G  K  T  T  D  K  S
ccattcgttatctatgacatgaattccttaatgatgggagaagataaaatcaagttcaaa
 P  F  V  I  Y  D  M  N  S  L  M  M  G  E  D  K  I  K  F  K
cacatcaccccctgcaggagcagagcaaagaggtggccatccgcatctttcagggctgc
 H  I  T  P  L  Q  E  Q  S  X  E  V  A  I  R  I  F  Q  G  C
cagtttcgctccgtggaggctgtgcaggagatcacagagtatgccaaaagcattcctggt
 Q  F  R  S  V  E  A  V  Q  E  I  T  E  Y  A  K  S  I  P  G
tttgtaaatcttgacttgaacgaccaagtaactctcctcaaatatggagtccacgagatc
 F  V  N  L  D  L  N  D  Q  V  T  L  L  K  Y  G  V  H  E  I
atttacacaatgctggcctccttgatgaataaagatggggttctcatatccgagggccaa
 I  Y  T  M  L  A  S  L  M  N  K  D  G  V  L  I  S  E  G  Q
ggcttcatgacaagggagtttctaaagagcctgcgaaagccttttggtgactttatggag
 G  F  M  T  R  E  F  L  K  S  L  R  K  P  F  G  D  F  M  E
cccaagtttgagtttgctgtgaagttcaatgcactggaattagatgacagcgacttggca
 P  K  F  E  F  A  V  K  F  N  A  L  E  L  D  D  S  D  L  A
atatttattgctgtcattattctcagtggagaccgcccaggtttgctgaatgtgaagccc
 I  F  I  A  V  I  I  L  S  G  D  R  P  G  L  L  N  V  K  P
attgaagacattcaagacaacctgctacaagccctggagctccagctgaaagctgaaccac
 I  E  D  I  Q  D  N  L  L  Q  A  L  E  L  Q  L  K  L  N  H
cctgagtcctcacagctgtttgccaagctgctccagaaaatgacagacctcagacagatt
 P  E  S  S  Q  L  F  A  K  L  L  Q  K  M  T  D  L  R  Q  I
gtcacggaacatgtgcagctactgcaggtgatcaagaagacggagacagacatgagtctt
 V  T  E  H  V  Q  L  L  Q  V  I  K  K  T  E  T  D  M  S  L
cacccgctcctgcaggagatctacaaggacttgtactaggtcgacaagcttgcggccgca
 H  P  L  L  Q  E  I  Y  K  D  L  Y  -
ctcgagcaccaccaccaccaccactgagat
```

Cebadores de PCR

PPARG	PPARG-S	GCTCAGACATATGGAGTCCGCTGACCTCCGGGC	(SEQ ID NO:___)
	PPARG-A	GTGACTGTCGACCTAGTACAAGTCCTTGTAGA	(SEQ ID NO:___)

PPARδ: (Ácido nucleico SEQ ID NO:___) (Proteína SEQ ID NO:___)

P1057. pET BAM6 PPARD G165-Y441-X

```
                                                    taatacgactcactatagggaattgt
gagcggataacaattcccctctagaaataattttgtttaactttaagaaggagatatacc
atgaaaaaaggtcaccaccatcaccatcacggatcccagtacaacccacaggtggccgac
 M  K  K  G  H  H  H  H  H  H  G  S  Q  Y  N  P  Q  V  A  D
ctgaaggccttctccaagcacatctacaatgcctacctgaaaaacttcaacatgaccaaa
 L  K  A  F  S  K  H  I  Y  N  A  Y  L  K  N  F  N  M  T  K
aagaaggcccgcagcatcctcaccggcaaagccagccacacggcgccctttgtgatccac
 K  K  A  R  S  I  L  T  G  K  A  S  H  T  A  P  F  V  I  H
gacatcgagacattgtggcaggcagagaaggggctggtgtggaagcagttggtgaatggc
 D  I  E  T  L  W  Q  A  E  K  G  L  V  W  K  Q  L  V  N  G
ctgcctccctacaaggagatcagcgtgcacgtcttctaccgctgccagtgcaccacagtg
```

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 L  P  P  Y  K  E  I  S  V  H  V  F  Y  R  C  Q  C  T  T  V
gagaccgtgcgggagctcactgagttcgccaagagcatccccagcttcagcagcctcttc
 E  T  V  R  E  L  T  E  F  A  K  S  I  P  S  F  S  S  L  F
ctcaacgaccaggttacccttctcaagtatggcgtgcacgaggccatcttcgccatgctg
 L  N  D  Q  V  T  L  L  K  Y  G  V  H  E  A  I  F  A  M  L
gcctctatcgtcaacaaggacgggctgctggtagccaacggcagtggctttgtcacccgt
 A  S  I  V  N  K  D  G  L  L  V  A  N  G  S  G  F  V  T  R
gagttcctgcgcagcctccgcaaacccttcagtgatatcattgagcctaagtttgaattt
 E  F  L  R  S  L  R  K  P  F  S  D  I  I  E  P  K  F  E  F
gctgtcaagttcaacgccctggaacttgatgacagtgacctggccctattcattgcggcc
 A  V  K  F  N  A  L  E  L  D  D  S  D  L  A  L  F  I  A  A
atcattctgtgtggagaccggccaggcctcatgaacgttccacgggtggaggctatccag
 I  I  L  C  G  D  R  P  G  L  M  N  V  P  R  V  E  A  I  Q
gacaccatcctgcgtgccctcgaattccacctgcaggccaaccaccctgatgcccagtac
 D  T  I  L  R  A  L  E  F  H  L  Q  A  N  H  P  D  A  Q  Y
ctcttccccaagctgctgcagaagatggctgacctgcggcaactggtcaccgagcacgcc
 L  F  P  K  L  L  Q  K  M  A  D  L  R  Q  L  V  T  E  H  A
cagatgatgcagcggatcaagaagaccgaaaccgagacctcgctgcaccctctgctccag
 Q  M  M  Q  R  I  K  K  T  E  T  E  T  S  L  H  P  L  L  Q
gagatctacaaggacatgtactaagtcgaccaccaccaccaccaccactgagatccggct
 E  I  Y  K  D  M  Y  -
ggccctactggccgaaaggaattcgaggccagcagggccaccgctgagcaataactagca
taacccctttggggcctctaaacgggtcttgaggggttttttg
```

Cebadores de PCR

PPARD	PPARD-G165	GTTGGATCCCAGTACAACCCACAGGTGGC	(SEQ ID NO:___)
	PPARD-A	GTGACTGTCGACTTAGTACATGTCCTTGTAGA	(SEQ ID NO:___)

Ejemplo 9: Selección Bioquímica

El ensayo de selección homogéneo Alpha se usó en el modo agonista para determinar la interacción dependiente de ligando de los PPAR (α, δ, γ) con el péptido coactivador Biotina-PGC-1 (biotina-AHX-DGTPPPQEAEEPSLLKKLLLAPANT-$CONH_2$ (SEQ ID NO: ____), suministrado por Wyeth). Todos los compuestos probados se diluyeron en seriada 1:3 en DMSO para un total de 8 puntos de concentración. Las muestras se separaron con PPAR-LBD etiquetado con His preparado por el Ejemplo 8. Se agregaron cuentecillas del aceptor Ni-quelato que se unen al PPAR-LBD etiquetado con his y se agregaron cuentecillas de donador de estreptavidina que se unen a la biotina del coactivador (Perkin-Elmer #6760619M) de modo que la actividad del agonista se correlaciona con la señal de las cuentecillas de donador y aceptor en proximidad cercana. Cada muestra se preparó al mezclar 1 µl de compuesto y 15 µl de mezcla receptor/péptido 1.33x, incubar durante 15 minutos a temperatura ambiente, y agregar entonces 4 µl de cuentecillas 4x en tampón de ensayo. El tampón de ensayo fue HEPES 50 mM, pH 7.5, KCl 50 mM, DTT 1 mM y 0.8% de

BSA. Las concentraciones finales para cada muestra fueron 25nM de péptido biotina-PGC-1, 20 nM de PPARγ o 10 nM de PPARα o δ, y cada cuentecilla a 5 µg/ml, con el compuesto agregado a la concentración deseada, lo que resulta en DMSO final de 5%. WY-14643 (PPARα), farglitazar (PPARγ) y bezafibrato (PPAR δ) se analizaron como muestras control. Las muestras se incubaron durante 1 hora en la oscuridad a temperatura ambiente antes de tomar la lectura en el lector Fusion alpha o Alpha Quest. La señal versus concentración de compuesto se usó para determinar la EC_{50}. Los datos se expresaron en µMol/L. Los puntos de datos del instrumento Fusion alpha se transfirieron al Assay Explorer® (MDL) para generar una curva y calcular el punto de inflexión de la curva como la EC_{50}.

Ejemplo 10: Ensayos de cotransfección

Este ensayo sirve para confirmar la actividad bioquímica observada (Ejemplo 9) sobre la modulación de la o las moléculas objetivo pretendidas en el nivel celular. Células 293T (ATCC) se cultivaron a 1-2 x 10^6 células por pozo de una placa de 6 pozos (Corning 3516) en 3 ml de medio de crecimiento (medio eagle de Dulbecco, Mediatech, con 10% de FBS). Estas se incubaron a 80-90% de confluencia y el medio se removió al aspirar. Estas células se transfectaron con PPAR LBD y luciferasa de modo que el agonista resultara en activación de la luciferasa. La medición de la actividad de luciferasa de las células transfectadas, tratadas con los compuestos, se correlaciona directamente con la actividad del agonista. A 100 µl de medio de crecimiento sin suero se agregó 1 µg de pFR-luc (Stratagene, número de catálogo 219050), 6 µl de Metafecteno (Biontex, Inc.) y 1 mg del pGal4-PPAR-LBD(α, γ o δ del Ejemplo 8). Este se mezcló al invertir, entonces se incubó durante 15 a 20 minutos a temperatura ambiente, y se diluyó con 900 µl de medio de crecimiento sin suero. Esto se colocó sobre las células 293T y se incubó durante 4-5 horas a 37°C en una incubadora de CO_2. El medio de transfección se removió al aspirar y se agregó medio de crecimiento y las células se incubaron durante 24 horas. Las células entonces se suspendieron en 5 ml de medio de crecimiento y se diluyeron con 15 ml adicionales de medio de crecimiento. Para cada muestra de prueba, se transfirieron 95 µl de las células transfectadas por pozo de una placa de cultivo de 96 pozos. Los compuestos probados se diluyeron en DMSO hasta 200x la concentración final deseada. Esto se diluyó 10x con medio de crecimiento y se agregaron 5

µl a los 95 µl de células transfectadas. La placa se incubó durante 24 horas a 37°C en una incubadora de CO_2. La mezcla de reacción de luciferasa se preparó al mezclar un 1 ml de tampón de lisis, 1 ml de sustrato en tampón de lisis y 3 ml de tampón de reacción (Roche Diagnostics Luciferase assay kit #1814036). Para cada pozo de muestra, el medio de crecimiento se reemplazó con 50 ml de la mezcla de reacción y la placa se agitó durante 15-20 minutos, y la luminiscencia se midió en un lector de placas Victor2 V (Perkin Elmer). La señal versus concentración de compuesto se usó para determinar la EC_{50}.

Este ensayo sirve para confirmar la actividad bioquímica observada (Ejemplo 9) sobre la modulación de la o las moléculas objetivo pretendidas en el nivel celular. Los compuestos que tienen una EC_{50} de menos de o igual a 1 µM en cualquier ensayo bioquímico del Ejemplo 9, o este ensayo basado en células, para por lo menos uno de los PPARs, se muestran en la Tabla 8. Compuestos adicionales descritos en la publicación PCT WO 2005/009958 demostraron una EC_{50} de menos de o igual a 1 µM para por lo menos uno de los PPARs. Estos fueron los compuestos 1, 22, 29, 41, 43, 45, 47, 51, 53, 55, 59, 63, 65, 67, 69, 77, 79, 82, 83, 90, 92, 94, 101, 102, 107, 108, 109, 110, 111, 112, 113, 115 y 116 de la Tabla 1 que comienza en la página 184 de la solicitud publicada, y el compuesto 119 (Ejemplo 81), compuesto 121 (Ejemplo 99) y Compuesto 126 (Ejemplo 103) de la solicitud.

Tabla 8. Compuestos que tienen una EC_{50} de menos de o igual a 1 μM en por lo menos uno de los ensayos de actividad de PPARα, PPARγ y PPARδ.

P-0001, P-0002, P-0003, P-0004, P-0007, P-0008, P-0010, P-0015, P-0016, P-0017, P-0018, P-0019, P-0020, P-0022, P-0026, P-0031, P-0032, P-0033, P-0034, P-0035, P-0037, P-0039, P-0046, P-0048, P-0049, P-0050, P-0051, P-0052, P-0053, P-0054, P-0055, P-0056, P-0057, P-0058, P-0060, P-0063, P-0064, P-0066, P-0067, P-0068, P-0069, P-0070, P-0071, P-0072, P-0080, P-0082, P-0092, P-0099, P-0100, P-0108, P-0144, P-0147, P-0149, P-0150, P-0151, P-0155, P-0158, P-0159, P-0160, P-0163, P-0165, P-0166, P-0167, P-0174, P-0175, P-0188, P-0203, P-0207, P-0208, P-0209, P-0210, P-0214, P-0215, P-0219, P-0220, P-0221, P-0222, P-0223, P-0224, P-0225, P-0226, P-0227, P-0228, P-0229, P-0230, P-0231, P-0236, P-0270, P-0276, P-0277, P-0278, P-0279, P-0280, P-0282, P-0283, P-0284, P-0285, P-0286, P-0289, P-0290, P-0293, P-0294, P-0295, P-0296, P-0297, P-0298, P-0308, P-0309, P-0310, P-0311, P-0315, P-0316, P-0317, P-0318, P-0319, P-0320, P-0322, P-0323, P-0324, P-0326, P-0327, P-0328, P-0329, P-0330, P-0331, P-0334, P-0335, P-0337, P-0340, P-0341, P-0343, P-0344, P-0347, P-0351, P-0356, P-0359, P-0360, P-0361, P-0362, P-0363, P-0364, P-0371, P-0373, P-0376, P-0377, P-0378, P-0379, P-0380, P-0381, P-0382, P-0383, P-0384, P-0385, P-0386, P-0387, P-0388, P-0389, P-0395, P-0396, P-0398, P-0399, P-0400, P-0401, P-0402, P-0404, P-0405, P-0408, P-0409, P-0411, P-0412, P-0413, P-0415, P-0419, P-0420, P-0422, P-0423, P-0424, P-0427, P-0430, P-0431, P-0434, P-0435, P-0436, P-0437, P-0438, P-0439, P-0440, P-0446, P-0447, P-0448, P-0449, P-0450, P-0451, P-0452, P-0454, P-0455, P-0456, P-0458, P-0462, P-0463, P-0464, P-0465, P-0466, P-0467, P-0468, P-0470, P-0471, P-0472, P-0473, P-0474, P-0475, P-0476, P-0477, P-0478, P-0479, P-0481, P-0482, P-0483, P-0484, P-0485, P-0486, P-0487, P-0488, P-0489, P-0490, P-0491, P-0492, P-0493, P-0494, P-0495, P-0496, P-0497, P-0498, P-0499, P-0501, P-0502, P-0503, P-0504, P-0505, P-0506, P-0508, P-0509, P-0510, P-0511, P-0512, P-0513, P-0514, P-0515, P-0516, P-0517, P-0518, P-0519, P-0520, P-0521, P-0523, P-0524, P-0529, P-0530, P-0533, P-0535, P-0537, P-0538, P-0539, P-0540, P-0541, P-0549, P-0552, P-0553, P-0555, P-0560, P-0561, P-0564, P-0566, P-0567, P-0568, P-0570, P-0572

Todas las patentes y otras referencias citadas en la especificación son indicativas del nivel de experiencia de aquellos experimentados en la técnica a la cual pertenece la invención, y se incorporan para referencia en sus totalidades, incluyendo cualesquiera tablas y figuras, en la misma magnitud como si cada referencia se hubiera incorporado para referencia en su totalidad individualmente.

Alguien experimentado en la técnica puede apreciar fácilmente que la presente invención se adapta bien para obtener los fines y ventajas mencionadas, así como aquellas inherentes en la misma. Los métodos, variaciones y composiciones descritas en la presente, como representativos actualmente de las modalidades preferidas, son ejemplares y no se pretenden como limitaciones en el alcance de la invención. Los cambios en la misma y otros usos se les ocurrirán a aquellos experimentados en la técnica, los cuales se abarcan dentro del espíritu de la invención, y se definen por el alcance de las reivindicaciones.

Será fácilmente aparente para alguien experimentado en la técnica, que diversas sustituciones y modificaciones pueden hacerse a la invención descrita en la presente, sin apartarse del alcance y espíritu de la invención. Por ejemplo, pueden hacerse variaciones a los compuestos ejemplares de I, Ia, Ib, II o III para proporcionar compuestos activos adicionales. De esta manera, tales modalidades adicionales están dentro del alcance de la presente invención y las siguientes reivindicaciones.

La invención descrita en forma ilustrativa en la presente, puede practicarse adecuadamente en ausencia de cualquier elemento o elementos, limitación o limitaciones, que no se describan específicamente en la presente. De esta manera, por ejemplo, en cada caso en la presente, cualquiera de los términos "que comprende", "que consiste esencialmente de" y "que consiste de", puede reemplazarse con cualquiera de los otros dos términos. Los términos y expresiones que se han empleado se usan como términos de descripción y no de limitación, y no hay intención, en el uso de tales términos y expresiones, de excluir cualesquier equivalentes de las características mostradas y descritas o porciones de las mismas, pero se reconoce que diversas modificaciones son posibles dentro del alcance de la invención reclamada. De esta manera, debe entenderse que, aunque la presente invención se ha descrito específicamente por modalidades

preferidas y características opcionales, la modificación y variación de los conceptos descritos en la presente puede consultarse por aquellos experimentados en la técnica, y que tales modificaciones y variaciones se consideran dentro del alcance de esta invención como se define por las reivindicaciones adjuntas.

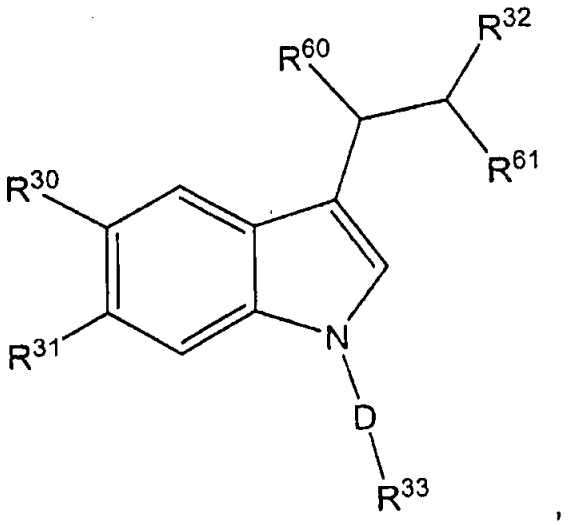
Además, donde las características o aspectos de la invención se describen en términos de grupos Markush u otra agrupación de alternativas, aquellos experimentados en la técnica reconocerán que la invención se describe por esto en términos de cualquier miembro individual o subgrupo de miembros del grupo Markush u otro grupo.

También, a menos que se indique lo contrario, donde se proporcionan diversos valores numéricos para las modalidades, se describen modalidades adicionales al tomar cualesquier 2 valores diferentes como los puntos extremos de un intervalo. Tales intervalos también se encuentran dentro del alcance la invención descrita.

De esta manera, modalidades adicionales se encuentran dentro del alcance de la invención y dentro de las siguientes reivindicaciones.

REIVINDICACIONES

1. Un compuesto que tiene la estructura química

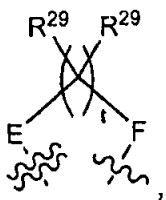


,

todas las sales, profármacos, tautómeros e isómeros de los mismos,

en donde:

R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, y $-S(O)_nR^{41}$; o

R^{30} y R^{31} se combinan para formar un anillo fusionado, en donde los R^{30} y R^{31} combinados son de la fórmula 

, en donde  indica el punto de unión de R^{30} al anillo indol y  indica el punto de unión de R^{31} al anillo indol;

E y F se seleccionan independientemente del grupo que consiste de $CR^{29}R^{29}$, O, $S(O)_2$ y NR^{44};

R^{29} en cada caso, se selecciona independientemente del grupo que consiste de hidrógeno, flúor, alquilo inferior opcionalmente sustituido con flúor, alcoxi inferior opcionalmente sustituido con flúor y alquiltio inferior opcionalmente sustituido con flúor;

R^{44} es hidrógeno o alquilo inferior;

t es 1 ó 2;

R^{32} se selecciona del grupo que consiste de $C(O)OR^{26}$, $-C(O)NR^{27}R^{28}$ y un isóstero de ácido carboxílico;

R^{33} es $L-R^{42}$ o heteroarilo opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-NO_2$, -CN $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

L es $-(CR^{51}R^{52})_m-$ o $-CR^{55}=CR^{56}-$;

D es $-CR^{51}R^{52}-$ o $-S(O)_2-$;

R^{34} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{34} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al O de $-OR^{34}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{34} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al O de $-OR^{34}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)R^{40}$ y $-C(Z)NR^{38}R^{39}$;

R^{35} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{35} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al S de $-SR^{35}$ o al O de $-OR^{35}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{35} es

alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al S de $-SR^{35}$ o al O de $-OR^{35}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{36} y R^{37} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{36} y/o R^{37} son alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $-NR^{36}R^{37}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{36} y/o R^{37} son alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $-NR^{36}R^{37}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$ y $-S(O)_2NR^{38}R^{39}$;

R^{38} y R^{39} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{38} y/o R^{39} son alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $NR^{38}R^{39}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{38} y/o R^{39} son alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $NR^{38}R^{39}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{40} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{40} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une a -C(Z)-, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{40} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une a -C(Z)-

, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, y $-OR^{35}$;

R^{41} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{41} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une a $-S(O)_n-$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{41} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une a $-S(O)_n-$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{42} es arilo o heteroarilo, en donde arilo o heteroarilo se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-NO_2$, -CN - OR^{34}, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

R^{51} y R^{52} se seleccionan independientemente del grupo que consiste de hidrógeno, flúor, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

o cualesquiera dos de R^{51} y R^{52} en el mismo carbono o en carbonos adyacentes pueden combinarse para formar un cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido o heterocicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido;

R^{55} y R^{56} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido; o

R^{55} y R^{56} se combinan para formar un cicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido o heterocicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido;

R^{60} y R^{61} son cada uno hidrógeno, o R^{60} y R^{61} se combinan para formar cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido;

R^{26} se selecciona del grupo que consiste de hidrógeno, alquilo inferior, fenilo, heteroarilo monocíclico de 5-7 miembros, cicloalquilo monocíclico de 3 a 7 miembros y heterocicloalquilo monocíclico de 5-7 miembros, en donde fenilo, heteroarilo monocíclico, cicloalquilo monocíclico y heterocicloalquilo monocíclico se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior, y alquiltio inferior sustituido con flúor, y en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, -OH, $-NH_2$, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor, con la condición, sin embargo, de que cuando R^{26} es alquilo inferior, cualquier sustitución en el carbono del alquilo inferior enlazado al O de OR^{26} es flúor;

R^{27} y R^{28} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior, fenilo, heteroarilo monocíclico de 5-7 miembros, cicloalquilo monocíclico de 3-7 miembros y heterocicloalquilo monocíclico de 5-7 miembros, en donde fenilo, heteroarilo monocíclico, cicloalquilo monocíclico y heterocicloalquilo monocíclico se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor, y en donde el alquilo inferior se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, -OH, $-NH_2$, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor, con la condición, sin embargo, de que cuando R^{27} y/o R^{28} es alquilo inferior, cualquier sustitución en el carbono del alquilo inferior enlazado al N de $NR^{27}N^{28}$ es flúor; o

R^{27} y R^{28}, junto con el nitrógeno al cual se unen, forman un heterocicloalquilo monocíclico de 5-7 miembros o un heteroarilo monocíclico que contiene nitrógeno de 5 ó 7 miembros, en donde el heterocicloalquilo monocíclico o heteroarilo que contiene nitrógeno monocíclico se sustituye opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, $-NH_2$, alquilo inferior, alquilo inferior sustituido con flúor, alcoxi inferior, alcoxi inferior sustituido con flúor, alquiltio inferior y alquiltio inferior sustituido con flúor;

n es 1 ó 2;

m es 1, 2 ó 3; y

Z es O o S.

con la condición, sin embargo, de que cuando D es $-S(O)_2-$, R^{30} es $-OCH_3$, R^{31} es H y R^{32} es COOH o $COOCH_3$, entonces R^{33} no es tiofenilo no sustituido

2. El compuesto de conformidad con la reivindicación **1**, caracterizado porque D es $-CR^{51}R^{52}-$.

3. El compuesto de conformidad con la reivindicación **1**, caracterizado porque D es $-S(O)_2-$.

4. El compuesto de conformidad con la reivindicación **1**, caracterizado porque R^{33} es heteroarilo sustituido.

5. El compuesto de conformidad con la reivindicación **4**, caracterizado porque:

R^{33} es heteroarilo sustituido con uno o más sustituyentes seleccionados del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^{34}, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

en donde en donde uno de R^{36} y R^{37} se selecciona del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -

$C(Z)R^{40}$, $-C(Z)NR^{38}R^{39}$, $-S(O)_2R^{41}$ y $-S(O)_2NR^{38}R^{39}$, y el otro de R^{36} y R^{37} es hidrógeno o alquilo inferior;

en donde uno de R^{38} y R^{39} se selecciona del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, y el otro de R^{38} y R^{39} es hidrógeno o alquilo inferior; y

en donde R^{34}, R^{35}, R^{40} y R^{41} se seleccionan independientemente del grupo que consiste de alquilo inferior, en donde el alquilo inferior se sustituye con arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido.

6. El compuesto de conformidad con la reivindicación **5**,

en donde

R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido, ariloxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, o

R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2 y cada R^{29} es hidrógeno.

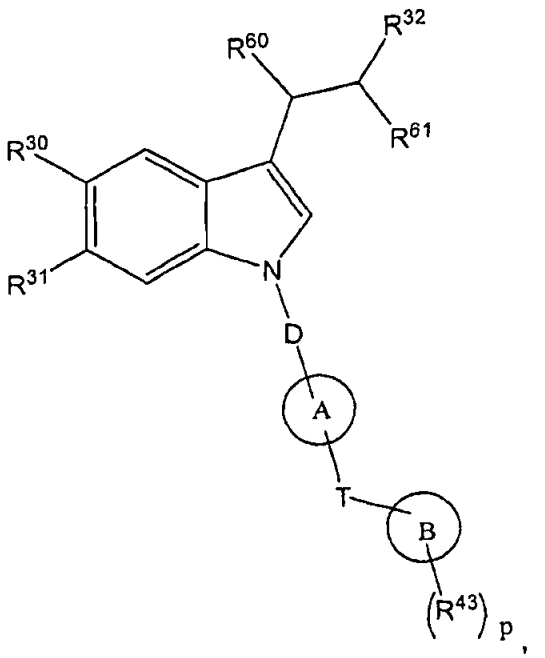
7. El compuesto de conformidad con la reivindicación **6**, caracterizado porque R^{31} es hidrógeno.

8. El compuesto de conformidad con la reivindicación **6**, caracterizado porque R^{30} y R^{31} en forma independiente son alcoxi inferior opcionalmente sustituido, o R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2 y cada R^{29} es hidrógeno.

9. El compuesto de conformidad con la reivindicación **6**, caracterizado porque D es $-S(O)_2-$.

10. El compuesto de conformidad con la reivindicación **6**, caracterizado porque D es $-CH_2-$.

11. Un compuesto que tiene la estructura química

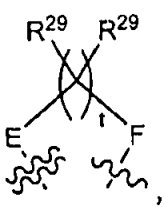


todas las sales, profármacos, tautómeros e isómeros de los mismos,

en donde:

D es $-CR^{51}R^{52}-$ o $-S(O)_2-$;

R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$, y $-S(O)_nR^{41}$; o

R^{30} y R^{31} se combinan para formar un anillo fusionado, en donde los R^{30} y R^{31} combinados son de la fórmula 

, en donde  indica el punto de unión de R^{30} al

anillo indol y  indica el punto de unión de R^{31} al anillo indol;

E y F se seleccionan independientemente del grupo que consiste de $CR^{29}R^{29}$, O, $S(O)_2$ y NR^{44};

E y F se seleccionan independientemente del grupo que consiste de $CR^{29}R^{29}$, O, $S(O)_2$ y NR^{44};

R^{29} en cada caso, se selecciona independientemente del grupo que consiste de hidrógeno, flúor, alquilo inferior opcionalmente sustituido con flúor, alcoxi inferior opcionalmente sustituido con flúor y alquiltio inferior opcionalmente sustituido con flúor;

R^{44} es hidrógeno o alquilo inferior;

t es 1 ó 2;

R^{32} se selecciona del grupo que consiste de $C(O)OR^{26}$, $-C(O)NR^{27}R^{28}$ y un isóstero de ácido carboxílico;

R^{60} y R^{61} son cada uno hidrógeno, o R^{60} y R^{61} se combinan para formar cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido;

A es arileno o heteroarileno, en donde el arileno o heteroarileno se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de halógeno, -OH, alquilo inferior, alcoxi inferior y alquiltio inferior, en donde el alquilo inferior y las cadenas alquilo inferior del alcoxi inferior y alquiltio inferior se sustituyen opcionalmente con uno o más sustituyentes seleccionados del grupo que consiste de flúor, -OH, alcoxi inferior y alquiltio inferior, con la condición, sin embargo, de que cualquier sustitución del carbono enlazado al O del alcoxi inferior o S del alquiltio inferior es flúor;

T es un enlace covalente o se selecciona del grupo que consiste de $-(CR^{51}R^{52})_m-$, $-(CR^{51}R^{52})_qO(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{53}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qS(O)_n(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qC(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}C(Z)NR^{54}(CR^{51}R^{52})_r-$, $-(CR^{51}R^{52})_qNR^{54}S(O)_2(CR^{51}R^{52})_r-$, $(CR^{51}R^{52})_qS(O)_2NR^{54}(CR^{51}R^{52})_r-$ y $-(CR^{51}R^{52})_qNR^{54}S(O)_2NR^{54}(CR^{51}R^{52})_r$;

R^{51} y R^{52} se seleccionan independientemente del grupo que consiste de hidrógeno, flúor, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

o cualesquiera dos de R^{51} y R^{52} en el mismo carbono o en carbonos adyacentes pueden combinarse para formar un cicloalquilo monocíclico de 3-7 miembros opcionalmente sustituido o heterocicloalquilo monocíclico de 5-7 miembros opcionalmente sustituido;

m es 1, 2 ó 3;

q y r son independientemente 0, 1 ó 2;

B se selecciona del grupo que consiste de cicloalquilo, heterocicloalquilo, arilo y heteroarilo;

R^{43} en cada caso se selecciona independientemente del grupo que consiste de halógeno, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$;

R^{53} se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{53} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $-NR^{53}-$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{53} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $-NR^{53}-$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_2R^{41}$;

R^{54}, en cada caso, se selecciona independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{54} es alquenilo de 3 a 6

átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $-NR^{54}-$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{54} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $-NR^{54}-$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

p es 0, 1, 2 ó 3;

n es 1 ó 2;

Z es O o S;

R^{34} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{34} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al O de $-OR^{34}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{34} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al O de $-OR^{34}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)R^{40}$ y $-C(Z)NR^{38}R^{39}$;

R^{35} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{35} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al S de $-SR^{35}$ o al O de $-OR^{35}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{35} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al S de $-SR^{35}$ o al O de $-OR^{35}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{36} y R^{37} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente

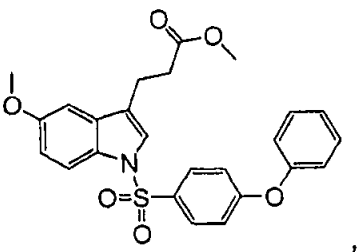
sustituido, con la condición, sin embargo, de que cuando R^{36} y/o R^{37} son alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de -$NR^{36}R^{37}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{36} y/o R^{37} son alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de -$NR^{36}R^{37}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -$C(Z)R^{40}$, -$C(Z)NR^{38}R^{39}$, -$S(O)_2R^{41}$ y -$S(O)_2NR^{38}R^{39}$;

R^{38} y R^{39} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{38} y/o R^{39} son alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une al N de $NR^{38}R^{39}$, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{38} y/o R^{39} son alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une al N de $NR^{38}R^{39}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

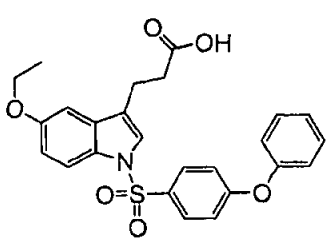
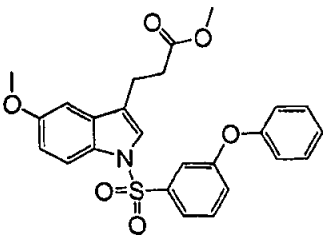
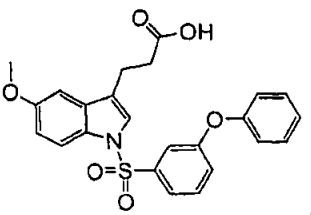
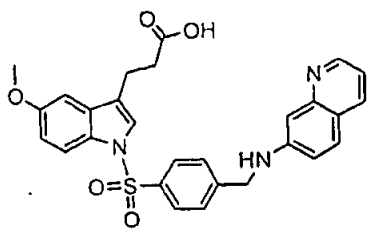
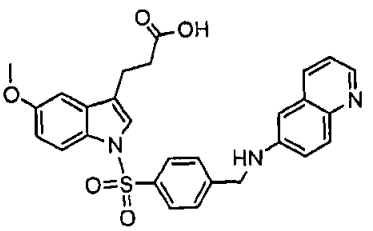
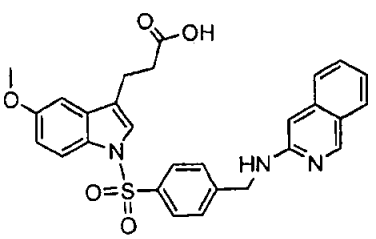
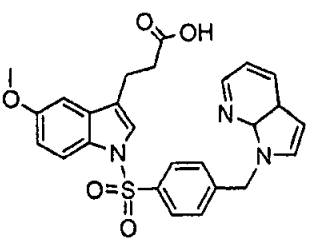
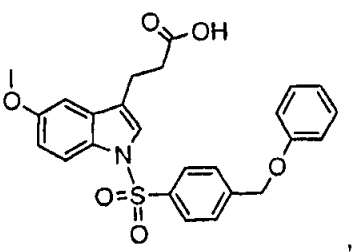
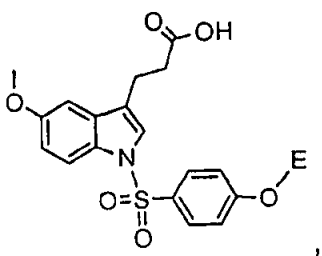
R^{40} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{40} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une a -C(Z)-, alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{40} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une a -C(Z)-, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, -OH, y -OR^{35};

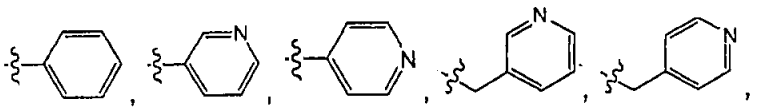
R^{41} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{41} es alquenilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alqueno del mismo se une a -$S(O)_n$-, alquinilo de 3 a 6 átomos de carbono

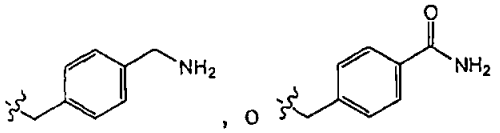
opcionalmente sustituido, con la condición, sin embargo, de que cuando R^{41} es alquinilo de 3 a 6 átomos de carbono opcionalmente sustituido, ningún carbono de alquino del mismo se une a -$S(O)_n$-, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente opcionalmente sustituido y heteroarilo opcionalmente sustituido;



con la condición, sin embargo, de que el compuesto no sea

en donde E es 

 en donde  indica el punto de union de E a O.

12. El compuesto de conformidad con la reivindicación **11**, caracterizado porque A es fenilo y T-B es orto hacia D.

13. El compuesto de conformidad con la reivindicación **12**, caracterizado porque D es $-S(O)_2-$.

14. El compuesto de conformidad con la reivindicación **12**, caracterizado porque D es $-CR^{51}R^{52}-$.

15. El compuesto de conformidad con la reivindicación **11**, caracterizado porque R^{43} se selecciona del grupo que consiste de halógeno, -OH, alquilo inferior opcionalmente sustituido, alquenilo inferior opcionalmente sustituido, alquinilo inferior opcionalmente sustituido, $-OR^{34}$, $-SR^{35}$, $-NR^{36}R^{37}$, $-C(Z)NR^{38}R^{39}$, $-C(Z)R^{40}$, $-S(O)_2NR^{38}R^{39}$ y $-S(O)_nR^{41}$, en donde R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40} y R^{41} son diferentes a un miembro seleccionado del grupo que consiste de cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, o alquilo inferior sustituido con cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido.

16. El compuesto de conformidad con la reivindicación **15**, caracterizado porque R^{30} y R^{31} se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, alcoxi inferior opcionalmente sustituido, ariloxi opcionalmente sustituido, heteroariloxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, o R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2, y cada R^{29} es hidrógeno.

17. El compuesto de conformidad con la reivindicación **16**, caracterizado porque R^{31} es hidrógeno.

18. El compuesto de conformidad con la reivindicación **16**, caracterizado porque R^{30} y R^{31} en forma independiente son alcoxi inferior opcionalmente sustituido, o R^{30} y R^{31} se combinan para formar un anillo fusionado en donde E y F son O, t es 1 ó 2 y cada R^{29} es hidrógeno.

19. El compuesto de conformidad con la reivindicación **11**, caracterizado porque D es $-S(O)_2-$.

20. El compuesto de conformidad con la reivindicación **11**, caracterizado porque D es $-CH_2-$.

21. El compuesto de conformidad con la reivindicación 11, caracterizado porque el compuesto se selecciona del grupo que consiste de ácido 3-{1-[5-(2,4-Dimetoxi-pirimidin-5-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico,

ácido 3-{5-Cloro-1-[5-(2,4-dimetoxi-pirimidin-5-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico,

ácido 3-{1-[5-(6-Benciloxi-piridin-3-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico,

ácido 3-{1-[5-(2,6-Dimetoxi-piridin-3-il)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico,

ácido 3-{1-[5-(4-Benciloxi-fenil)-tiofen-2-sulfonil]-5-etoxi-1H-indol-3-il}-propiónico,

ácido 3-{5-Etoxi-1-[5-(6-metoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico,

ácido 3-{1-[5-(3-Cloro-4-fluoro-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico,

ácido 3-{1-[5-(3-Fluoro-4-metoxi-fenil)-tiofen-2-sulfonil]-5-metoxi-1H-indol-3-il}-propiónico,

ácido 3-{5-Metoxi-1-[5-(6-metoxi-piridin-3-il)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico,

ácido 3-{5-Metoxi-1-[5-(4-trifluorometoxi-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-

propiónico,

ácido 3-{1-[5-(4-Etoxi-fenil)-tiofen-2-sulfonil]-5-metox-1H-indol-3-il}-propiónico,

ácido 3-{5-Metoxi-1-[5-(4-trifluorometil-fenil)-tiofen-2-sulfonil]-1H-indol-3-il}-propiónico,

ácido 3-[5-Etoxi-1-(4'-propil-bifenil-2-sulfonil)-1H-indol-3-il]-propiónico,

ácido 3-[1-(3',4'-Dimtil-bifenil-2-sulfonil)-5-etoxi-1H-indol-3-il]-propiónico,

ácido 3-[5-Etoxi-1-(5-metil-3-p-tolil-tiofen-2-sulfonil)-1H-indol-3-il]-propiónico,

ácido 3-[1-(4'-Trifluorometil-bifenil-3-sulfonil)-1H-indol-3-il]-propiónico, y

ácido 3-[5-Metoxi-1-(4'-trifluorometil-bifenil-3-sulfonil)-1H-indol-3-il]-propiónico.

22. Un método para tratar a un sujeto que adolece o está en riesgo de una enfermedad o padecimiento para el cual la modulación del PPAR proporciona un beneficio terapéutico, caracterizado porque comprende administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto de conformidad con la Reivindicación **1**.

23. Un método para tratar a un sujeto que adolece o está en riesgo de una enfermedad o padecimiento para el cual la modulación del PPAR proporciona un beneficio terapéutico, caracterizado porque comprende administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto de conformidad con la Reivindicación **11**.

24. El método de conformidad con la reivindicación **22** ó **23**, caracterizado porque el compuesto se aprueba para su administración a un humano.

25. El método de conformidad con la reivindicación **22** ó **23**, caracterizado porque la enfermedad o padecimiento es una enfermedad o padecimiento mediado por PPAR.

26. El método de conformidad con la reivindicación **22** ó **23**, caracterizado porque la enfermedad o padecimiento se selecciona del grupo que consiste de obesidad, condición de sobrepeso, bulimia, anorexia nerviosa, hiperlipidemia, dislipidemia, hipoalfalipoproteinemia, hipertrigliceridemia, hipercolesterolemia, baja HDL, Síndrome Metabólico, diabetes mellitus Tipo II, diabetes Tipo I, hiperinsulinemia, intolerancia a la glucosa, resistencia a la insulina, una complicación diabética de neuropatía, nefropatía, retinopatía, úlcera de pies por diabetes o cataratas, hipertensión, enfermedad cardiaca coronaria, falla cardiaca, falla cardiaca congestiva,

ateroesclerosis, arterioesclerosis, apoplejía, enfermedad cerebrovascular, infarto del miocardio, enfermedad vascular periférica, vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis, hepatitis, eccema, psoriasis, dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, trombosis, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático o inflamatorio, infertilidad y cáncer.

27. Una composición, caracterizada porque comprende: un portador farmacéuticamente aceptable; y

un compuesto de conformidad con la Reivindicación **1**,

28. Una composición, caracterizada porque comprende: un portador farmacéuticamente aceptable; y

un compuesto de conformidad con la Reivindicación **11**,

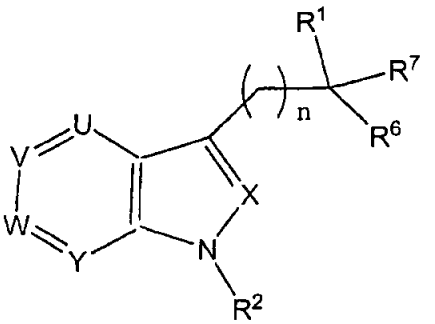
29. Un equipo, caracterizado porque comprende un compuesto de conformidad con la reivindicación **1**.

30. Un equipo, caracterizado porque comprende un compuesto de conformidad con la reivindicación **11**.

31. Un equipo, caracterizado porque comprende una composición de conformidad con la reivindicación **27**.

32. Un equipo, caracterizado porque comprende una composición de conformidad con la reivindicación **28**.

33. Un método para tratar a un sujeto que adolece o está en riesgo de una enfermedad o padecimiento para el cual la modulación de PPAR proporciona un beneficio terapéutico, caracterizado porque comprende: administrar al sujeto una cantidad terapéuticamente efectiva de un modulador de PPAR que tiene la estructura química de



,

todas las sales, profármacos, tautómeros e isómeros de los mismos,xxxxx

en donde:

U, V, W, X, y Y son independientemente N o CR^8, en donde, como máximo, dos de U, V, W, y Y son N;

R^1 se selecciona del grupo que consiste de $C(O)OR^{16}$ y un isóstero de ácido carboxílico;

R^2 se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$;

R^6 y R^7 se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido; o

R^6 y R^7 se combinan para formar un cicloalquilo monocíclico de 3-7 miembros o heterocicloalquilo monocíclico de 5-7 miembros;

R^8 se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido,

heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^9, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$;

R^9 se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{10} y R^{11} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido; o

R^{10} y R^{11} junto con el nitrógeno al cual se unen, forman un heterocicloalquilo monocíclico de 5-7 miembros o un heteroarilo que contiene nitrógeno monocíclico de 5 ó 7 miembros;

R^{16} se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{20} se selecciona del grupo que consiste de $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{21} se selecciona del grupo que consiste de $-OR^{17}$, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{12}, R^{13}, R^{14} y R^{15} se seleccionan independientemente del grupo que consiste de alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

R^{17} se selecciona del grupo que consiste de alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido y $-C(O)R^{18}$;

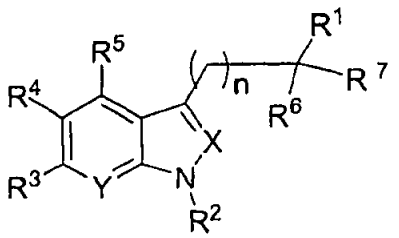
R^{18} se selecciona del grupo que consiste de hidrógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido;

Z es O o S; y

n = 0, 1 ó 2.

en donde la enfermedad o padecimiento se selecciona del grupo que consiste de vitiligo, uveítis, pénfigo foliáceo, miositis de cuerpos de inclusión, polimiositis, dermatomiositis, esclerodermia, enfermedad de Grave, enfermedad de Hashimoto, enfermedad crónica injerto contra huésped, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, lupus eritematoso sistémico, Síndrome de Sjogren, esclerosis múltiple, asma, enfermedad pulmonar obstructiva crónica, enfermedad renal poliquística, síndrome ovárico poliquístico, pancreatitis, nefritis y hepatitis), dermatitis, cicatrización defectuosa, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, lesión de médula espinal, encefalomielitis diseminada aguda, síndrome de Guillain-Barre, infarto del intestino grueso o delgado, insuficiencia renal, disfunción eréctil, incontinencia urinaria, vejiga neurogénica, inflamación oftálmica, degeneración macular, neovascularización patológica, infección por HCV, infección por HIV, infección por Helicobacter pylori, dolor neuropático, dolor inflamatorio e infertilidad

34. El método de conformidad con la reivindicación **33**, caracterizado porque el modulador de PPAR tiene la estructura química de



en donde:

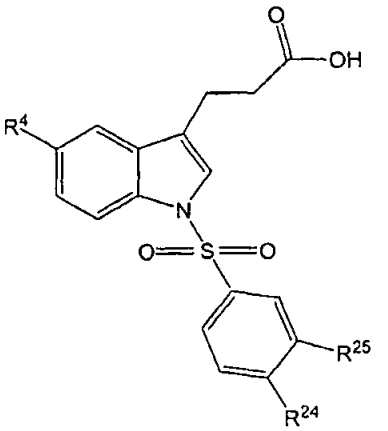
U es CR^8, en donde R^8 is R^5;

V es CR^8, en donde R^8 is R^4;

W es CR^8, en donde R^8 is R^3;

R^3, R^4 y R^5 se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, $-CH_2-CR^{12}=CR^{13}R^{14}$, $-CH_2-C\equiv CR^{15}$, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^9, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$.

35. El método de conformidad con la reivindicación **33**, caracterizado porque el modulador de PPAR tiene la estructura química de



en donde:

U es CR^8, en donde R^8 is H;

V es CR^8, en donde R^8 is R^4;

W es CR^8, en donde R^8 is H;

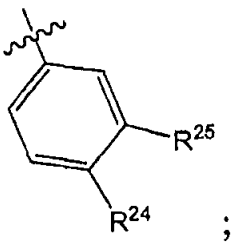
X es CR^8, en donde R^8 is H;

Y es CR^8, en donde R^8 is H;

n es 1;

R^1 es -COOH;

R^6 y R^7 son hidrógeno;


;

R^2 es $-S(O)_2R^{21}$, en donde R^{21} es

R^4 se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, OR^9, $-SR^9$, $-NR^{10}R^{11}$, $-C(Z)NR^{10}R^{11}$, $-C(Z)R^{20}$, $-S(O)_2NR^{10}R^{11}$ y $-S(O)_2R^{21}$;

R^{24} se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido, $-OR^{19}$ y $-O(CH_2)_pO$-arilo;

p es 1, 2, 3 ó 4;

R^{25} se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo inferior opcionalmente sustituido y $-OR^{19}$; o

R^{24} y R^{25} se combinan para formar cicloalquilo, heterocicloalquilo, arilo o heteroarilo fusionado con el anillo fenilo; y

R^{19} se selecciona del grupo que consiste de alquilo inferior opcionalmente sustituido y arilo opcionalmente sustituido.

36. El método de conformidad con la reivindicación **33**, **34** ó **35**, caracterizado porque la enfermedad o padecimiento se selecciona del grupo que consiste de enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular.

37. El método de conformidad con la Reivindicación **22** ó **23**, caracterizado porque la enfermedad o padecimiento se selecciona del grupo que consiste de enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, artritis reumatoide, síndrome de inflamación del intestino, enfermedad de Crohn, esclerosis múltiple, infertilidad, asma, enfermedad pulmonar obstructiva crónica y degeneración macular.

LISTA DE SECUENCIAS

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SEQ ID NO:2 (GenBank NP_005027)

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 361 famkfnalel ddsdislfva aiiccgdrpg llnvghiekm qegivhvlrl hlqsnhpddi
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SEQ ID NO:3 (GenBank NM_015869)

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1861 aaa
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SEQ ID NO:4 (GenBank NP_056953)

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 181 rihkksrnkc qycrfqkcla vgmshnairf grmpqaekek llaeissdid qlnpesadlr
 241 alakhlydsy iksfpltkak arailtgktt dkspfviydm nslmmgedki kfkhitplqe
 301 qskevairif qgcqfrsvca vqeiteyaks ipgfvnldln dqvtllkygv heiiytmlas
 361 lmnkdgvlis egqgfmtref lkslrkpfgd fmepkfefav kfnaleldds dlaifiavii
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SEQ ID NO:5 (GenBank NM_006238)

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3121 cacctccccc tccccggcca catgccgcgt ccctgccccg acccgggtct ggtgctgagg
3181 atacagctct tctcagtgtc tgaacaatct ccaaaattga aatgtatatt tttgctagga
3241 gccccagctt cctgtgtttt taatataaat agtgtacaca gactgacgaa actttaaata
3301 aatgggaatt aaatatttaa aaaaaaaa
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SEQ ID NO:6 (GenBank NP_006229)

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 241 isvhvfyrcq cttvetvrel tefaksipsf sslflndqvt llkygvheai famlasivnk
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 421 kktetetslh pllqeiykdm y
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039363-2903 RJW Sec 3CK Plexxikon resp. written opinion due: 7/24/07 490

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

(PCT Rule 44.1)

To:
FOLEY & LARDNER LLP
Attn. Warburg, Richard J.
P.O. Box 80278
San Diego, CA 92138-0278
ETATS-UNIS D'AMERIQUE

RECEIVED
MAY 02 2007
I.P. DEPT.
FOLEY & LARDNER

Date of mailing *(day/month/year)*	24/04/2007
Applicant's or agent's file reference: 039363-2903	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US2006/034747	International filing date *(day/month/year)*: 06/09/2006
Applicant: PLEXXIKON, INC.	

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

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

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

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

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

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

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

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

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

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

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

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Federico Bonomelli

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
039363-2903		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2006/034747	06/09/2006	07/09/2005
Applicant		
PLEXXIKON, 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 6 sheets.

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

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

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

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

4. With regard to the **title**,
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   1,3-DISUBSTITUTED INDOLE DERIVATIVES FOR USE AS PPAR MODULATORS

5. With regard to the **abstract**,
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/034747

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [ ] contained in the international application as filed

   [ ] filed together with the international application in electronic form

   [X] furnished subsequently to this Authority for the purpose of search

2. [ ] 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.

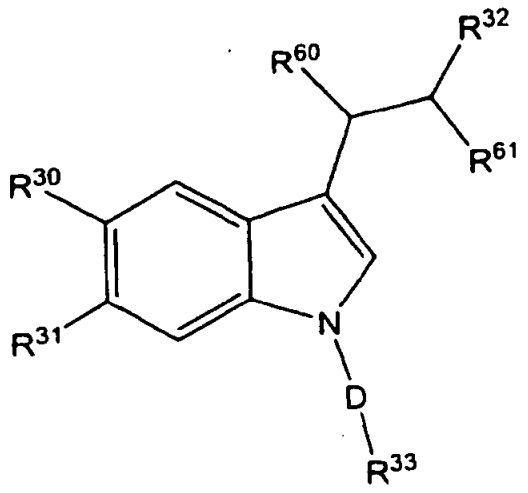
3. Additional comments:

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US2006/034747

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

Compounds are described that are active on PPARs, including pan-active compounds and compounds selective for any one or any two of PPARα, PPARγ and PPARδ. Also described are methods of use of the compounds in treating various diseases.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/034747

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/14 C07D413/14 A61K31/405 A61P3/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/009958 A (PLEXXIKON INC [US]; ARNOLD JAMES [US]; ARTIS DEAN R [US]; HURT CLARENC) 3 February 2005 (2005-02-03) cited in the application the whole document	1-37

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2007	24/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Johnson, Claire

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/034747

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 22-26, 33-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

mation on patent family members

ernational application No
PCT/US2006/034747

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005009958 A	03-02-2005	AU 2004259738 A1	03-02-2005
		BR PI0412684 A	03-10-2006
		CA 2532403 A1	03-02-2005
		EP 1648867 A1	26-04-2006
		KR 20060112710 A	01-11-2006

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/034747	06.09.2006	07.09.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D409/14 C07D413/14 A61K31/405 A61P3/10

Applicant
PLEXXIKON, 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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

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

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

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

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

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Johnson, Claire Telephone No. +49 89 2399-8287

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/034747

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☒ furnished subsequently to this Authority for the purposes of search.

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/US2006/034747

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. 22-26,33-37

because:

☒ the said international application, or the said claims Nos. 22-26,33-37 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/034747

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

1. Statement

Novelty (N)	Yes:	Claims	12-14, 21
	No:	Claims	1-11, 15-20, 22-37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-21,27-32
	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

III. Non-establishment of opinion

Claims 22-26 and 33-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

The claims include isomers of the compounds of the general formulae. The term isomers includes constitutional isomers, positional isomers, etc. There is however no support or disclosure (Articles 5 and 6 PCT) in the application for compounds which do not have the structure given in the formulae of the claims, i.e. an indole core substituted at the 3-position by a carboxylic acid group. No search or examination will be performed for isomers of the present formulae.

The term prodrug is not considered to define the matter for which protection is sought in a clear manner as required by Article 6 PCT. There are many possible functional groups present in the compound of formula I. There is no information in the application or the prior art as to which functional groups in which positions may be derivatised to give compounds having the attributes of prodrugs (i.e. compounds which are inactive per se, and which are broken down in the body to give active compounds). The skilled man would only be able to ascertain whether particular compounds were within the scope of claim 1 by performing in vivo tests, which is considered to go beyond the routine experimentation to be reasonably expected of him.

V. Reasoned statement

Reference is made to the following document:
D1: WO2005/009958

Novelty

D1 discloses compounds of formula (I) useful as PPAR modulators. Formula (I) encompasses the subject matter of all the present claims. It must be noted that the disclosure of this document is not confined to the examples but embraces the general formulae as well, and that novelty cannot therefore be established by merely

excluding the specific examples given in this document. As D1 does not appear to specifically disclose the possibility that the R^2 optionally substituted aralkyl group is ortho-substituted by a group equivalent to present T-B, claims 12-14 may be considered a novel selection from D1, as may the specific compounds of present claim 21.
Claims 1-11, 15-20 and 22-37 do not fulfil the requirements of Article 33(2) PCT.

Inventive step

In view of their lack of novelty, claims 1-11, 15-20 and 22-37 cannot be inventive.
Re. claims 12 and 21:
The technical problem underlying these claims appears to be the provision of PPAR modulators. D1 describes compounds of a general formula encompassing the subject matter of claims 12 and 12 for use as PPAR modulators. It would be obvious for the skilled person to solve this problem by selecting compounds already generically known from D1 to have the desired activity.
Claims 1-37 do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-21 and 27-32 fulfil the requirements of Article 33(4) PCT.
No unified criteria exist in the PCT Contracting States for assessing whether present claims 22-26 and 33-37 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII. Certain observations

Claim 11 contains two moieties defined as E. Claims 34 and 35 contain definitions of moieties that are not present in the formulae.

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(19) World Intellectual Property Organization
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(21) International Application Number:
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(72) Inventors; and

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(74) Agents: **WARBURG, Richard J.** et al.; Foley & Lardner LLP, P.O. Box 80278, San Diego, CA 92138-0278 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: 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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

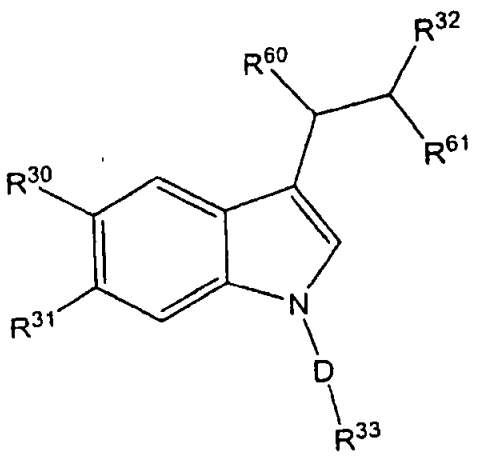
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
13 September 2007

[Continued on next page]

(54) Title: 1, 3-DISUBSTITUTED INDOLE DERIVATIVES FOR USE AS PPAR MODULATORS



(57) Abstract: Compounds are described that are active on PPARs, including pan-active compounds and compounds selective for any one or any two of PPARα, PPARγ and PPARδ. Also describe are methods of use of the compounds in treating various diseases.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/034747

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/14 C07D413/14 A61K31/405 A61P3/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/009958 A (PLEXXIKON INC [US]; ARNOLD JAMES [US]; ARTIS DEAN R [US]; HURT CLARENC) 3 February 2005 (2005-02-03) cited in the application the whole document	1-37

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2007	24/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, Claire

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/034747

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 22-26, 33-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/034747

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005009958 A	03-02-2005	AU 2004259738 A1	03-02-2005
		BR PI0412684 A	03-10-2006
		CA 2532403 A1	03-02-2005
		EP 1648867 A1	26-04-2006
		KR 20060112710 A	01-11-2006

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-033466- -00000-0000

Fecha: 2008-04-03 16:00:53 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 508

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

FOO B

Firma Responsable

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
PLEXXIKON, INC

REFERENCIA	Radicación No.	08 33466
	Solicitud internacional	PCT/US2006/034747
	Fecha inicio fase nacional	07/04/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5953

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 MAYO 2008
adpa11