08-7227

CSA054883

08-7227

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

Organizacion y
Digitalizacion CSA Ltda

Delegatura de Propiedad Industrial

División de Nuevas Creciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

EXPEDIENTE No. 08-7227

TÍTULO MODULADORES DE LXR BASADOS EN IMIDAZOL

CLASIFICACIÓN INTERNACIONAL A61K 31/416

SOLICITANTE EXELIXIS, INC.

DOMICILIO SOUTH SAN FRANCISCO, CA, USA

APODERADO CARLOS ORLANDO MAYA RODRIGUEZ

BOGOTÁ, D. C., 25 de ENERO de 2008

PEDIDO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-007227- -00000-0000
Fecha: 2008-01-25 15:14:35 Dep: 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 853

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1. SOLICITUD DE:

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

[X] Capitulo I [ ] Capitulo II

SOLICITANTE (71)

Nombre: **Exelixis, Inc.**
Dirección: 210 East Grand Avenue, P.O. Box 511
South San Francisco. California
Domicilio:
South San Francisco, California 94083-0511, US
Lugar de Constitución: **DELAWARE**
Teléfono: Fax
E-mail:

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número:

3. REPRESENTANTE O APODERADO

Nombre: **CARLOS ORLANDO MAYA RODRIGUEZ**
Dirección: **Cr. 13 A No 28-38, Mz 2 Bufete 245. Parque Central Bavaria**
Teléfono: 3419841 Fax 3368592
E-mail: **patent@tmtamayo.net**

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número: **17.117.818** TP: **17.402**

4. INVENTOR(ES) (72)

Nombres: **1.- BUSCH, Brett, B.**
2.- FLATT, Brenton, T.
Dirección: **1.-** 7523 Mona Lane, San Diego, CA 92130 (US)
2.- 12721 Pedriza Drive, Poway, CA 92064 (US)
Nacionalidad o Domicilio: 1.- CIUDADANO DE: EE.UU
2.- CIUDADANO DE: EE.UU

OTROS INVENTORES EN HOJA ANEXA

5. PCT (86)
Solicitud internacional No. **PCT/US2006/024757** Fecha: **Junio 26 de 2006**
Publicación internacional No. **WO 2007/002563 A1** Fecha: **ENERO 04 2007**

6. Título (54) MODULADORES DE LXR BASADOS EN IMIDAZOL

7. Clasificación Internacional (51)

8. Prioridad Si [X] No [ ]

(33) País de Origen	(32) Fecha	(31) Número deSolicidud
EE.UU.	27-Jun-05	60/694,372
EE.UU.	10-Nov-05	60/736,120

9. Comprobante de pago No. **08- 6,813 Y 08-6,815** Fecha **ENERO 25/2008**

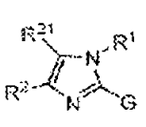
HOJA ANEXA INVENTORES

4.	Nombres:	3 **GU, Xiao-Hui** 4 **LU, Shao-Po** 5 **MARTIN, Richard** 6 **MOHAN, Raju** 7 **NYMAN, Michael, Charles** 8 **SCHWEIGER, Edwin** 9 **STEVENS, William, C., Jr.** 10 **WANG, Tie-Lin** 11 **XIE, Yinong**
INVENTOR(ES) **(72)**	Dirección:	3 7699 Palmilla Drive, #3408, San Diego, CA 92122 (US) 4 11693 Ramsdell Court, San Diego, CA 92131 (US). 5 4293 Cordobes Cove, San Diego, CA 92130 (US). 6 3125 Caminito Ricardo, Encinitas, CA 92024 (US). 7 4511 Rhode Island Street, San Diego, CA 92116 (US). 8 4703 Vereda Luz Del Sol, San Diego, CA 92130 (US). 9 11632 Candy Rose Way, San Diego, California 92131 (US). 10 7746 Roan Road, San Diego, CA 92129 (US). 11 9669 Gold Coast Drive, #31, San Diego, CA 92126 (US).
	Nacionalidad o Domicilio:	3 CIUDADANO DE CHINA 4 CIUDADANO DE EE.UU. 5 CIUDADANO DE CANADA 6 CIUDADANO DE EE.UU. 7 CIUDADANO DE EE.UU. 8 CIUDADANO DE EE.UU. 9 CIUDADANO DE EE.UU. 10 CIUDADANO DE EE.UU. 11 CIUDADANO DE CHINA

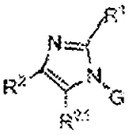
10. Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud Internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extrajero 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 (FOTOCOPIA CARATULA DE LA PUBLICACION INTERNACIONAL)**

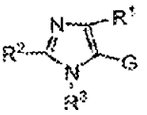
11. FIGURA CARACTERISTICA



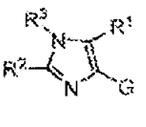
IIa



IIb



IIc



IId

12. Solicito la concesión de la patente,

NOMBRE: **CARLOS ORLANDO MAYA RODRIGUEZ**

FIRMA:

C.C **17.117.818** TP **17.402**

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-007227- -00000-0000

Fecha: 2008-01-25 15:14:35 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 853

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 6,813
FECHA : ENERO 25 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
CARLOS TAMAYO Y ASOCIADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	1921259	25/01/2008	1,279,000.00

***** 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._____

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 8 - 6,815
FECHA : ENERO 25 DE 2008

Ri

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARLOS TAMAYO Y ASOCIADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	1921259	25/01/2008	1,279,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1350	50005-01-01 SOLICITUDES	117 PALABRA ADICIONAL (DE MAS DE 150)		675,000.00
		TOTAL :	$	675,000.00

SON: SEISCIENTOS SETENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO No.

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ACTUACION NOTARIAL
LEY 404

N 007410568

0702190835O6 $20.00 19/02/2007 14:42:24

0702190538B3 $39.00 19/02/2007 14:42:29

FOLIO 336.- PRIMERA COPIA.- ESCRITURA NUMERO CIENTO SESENTA Y OCHO.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a nueve de febrero de dos mil siete, ante mi, Escribano Autorizante, COMPARECE don **Daniel GOYTIA**, argentino, mayor de edad, casado, Libreta de Enrolamiento número 4.526.965, domiciliado en Bartolomé Mitre 226, 4º piso, de esta Ciudad.- El compareciente es persona de mi conocimiento, doy fe, así como que DICE: I.- Que por escritura del dia de la fecha pasada ante mi, al folio 327 del Protocolo de este mismo Registro, se protocolizó un **Poder** otorgado por **EXELIXIS, INC.**, con domicilio en 170 Harbor Way P.O. Box 511, South San Francisco, California 94083, USA, a su favor.- II.- Que viene por la presente a **SUSTITUIR** el citado mandato, reservándose para si las facultades, a favor de **"CARLOS TAMAYO & ASOCIADOS" y/o Carlos Orlando Maya Rodriguez y/o Gustavo Calderon Rosero y/o Carmen Graciela Florez y/o Clara Cortes Charry y/o Mayerling Rocio Castelblanco S.**, con domicilio en Carrera 13A Nº 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá, **COLOMBIA**, para actuar en dicho país con las siguientes facultades: "... poder amplio y suficiente para recabar de las autoridades nacionales que corresponda, sean estas administrativas y/o judiciales, la obtención de **"PATENTES, MARCAS, MODELOS, DISEÑOS Y SUS RENOVACIONES"**, y realizar todos los trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales todos los trámites necesarios a los objetos indicados, presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas, desistir, arreglar y transigir; aceptar cesiones y transferencias; solicitar testimonios; recibir documentos y

Como Notario Dieciocho (E) de este Círculo hago constar que la FOTOCOPIA que antecede coincide con su original que he tenido a la vista.
25 ENE. 2008
Gonzalo Espinel Quintana
NOTARIO DIECIOCHO
BOGOTA

N 007410568

otros valores; justificar explotaciones; cobrar y percibir; firmar instrumentos públicos, privados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue. Este documento tiene validez a partir del 01 de diciembre de 2006...".- LO TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó, por ante mi, doy fe.- "SIGUE UNA FIRMA".- Esta mi sello.- Ante mi: ALEJANDRO M. LIPORACE.- CONCUERDA con su escritura matriz que pasó ante mi, al folio 336 del Protocolo del Registro 1331, a mi cargo. PARA LOS APODERADOS expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial número N 007410568 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.-

Notaría Dieciocho (E) de este Círculo hago constar que la FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Espinel Quintana
NOTARIA DIECIOCHO (E)
BOGOTA, D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

6

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

LEGALIZACION

LEY 404

L 007464707

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº 070219083506/6 La presente legalización no juzga sobre el contenido y forma del documento.

Buenos Aires, Lunes 19 de Febrero de 2007

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

ESC. EDDA ENRIQUETA SINEL
COLEGIO DE ESCRIBANOS
CONSEJERA

Circulación de la Copia (F) de éste FOLIO ... que ésta ... que he tenido a la vista

25 ENE. 2008

Gonzalo Espinel Quintana
NOTARIA DIECIOCHO
BOGOTA, D.C.

7

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00104498

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por EDDA ENRIQUETA SINELLI

3. Quien actúa en calidad de CONSEJERA

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 19/02/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: 070219053883

9. Sello / Timbre

COLEGIO DE ESCRIBANOS · APOSTILLA ·

10. Firma

Como Notaria Diecinueve (E) de esta Ciudad hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista

25 ENE. 2008

Gonzalo Espinel Quintana

NOTARIA DIECINUEVE BOGOTA, D.C.

Power of Attorney

The undersigned (1)

EXELIXIS, INC.

Residing at (2)
170 Harbor Way P.O. Box 511. South San Francisco, California 94083. USA.

hereby grants to DANIEL GOYTIA

residing in Buenos Aires, Argentina
full and ample power of attorney to represent him (it) and to apply to the proper national authorities, either administrative or judiciary for

Patents, Trademarks, Models, Designs and their Renewals

and to carry out all the necessary steps to protect our rights, to which effect they are empowered to take all necessary steps before the said national authorities, either administrative and/or judicial, for the aforementioned purposes, including to file petitions, arguments oppositions, protests, appeals and claims, to waive, settle and compromise; to accept assignments and transfers; to apply for certified copy; to receive documents and other valuable things; to prove workings; to collect monies; to sign public and private instruments and deeds; to either waive or not at their discretion the right of resorting to court proceedings; to do all and whatever shall be necessary before any national judicial and/or administrative authorities to protect the constituent's interests, either as plaintiff or defendant, with power to substitute this instrument and to revoke such substitution. It being understood that the above powers enumerated in this mandate are merely exemplifying and not limitative of other powers and therefore the attorneys-in-fact are authorized to exercise without any restriction whatsoever, all the rights granted by Law or emerging from it or which, may be a consequence of the objects of this mandate and whether this be under legislation at present in force or legislation which may be promulgated in the future.

Dated (3)
Day 24 Of January 2007

Poder

52465

El abajo firmante (1)

EXELIXIS, INC.

Domiciliado en (2)
170 Harbor Way P.O. Box 511. South San Francisco, California 94083. USA

por el presente otorga a DANIEL GOYTIA

domiciliado en Buenos Aires, Argentina
poder amplio y suficiente para recabar de las autoridades nacionales que corresponda, sean éstas administrativas y/o judiciales, la obtención de

Patentes, Marcas, Modelos, Diseños y sus renovaciones

y realizar todos los tramites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales, todos los tramites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; desistir, arreglar y transigir; aceptar cesiones y transferencias, solicitar testimonios, recibir documentos y otros valores; justificar explotaciones, cobrar y percibir; firmar instrumentos públicos, privados y escrituras publicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue.

(3) Fechado el
de de 2007

(4) .....
Pamela A. Simonton, Senior Vice President, Patents & Licensing
(1) Applicant's name – (2) Applicant's address – (3) Date – (4) Applicant's Signature

This document is effective as of December 01, 2006

Como Notario Dieciocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Espinel Zuinaga
NOTARIA DIECIOCHO
BOGOTA, D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

compareció(eron) personalmente

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo

personally appeared

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

--- NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO --- NOTARY PUBLIC OR ATTESTING OFICIAL ---

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los _____ días del mes de _____

de 200 _____ compareció(eron) ante mí,

Quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía denominada

Certifico:

1. Que he visto los siguientes documentos:*

2.Que dichos documentos prueban lo siguiente:

2.1.Que es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes del Estado de

2.2.Que el domicilio de dicha Sociedad/Compañía es

2.3. Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía.

2.4.Que el(los) Sr.(Sres.) _____

está(n) autorizado(s) para otorgar el presente Poder.

Ciudad _____

Estado _____

Hoy _____ de 200 __

--- NOTARIO PÚBLICO O FUNCIONARIO AUTORIZA

NOTARIAL CERTIFICATION (CORPORATION)

On this _____ day of _____

200 ____ appeared before me

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company named

I certify:

1. That I have seen the following documents:*
   Articles of Incorporation;
   Statement of Information from the Secretary of State of the State of California;
   Certificate of Good Standing from the Secretary of State of the State of Delaware;

2. That the above documents duly prove the following:
2.1. That is a Corporation/Company legally constituted and in existence in accordance with the laws of the State of Delaware

2.2 That the domicile of said Corporation/Company is California

2.3. That the purpose or purposes for which the present Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Corporation/Company.

2.4. That Mr.(Messrs.) Pamela A. Simonton

is(are) authorized to grant the present Power of Attorney

City: South San Francisco
State: California, United States of America
This 25th day of January, 2007

ATTESTING OFFICIAL
Christoph Pereira
Vice President, Legal Affairs and Secretary

Como Notario Dieciocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Carmel Zuluaga
NOTARIA DIECIOCHO
BOGOTA, D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

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 J. COHEN*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of J. COHEN, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 6th day of February 2007*
7. *by Deputy Secretary of State, State of California*
8. *No. 351842*
9. *Seal/Stamp:*

THE GREAT SEAL OF THE STATE OF CALIFORNIA

10. *Signature*

Debra Bowen
Secretary of State

OFFICE SECRETARY

NP-24 A (REV. 1-07)

BY

OSP 06 99602

Como Notario Dieciocho (E) de ... que ... 25 ENE. 2008 Gonzalo Espinel Quintana NOTARIA DIECIOCHO BOGOTA, D.C.

EL GRAN SELLO DEL ESTADO DE CALIFORNIA

ALEJANDRO M. LIPORACE
Matrícula 3837
ESCRIBANO PUBLICO

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California

County of San Mateo

On 24 January 2007 (Date) before me, J. Cohen, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared Pamela A. Simonton & Christoph Pereira (Name(s) of Signer(s))

☑ personally known to me

☐ (or 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.

WITNESS my hand and official seal.

J. COHEN
Commission # 1417900
Notary Public - California
San Mateo County
My Comm. Expires Jun 11, 2007

Place Notary Seal Above

Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: Power of Attorney

Document Date: _____ Number of Pages: 1 page + certs.

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer(s)

Signer's Name: Pamela A Simonton	Signer's Name: Christoph Pereira
☐ Individual	☐ Individual
☑ Corporate Officer — Title(s): Senior Vice President	☑ Corporate Officer — Title(s): Secretary
☐ Partner — ☐ Limited ☐ General	☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact	☐ Attorney in Fact
☐ Trustee	☐ Trustee
☐ Guardian or Conservator	☐ Guardian or Conservator
☐ Other: _____	☐ Other: _____
Signer Is Representing: Exelixis, Inc	Signer Is Representing: Exelixis
RIGHT THUMBPRINT OF SIGNER — Top of thumb here	RIGHT THUMBPRINT OF SIGNER — Top of thumb here

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Como Notario Diplomático Circulo hago constar que la FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Espinal Quintero
NOTARIA DIECIOCHO
BOGOTA D.C.

EL GRAN SELLO DEL ESTADO DE CALIFORNIA

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

TRADUCCIÓN PÚBLICA ----------

[Página 1] ----------

DANIEL GOYTÍA - PATENTES Y MARCAS ----------

[Luego de un PODER, redactado en idiomas inglés y español aparece lo siguiente:] ----------

(3) Fechado a los 24 días de enero de 2007 ----------

(4) [Aparece una firma ilegible debajo de la cual se lee:] Pamela A. Simonton, Vicepresidente Senior, Patentes y Licencias

(1) Nombre del Solicitante, (2) Domicilio del Solicitante, (3) Fecha, (4) Firma del Solicitante ----------

*****Este documento tiene validez a partir del 01 de diciembre de 2006***** ----------

---

[Página 2] ----------

[Siguen dos Certificados Notariales en idiomas español e inglés. Luego del segundo Certificado Notarial aparece lo siguiente:] ----------

Ciudad: San Francisco. ----------

Estado: California, Estados Unidos de Norteamérica. ----------

A los 24 días de enero de 2007. ----------

[Aparece una firma ilegible debajo de la cual se lee:] FUNCIONARIO CERTIFICANTE. Christoph Pereira, Vicepresidente, Asuntos Legales y Secretario. ----------

---

[Página 3] ----------

ESTADO DE CALIFORNIA ----------

EL GRAN SELLO DEL ESTADO DE CALIFORNIA ----------

Como Notario Dieciocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista

25 ENE. 2008

Gonzalo Espinel Zuñiga
NOTARIA DIECIOCHO
BOGOTA D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

SECRETARIO DE ESTADO ----------

APOSTILLA ----------

[Aparece una frase en otro idioma] ----------

1. País: Estados Unidos de Norteamérica ----------

Este documento público ----------

2. ha sido firmado por J. COHEN ----------

3. actuando en carácter de Escribano Público, Estado de California ----------

4. lleva el sello/timbre de J. COHEN, Escribano Público, Estado de California ----------

CERTIFICADO ----------

5. en Sacramento, California ----------

6. el 06 de febrero de 2007 ----------

7. por el Subsecretario de Estado, Estado de California -------

8. No. 351842 ----------

9. Sello/Timbre: El Gran Sello del Estado de California ------

10. Firma: [Aparece una firma ilegible debajo de la cual se lee:] Secretario de Estado. ----------

Por: [Aparece una firma ilegible] ----------

[Sigue un sello circular que reza:] OFICINA DEL SECRETARIO DE ESTADO, EL GRAN SELLO DEL ESTADO DE CALIFORNIA ----------

---

[Página 4] ----------

CERTIFICACIÓN PARA TODOS LOS PROPÓSITOS DE CALIFORNIA----------

Estado de California. Condado de San Mateo.----------

A los (FECHA) 24 días del mes de enero de [illegible], por ante mí, (NOMBRE Y CARGO DEL FUNCIONARIO) DIANE DOE, ESCRIBANO

Como Notaria Dieciocho (E) del Círculo, hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Espinel Quintero
NOTARIA DIECIOCHO
BOGOTA, D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

PÚBLICO)) J. Cohen, Escribano Público, compareció personalmente (NOMBRE DE LA PERSONA(S) FIRMANTE(S)) Pamela A. Simonton & Christoph Pereira, [X] a quienes conozco personalmente---------

[ ] (o demostraron ante mí con pruebas suficientes)----------

que son las personas cuyos nombres suscriben el instrumento adjunto y certificaron ante mí que lo otorgaron en su carácter de autorizados, y que con sus firmas en el instrumento las personas o la persona de existencia ideal en nombre de la cual actuaron las personas, otorgaron el instrumento.----------

CERTIFICO con mi firma y sello oficial.----------

[Aparece una firma ilegible debajo de la cual se lee:] Firma del Escribano Público----------

Colocar el sello notarial más arriba [Aparece un sello que reza:] El Gran Sello del Estado de California. J. COHEN. MANDATO NO. 1417900. ESCRIBANO PÚBLICO - CALIFORNIA. CONDADO DE SAN MATEO. Mi mandato vence el 11 de junio de 2007----------

INFORMACIÓN OPTATIVA----------

La información que aparece a continuación no ese exigida por ley. Sin embargo, podría ser valiosa para las personas que confían en el documento e impediría que la presente certificación se adjunte en forma fraudulenta a otro documento.----------

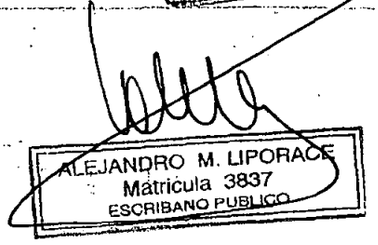
Descripción del Documento Adjunto.----------

Título o Tipo de Documento: **Poder**----------

Fecha del Documento: [en blanco] ----------

Número de Páginas: 1 página más cert[illegible]----------

Persona(s) Firmante(s) distinta de la mencionada anteriormente:



[en blanco].----------

CARÁCTER INDICADO POR EL FIRMANTE----------

Nombre de la Persona Firmante: Pamela A. Simonton----------

[ ] Persona Física----------

[X] Funcionario de Sociedad Anónima. Cargo(s): Vicepresidente Senior----------

[ ] Socio(s) - [ ] Limitado [ ] General----------

[ ] Apoderado----------

[ ] Síndico----------

[ ] Tutor o Curador----------

[ ] Otro: [en blanco]----------

El firmante representa a: **Exelixis, Inc.**----------

Huella digital del pulgar derecho del firmante----------

[Aparece un casillero en blanco con una leyenda que reza:] Coloque aquí la parte superior de la huella digital del pulgar derecho.----------

Nombre de la Persona Firmante: Christoph Pereira.----------

[ ] Persona Física----------

[X] Funcionario de Sociedad Anónima. Cargo(s): Secretario.-----

[ ] Socio(s) - [ ] Limitado [ ] General----------

[ ] Apoderado----------

[ ] Síndico----------

[ ] Tutor o Curador----------

[ ] Otro: [Aparece una línea en blanco]----------

El firmante representa a: Exelixis----------

Huella digital del pulgar derecho del f---

Como Notario Dieciocho (E) de este FOTOCOPIA concuerda con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Espinel Qui
NOTARIA DIECIOCH
BOGOTA, D.C.

ALEJANDRO, M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

[Aparece un casillero en blanco con una leyenda que reza:] Coloque aquí la parte superior de la huella digital del pulgar derecho.----------

2006 Asociación Nacional de Escribanos. 9350 De Soto Ave., P.O. Box 2402, Chatsworth, CA 91313-2402, Ítem No. 5907, Nuevo Pedido: Llamar a la línea gratuita 1-800-876-6827. ----------

---

CERTIFICO POR LA PRESENTE QUE LO QUE ANTECEDE ES TRADUCCIÓN FIEL Y COMPLETA AL ESPAÑOL DE LAS PARTES PERTINENTES EN IDIOMA INGLÉS DEL DOCUMENTO ORIGINAL QUE TUVE ANTE MÍ Y AL CUAL ME REMITO. EN LA CIUDAD DE BUENOS AIRES, A LOS 09 DÍAS DEL MES DE FEBRERO DE DOS MIL SIETE. ----------

COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES
Corresponde a la Legalización
Nº 44-3424/07
ESTEBAN SANTIAGO ALLEGRETTI

DANIEL GOYTIA
AGENTE Nº 464

Como Notario Dieciocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
NOTARIA DIECIOCHO
BOGOTA, D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

N° 00960454

17

COLEGIO DE TRADUCTORES PÚBLICOS
DE LA CIUDAD DE BUENOS AIRES

REPÚBLICA ARGENTINA
LEY 20.305

LEGALIZACIÓN

Por la presente, el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES, en virtud de la facultad que le confiere el artículo 10, inc. d) de la Ley 20.305, certifica únicamente que la firma y el sello que aparecen en la traducción adjunta, concuerdan con los correspondientes al Traductor Público **FIORI UGARTE, VALERIA**

que obran en los registros de esta institución en el folio tomo

INGLES	233	13

Buenos Aires, **Legalización Número: 3424 / 2007 / T4**

Fecha: 09/02/07

Como Notario Diecíocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he visto o a la vista

25 ENE. 2008

MARCELO F. SIGALOFF
NOTARIA DIECIOCHO
Encargado Dto. de Legalizaciones
Colegio de Traductores Públicos
de la Ciudad de Buenos Aires

ESTA LEGALIZACIÓN NO SE CONSIDERARÁ VÁLIDA SIN EL CORRESPONDIENTE TIMBRADO EN LA ÚLTIMA HOJA DE LA TRADUCCIÓN ADJUNTA

Pursuant to Section 10, Paragraph D of Act 20.305, the *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Sworn Translators Association of the City of Buenos Aires) hereby certifies that the signature and seal affixed hereto appear to match the specimen signature and seal of the *Traductor Público* (Sworn Translator) whose name is subscribed to the attached translation, as such specimen signature and seal are kept on file in our office.
THIS CERTIFICATION IS NOT VALID WITHOUT THE STAMP ON THE LAST PAGE OF THE ATTACHED TRANSLATION.

ALEJANDRO M. Matricula ESCRIBANO

Vu par le *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Ordre de Traducteurs Officiels de la ville de Buenos Aires), en vertu des attributions qui lui ont été accordées par l'article 10, alinéa d) de la Loi nº 20.305, pour la seule légalisation matérielle de la signature et du sceau du *Traductor Público* (Traducteur Officiel) apposés sur la traduction du document ci-joint, qui sont conformes à ceux déposés aux archives de cette Institution.
LE TIMBRE APPOSÉ SUR LA DERNIÈRE PAGE DE LA TRADUCTION FERA PREUVE DE LA VALIDITÉ DE LA LÉGALISATION.

Con la presente il *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Collegio dei Traduttori Giurati della Città di Buenos Aires) ai sensi della facoltà conferitagli dall'articolo 10, comma d), della Legge 20.305, CERTIFICA, esclusivamente, la firma ed il timbro del *Traductor Público* (Traduttore Giurato), apposti in calce alla qui unita traduzione, in conformità alla firma ed al timbro depositati nei propri registri.
LA PRESENTE LEGALIZZAZIONE SARÀ PRIVA DI VALIDITÀ OVE NON VENGA TIMBRATA NELL'ULTIMO FOGLIO DELLA TRADUZIONE.

Através da presente o *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Colégio de Tradutores Públicos da Cidade de Buenos Aires), em virtude das atribuições conferidas pelo art. 10 inc. d) da Lei 20.305, certifica unicamente que a assinatura e o carimbo do *Traductor Público* (Tradutor Público) que subscreve a tradução adjunta conferem com a assinatura e o carimbo arquivados nos registros desta instituição.
A PRESENTE LEGALIZAÇÃO SÓ SERÁ CONSIDERADA VÁLIDA COM A CORRESPONDENTE CHANCELA MECÂNICA APOSTA NA ÚLTIMA FOLHA DA TRADUÇÃO.

Kraft der Befugnis, die ihr durch Art. 10, Abs. d) im Gesetz 20.305 verliehen wird, bestätigt hiermit der *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Kammer der Vereidigten Übersetzer der Stadt Buenos Aires) lediglich, dass Unterschrift und Siegel, des *Traductor Público* (Vereidigten Übersetzers), mit denen die beigefügte Übersetzung versehen ist, mit den entsprechenden Registereintragungen dieser Institution übereinstimmen.
VORLIEGENDE BEGLAUBIGUNG IST UNGÜLTIG OHNE DEN ENTSPRECHENDEN GEBÜHRENSTEMPEL AUF DEM LETZTEN BLATT DER BEIGESCHLOSSENEN ÜBERSETZUNG.

CERTIFICO EN SELLO DE ACTUACION NOTARIAL Nº TO[illegible]4431
BUENOS AIRES 14/2/[illegible]

Como Notario Dieciocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
25 ENE. 2008
Gonzalo Espinel Quintana
NOTARIA DIECIOCHO
BOGOTA, D.C.

ALEJANDRO M. LIPOBACE
Matricula 3837
ESCRIBANO PUBLICO

EXP. 08-7227

Agosto
Viernes

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• Septiembre 2007

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SANTO
TOMAS

Para distinguir	:	BEBIDAS ALCOHÓLICAS (Productos de la clase33ª de la Clasificación Internacional de Niza).
Titular	:	PDC VINOS Y LICORES LTDA.
Domicilio	:	BOGOTÁ D.C., CUNDINAMARCA, COLOMBIA.
Dirección	:	AVENIDA AMÉRICAS No. 50 – 80.
Vigencia	:	DIEZ (10) AÑOS CONTADOS A PARTIR DE LA FECHA DE LA PRESENTE RESOLUCIÓN.

ARTÍCULO TERCERO. Asignar número de certificado al derecho concedido, previa inscripción en los libros de la propiedad industrial.

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

CERTIFICACION DE REPRODUCCIONES

LEY 404

T 005904431

L. LIPORACE
3837
UBLICO

Buenos Aires, 14.- de Febrero.- de 2007.-

En mi carácter de Escribano Titular del Registro 1331 de Capital Federal.-

CERTIFICO que la reproducción anexa, extendida en Diez.-

foja/s, que sello y firmo, es COPIA FIEL de su original, que tengo a la vista, doy fe.

El Autorizante deja constancia que el documento cuyas fotocopias se certifican consiste en un PODER redactado en idioma extranjero con su correspondiente traducción al español.-

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

Como Notario Dieciocho (E) de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista

25 ENE. 2008

Gonzalo Espinel Quintero
NOTARIA DIECIOCHO
BOGOTA D.C.

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APOSTILLA
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$38.00
19/02/2007 14:42:29

CECBA - LEY404 GCBA
LEGALIZACION
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COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

LEGALIZACION

LEY 404

L 007464710

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE

obrantes en el documento anexo, presentado en el día de la fecha bajo el N° 0702190835 10/8 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Lunes 19 de Febrero de 2007

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS (F.) de la
CONSEJERA

Como hago constar que la
Círculo FOTOCOPIA coincide con su original
que he tenido a la vista.

25 ENE. 2008

Gonzalo Espinel Quinto
NOTARIA DIECIOCHO
BOGOTA, D.C.

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00104499

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por EDDA ENRIQUETA SINELLI

3. Quien actúa en calidad de CONSEJERA

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 19/02/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: 070219053886

9. Sello / Timbre

COLEGIO DE ESCRIBANOS APOSTILLA

10. Firma

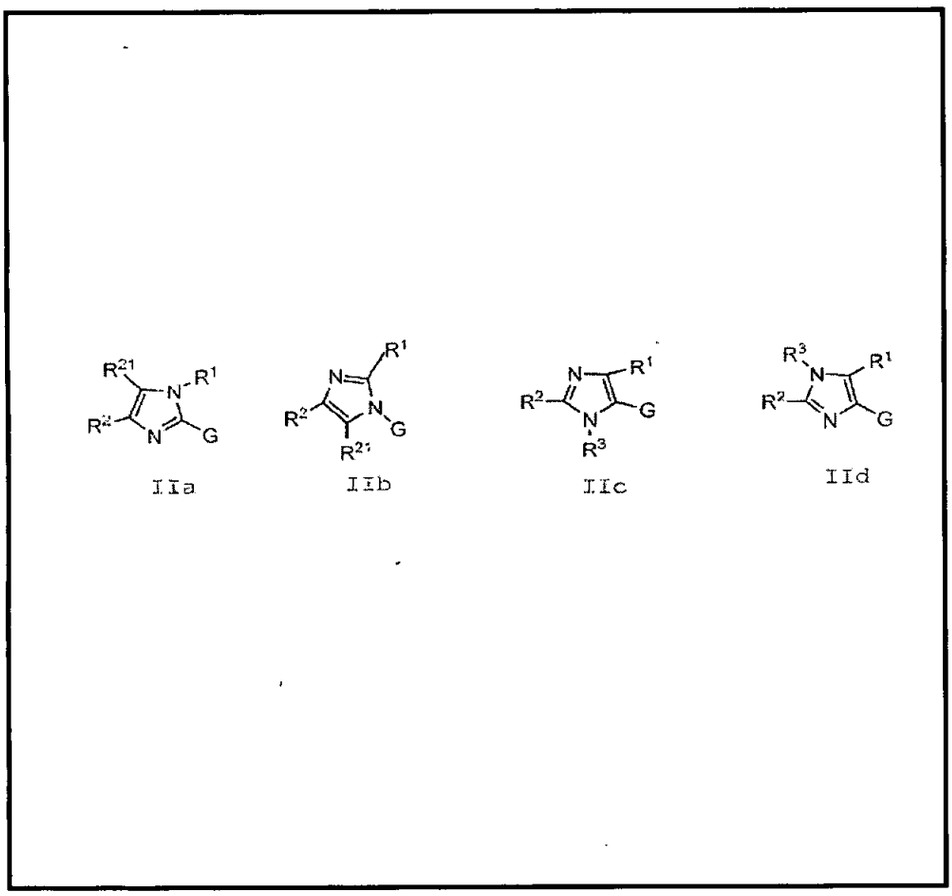
ESC
CO

Como Notario Dieciocho (E) de este Círculo hago constar que ésta FOTOCOPIA coincide con su original que he tenido a la vista

25 ENE. 2008

Gonzalo Espinel Zuluaga

NOTARIA DIECIOCHO BOGOTA, D.C.


R21
R1
R2
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IIa
R1
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R2
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R21
IIb
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R1
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R3
IIc
R3
N
R1
R2
N
G
IId

PUBLICACION
PCT

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2007 (04.01.2007)

PCT

(10) International Publication Number
WO 2007/002563 A1

(51) International Patent Classification:
C07D 233/54 (2006.01) *A61K 31/4164* (2006.01)
C07D 409/04 (2006.01) *A61P 3/10* (2006.01)
C07D 401/04 (2006.01)

(21) International Application Number:
PCT/US2006/024757

(22) International Filing Date: 26 June 2006 (26.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/694,372 27 June 2005 (27.06.2005) US
60/736,120 10 November 2005 (10.11.2005) US

(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; 170 Harbor Way, P.o. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BUSCH, Breet, B.** [US/US]; 7523 Mona Lane, San Diego, CA 92130 (US). **FLATT, Brenton, T.** [US/US]; 12721 Pedriza Drive, Poway, CA 92064 (US). **GU, Xiao, Hui** [CN/US]; 7699 Palmilla Drive, #3408, San Diego, CA 92122 (US). **LU, Shao, Po** [US/US]; 11693 Ramsdell Court, San Diego, CA 92131 (US). **MARTIN, Richard** [CA/US]; 4293 Cordobes Cove, San Diego, CA 92130 (US). **MOHAN, Raju** [US/US]; 3125 Caminito Ricardo, Encinitas, CA 92024 (US). **NYMAN, Michael, Charles** [US/US]; 4511 Rhode Island Street, San Diego, CA 92116 (US). **SCHWEIGER, Edwin** [US/US]; 4703 Vereda Luz Del Sol, San Diego, CA 92130 (US). **STEVENS, William, C., Jr.** [US/US]; 8850 West Lilac Road, Escondido, CA 92026 (US). **WANG, Tie, Lin** [US/US]; 7746 Roan Road, San Diego, CA 92129 (US). **XIE, Yinong** [CN/US]; 9669 Gold Coast Drive, #31, San Diego, CA 92126 (US).

(74) Agent: **GREENFIELD, Michael, S.**; McDonnell Boehnen Hulbert & Berghoff LLP, 300 Ssouth Acker Drive, Suite 3100, Chicago, IL 60606 (US).

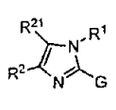
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, 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*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

(54) Title: IMIDAZOLE BASED LXR MODULATORS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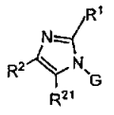
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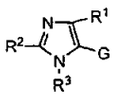
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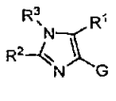

(IId)

(57) Abstract: Compounds of the invention, such as compounds of Formulae IIa, IIb, IIc or IId, and pharmaceutically acceptable salts, isomers, and prodrugs thereof, are useful as modulators of the activity of liver X receptors, where R^1, R^2, R^{21}, R^3 and G are defined herein. Pharmaceutical compositions containing the compounds and methods of using the compounds are also disclosed.

WO 2007/002563 A1

IMIDAZOLE BASED LXR MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to United States Provisional Application Number 60/694,372, filed June 27, 2005, and United States Provisional Application Number 60/736,120, filed November 10, 2005, both of which are hereby incorporated by reference in their entirety.

Field of the Invention

This invention relates to compounds that modulate the activity of liver X receptors (LXRs). The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of utilizing those compositions for modulating the activity of liver X receptor. In particular, imidazole isomers and derivatives are provided for modulating the activity of LXRs.

BACKGROUND OF THE INVENTION

Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science 240*:889-895). These proteins bind to *cis*-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev.15*:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptors or PPARs) and ecdysone, bind to HREs as heterodimers with a common partner, the retinoid X receptors (*i.e.*, RXRs, also known as the 9-*cis* retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature 355*:359-361 and Heyman *et al.* (1992) *Cell 68*:397-406).

RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell 83*:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression.

There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), coding for RXRα, β, and γ, all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol. 17*:3013-3020). In the adult liver, RXRα is the most abundant of the three

RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol. 20*:4436-4444..

Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin et al., (1992), *supra* and Heyman et al., (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for the farnesoid X receptor (FXR).

Because it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, *e.g.*, Tomkins (1975) *Science 189*:760-763 and O'Malley (1989) *Endocrinology 125*:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

LXRα and LXRβ

LXRα is found predominantly in the liver, with lower levels found in kidney, intestine, spleen and adrenal tissue (see, *e.g.*, Willy, et al. (1995) Gene Dev. 9(9):1033-1045)LXRβ is ubiquitous in mammals and was found in nearly all tissues examined. LXRs are activated by certain naturally occurring, oxidized derivatives of cholesterol (see, *e.g.*, Lehmann, et al. (1997) J. Biol. Chem. 272(6):3137-3140). LXRα is activated by oxycholesterol and promotes cholesterol metabolism (Peet et al. (1998) Cell 93:693-704). Thus, LXRs appear to play a role in, *e.g.*, cholesterol metabolism (see, *e.g.*, Janowski, et al. (1996) Nature 383:728-731).

Nuclear Receptors and Disease

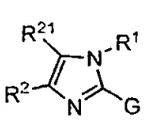
Nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), atherosclerosis and gallstones (see, *e.g.*, International Patent Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No.

WO 98/32444), acne (see, *e.g.*, International Patent Application Publication No. WO 00/49992), and cancer, Parkinson's disease and Alzheimer's disease (see *e.g.*, International Patent Application Publication No. WO 00/17334). Activity of nuclear receptors, including LXRs, FXRs and PPARs, and orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7α-hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang et al. (2000) J. Biol. Chem. 275:10918-10924), HDL metabolism (see, *e.g.*, Urizar et al. (2000) J. Biol. Chem. 275:39313-39317 and International Patent Application Publication No. WO 01/03705), and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

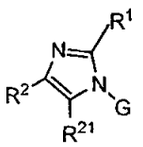
Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including LXRs, FXRs, PPARs and orphan nuclear receptors. Such compounds are useful in the treatment, prevention, inhibition or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

SUMMARY OF THE INVENTION

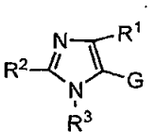
In one aspect, the present invention provides a compound according the following formulas IIa-d,



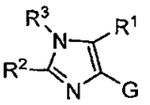
IIa



IIb



IIc



IId

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, which are useful as modulators of the activity of liver X receptors (LXR), where R^1, R^2, R^{21}, R^3, and G are defined herein.

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds of the invention which are useful for modulating liver X receptors, LXRα and LXRβ, FXR, PPAR and/or orphan nuclear receptors are provided.

In one embodiment, the compounds provided herein are agonists of LXR. In another embodiment, the compounds provided herein are antagonists of LXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists.

Another aspect of this invention is directed to methods of treating, preventing, inhibiting, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, comprising administering to a

subject in need thereof a therapeutically effective amount of a compound of formulae IIa, IIb, IIc, or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of reducing cholesterol levels in a subject in need thereof, comprising administering an effective cholesterol level-reducing amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of treating, preventing, inhibiting, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of modulating cholesterol metabolism, comprising administering an effective cholesterol metabolism-modulating amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of treating, preventing, inhibiting or ameliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of increasing cholesterol efflux from cells of a subject, comprising administering an effective cholesterol efflux-increasing amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of increasing the expression of ATP-Binding Cassette (ABC1) in the cells of a subject, comprising administering an effective ABC1 expression-increasing mount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to in vitro methods for altering nuclear receptor activity, comprising contacting the nuclear receptor with a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

Another aspect of this invention is directed to methods of reducing cholesterol levels in a subject in need thereof, comprising administering an effective cholesterol level-reducing amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

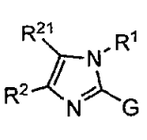
Another aspect of this invention is directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier, excipient and/or diluent and a compound of formulae IIa, IIb, IIc or IId.

Another aspect of this invention is directed to regulation of cholesterol transport and inflammatory signaling pathways that are implicated in human disease pathology including atherosclerosis and associated diseases such as myocardial infarction and ischemic stroke in a subject in need thereof, comprising administering an effective cholesterol transport and inflammatory signaling pathways regulating amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

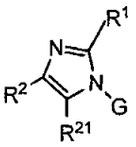
Another aspect of this invention is directed to treatment of the metabolic syndrome which comprises a constellation of disorders of the body's metabolism including obesity, hypertension and insulin resistance and diabetes including treatment of diseases resulting from compromised metabolism and immunity including atherosclerosis and diabetes as well as autoimmune disorders and diseases in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of formulae IIa, IIb, IIc or IId, or a pharmaceutically acceptable derivative thereof.

DETAILED DESCRIPTION OF THE INVENTION

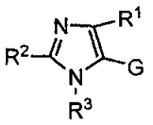
In a first embodiment, the present invention provides a compound according to one of the following formulas,



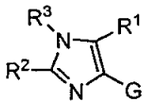
IIa



IIb



IIc



IId

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein,

(A) R^1 is $-L^1-R^5$, wherein

L^1 is a bond, L^5, L^6, $-L^5-L^6-L^5-$, or $-L^6-L^5-L^6-$, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_6)haloalkyl; and

each L^6 is independently -CS-, -CO-, $-SO_2-$, -O-, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, or $-C(=NN(R^{11})_2)-$, -aryl-, $-C_3-C_8$cycloalkyl-, -heteroaryl-, or -heterocyclyl-,

wherein the aryl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more R^{14};

or each L^6 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, $-CON(R^{10})$-, -CO-, $-CO_2$-, -OC(=O)-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, or $-SO_2N(R^{10})$; and

R^5 is aryl, heterocyclyl, heteroaryl, $-(C_3$-$C_6)$cycloalkyl, -C, or -B-C, wherein

B is $-[C(R^{15})_2]_m$- or $-C_3$-C_8 cycloalkyl-; and

C is halogen, $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, or $-N(R^{11})_2$,

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, $-C_1$-C_6 alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, C_1-C_6 haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 and R^{2I} are $-L^3$-R^7, wherein

each L^3 is independently a bond or $-(CH_2)_m$-V^1-$(CH_2)_n$-, wherein

n is 0-6; and

V^1 is $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, $-NR^{11}$-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, -OCO-, -CO-, -CS-, $-CONR^{10}$-, $-C(=N\text{-}R^{11})$-, $-C(=N\text{-}OR^{11})$-, $-C[=N\text{-}N(R^{11})_2]$, $-CO_2$-, -OC(=O)-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, $-SO_2N(R^{10})$-, $-NR^{10}CONR^{10}$-, $-NR^{10}CSNR^{10}$-, C_3-C_6cyclo alkyl, or C_3-C_6 cyclohaloalkyl;

or each L^3 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, or $-SO_2N(R^{10})-$; and

each R^7 is independently hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, -Y-Z, or –X-Y-Z, wherein

X is –O-;

Y is $-[C(R^{15})_2]_m-$, C_2-C_6alkenyl, or $-C_3$-C_8cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, or $-OC(=O)-N(R^{11})_2$,

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen, haloaryl, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, $C(R^{11})=C(R^{11})$-COOH, aryl, heteroaryl, heterocyclyl, heterocyclyloxy, heteroaryloxy, -Z', -Y'-Z', or –X'-Y'-Z', wherein

X' is –O-;

Y' is $-[C(R^{15})_2]_m-$ or $-C_3$-C_8cycloalkyl; and

Z' is –H, halogen, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)\ R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-OR^{11}$, $-N(R^{11})C(=O)-R^{11}$, or $-N(R^{11})S(O=)_2R^{11}$,

wherein each R^{7a} is optionally substituted with one or more R^8,

wherein each R^8 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyl(OR^{11}), C_0-C_6 alkylOR^{11}, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, or C_0-C_6 alkylSO_2R^{11},

provided that R^2 and R^{21} are not simultaneously hydrogen,

R^3 is –L-R^6, wherein

L is a bond, $-X^3-(CH_2)_n-X^3-$, $-(CH_2)_m-X^3-(CH_2)_n-$ or $-(CH_2)_{l+w}-Y^3-(CH_2)_w-$, wherein

n is 0-6; each w is independently 0 – 5; and

each X^3 is independently a bond, $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C\equiv C-$, -CO-, -CS-, $-CONR^{10}-$, $-C(=N)(R^{11})-$, $-C(=N\text{-}OR^{11})-$, $-C[=N\text{-}N(R^{11})_2]$, $-CO_2-$, $-SO_2-$, or $-SO_2N(R^{10})-$; and

Y^3 is -O-, -S-, -NR^7-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -OCO-, -$OC(=O)N(R^{10})$-, -$NR^{10}CONR^{10}$-, -$N(R^{10})SO_2$-, or -$NR^{10}CSNR^{10}$-;

or L is C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -CO-, -CO_2-, -OC(=O)-, -$OC(=O)N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$; and

R^6 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, -CN, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with with one or more R^{6a}, wherein

each R^{6a} is independently -Z", –Y"-Z", or –X"-Y"-Z", wherein

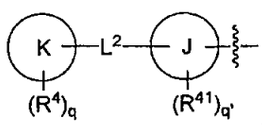
X" is –O-;

Y" is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with at least one group which is each independently Z";

Z" is -H, -CN, halogen, -OR^{11}, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -N_3, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$N(R^{11})C(=O)N(R^{11})_2$, -OC(=O)-$OR^{11}$, -$C(=O)N(R^{11})(OR^{11})$, -OC(=O)-$R^{11}$, -$OC(=O)$-$N(R^{11})_2$, or -$N(R^{11})COOR^{11}$; and

G is a group of the formula,



, wherein

J is aryl, heteroaryl, or absent;

K is aryl, heteroaryl, or absent;

provided that

(i) if K is absent, then q is 1 and R^4 is bonded directly to L^2; and

each R^4 and R^{41} is independently halogen, oxo, nitro, CR^{11}=$CR^{11}COOR^{11}$, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, -G^1, -E-G^1, or –D-E-G^1, wherein

D is –O-;

E is -[C(R^{15})$_2$]$_m$- or -C_3-C_8cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$OCON(R^{11})_2$, -$OCOOR^{11}$, -N_3, -$NR^{11}COR^{11}$, -$NR^{11}SO_2R^{11}$, -$N(R^{11})_2$, -$NR^{11}COOR^{11}$, -SO_2R^{11}, -$SO_2NR^{11}COR^{11}$, -$SO_2N(R^{11})_2$, -SOR^{11}, or -SR^{11},

wherein each R^4 is optionally substituted with one or more R^{4a},

wherein each R^{4a} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, C_1-C_6 alkoxyaryl, arylC_0-C_6 alkylcarboxy, -G', -E'-G', or –D'-E'-G', wherein

D' is –O-;

E' is -[C(R^{15})$_2$]$_m$- or -C_3-C_8cycloalkyl-; and

G' is –H, -halogen, -COR^{11}, -$COOR^{11}$, -C≡N, -OR^{11}, -$NR^{11}SO_2R^{11}$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11},

L^2 is a bond or –[C(R^{15})$_2$]$_m$-V^2-[C(R^{15})$_2$]$_n$-, wherein

V^2 is independently –C(R^{11})$_2$-, -C(R^{11})$_2$C(R^{11})$_2$-, -C(R^{11})=C(R^{11})-, -C(R^{11})$_2$O-, -C(R^{11})$_2$NR^{11}-, -C≡C-, -O-, -S-, -SO_2-, -N(R^{10})CO-, -N(R^{10})CO_2-, -CON(R^{10})-, -CON(R^{11})-, -CON(R^{11})O-, -CO-, -CS-, -CO_2-, -OC(=O)-, -OC(=O)N(R^{10})-, -N(R^{10})SO_2-, -SO_2N(R^{10})-, -$NR^{10}CONR^{10}$-, -$NR^{10}CSNR^{10}$-, C_3-C_6cyclo alkyl-, or C_3-C_6cyclohaloalkyl,

or V^2 is C_{2-6} alidiyl,

wherein alidiyl chain is optionally interrupted by –C(R^{11})$_2$-, -C(R^{11})$_2$C(R^{11})$_2$-, -C(R^{11})=C(R^{11})-, -C(R^{11})$_2$O-, -C(R^{11})$_2$NR^{11}-, -C(R^{11})$_2$NR^{11}-, -C≡C-, -O-, -S-, -N(R^{10})CO-, -N(R^{10})CO_2-, -CON(R^{10})-, -CON(R^{11})-, -CON(R^{11})O-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)N(R^{10})-, -SO_2-, -N(R^{10})SO_2- or -SO_2N(R^{10})-;

or V^2 is aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more R^9, wherein

each R^9 is independently halogen, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkyloxy, C_0-C_6 alkyl or C_1-C_6 alkyl$COOR^{11}$;

each m is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, or 5,

provided that q is 0 if and only if K is not phenyl; and

q' is 0, 1, 2, 3, or 4,

each R^{10} is independently -R^{11}, -C(=O)R^{11}, -CO_2R^{11}, or -SO_2R^{11};

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_1-C_6 haloalkyl,

$-N(R^{12})_2$, aryl, $-(C_1-C_6)$alkyl-aryl, heteroaryl, $-(C_1-C_6)$alkyl-heteroaryl, heterocyclyl, or $-(C_1-C_6)$alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, -C_0-C_6 alkyl$N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, or -$OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1.C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$; and

(B) provided that

(i) when L^2 is a bond, both J and K are not absent;

(ii) if the compound if defined by formula IIa, then

a. if J is phenyl and K is thienyl, furyl, or thiazoyl and q is 0, then R^1 is not 4-(NH_2SO_2)phenyl, 4-(NH_2SO_2)-3-fluorophenyl, p-(CH_3SO_2)phenyl-, or 4p-(CH_3SO_2)-3-fluorophenyl-; and

b. if R^5 is pyridyl or phenyl optionally substituted with one or more R^{5a} and L^1 is a bond, then G is not p-(NH_2SO_2)phenyl or p-(CH_3SO_2)phenyl-;

(iii) if the compound is defined by formula IIc or IId, then G is not p-(NH_2SO_2)phenyl or p-(CH_3SO_2)phenyl-;

(iv) the compound is not 1-(biphenyl-4-yl)-2,5-diphenyl-1H-imidazole.

In one embodiment, the invention provides the compound according to formula IIa, IIb, IIc, or IId, wherein:

R^1 is $-L^1-R^5$, wherein

L^1 is a bond, L^5, L^6, $-L^5-L^6-L^5-$, or $-L^6-L^5-L^6-$, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

m is 0, 1, 2, 3, or 4; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

L^6 is -CO-, $-SO_2-$, -O-, $-CON(R^{11})-$, -C_3-C_6cycloalkyl-, or -heterocyclyl-,

wherein the cycloalkyl, or heterocyclyl is optionally substituted with one or more R^{14}; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C, wherein

B is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl-; and

C is halogen, $-C_1-C_6$alkyl, or $-C_1-C_6$haloalkyl;

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-; aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, $-C_1-C_6$ alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, $-C_1-C_6$ haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 is-L^3-R^7, wherein L^3 is a bond; and

R^7 is halogen, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, or $-C(=O)N(R^{11})(OR^{11})$;

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen -Z', -Y'-Z', or –X'-Y'-Z', wherein

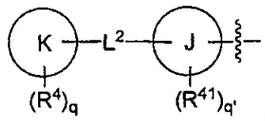
X' is –O-;

Y' is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl; and

Z' is –H, halogen, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, or $-N(R^{11})S(O=)_2R^{11}$;

R^{21} and R^3 are each independently hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl; and

G is a group of the formula,



, wherein

J is aryl or heteroaryl;

K is aryl or heteroaryl;

each R^4 and R^{41} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, -G^1, -E- G^1, or –D-E- G^1, wherein

D is –O-;

E is -$[C(R^{15})_2]_m$- or -C_3-C_6cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$OCON(R^{11})_2$, -$NR^{11}COR^{11}$, -$NR^{11}SO_2R^{11}$, -$N(R^{11})_2$, -$NR^{11}COOR^{11}$, -SOR^{11}, -SO_2R^{11}, -$SO_2NR^{11}COR^{11}$, -$SO_2N(R^{11})_2$, or -SR^{11},

L^2 is a bond;

q is 1, 2, or 3; and

q' is 0, 1, 2, or 3;

each R^{10} is independently -R^{11}, -C(=O)R^{11}, -CO_2R^{11}, or -SO_2R^{11};

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-; C_1.C^6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_3-C_8 cycloalkyl, -C_1-C_6 haloalkyl, -$N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_0-C_6alkyl$N(R^{13})_2$, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, C_0-C_6 alkyl, -$NR^{13}SO_2$ R^{13}, or -$OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1.C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-; and

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$.

In one embodiment, the invention provides the compound according to formula IIa, IIb, IIc, or IId, wherein:

R^1 is $-L^1-R^5$, wherein

L^1 is a bond, $-C_3-C_8$ cycloalkyl- or L^5, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

m is 0, 1, 2, or 3; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C, wherein

B is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl-; and

C is $-C_1-C_6$alkyl or $-C_1-C_6$haloalkyl;

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(C_3-C_8$ cycloalkyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkenyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, $-C_1-C_6$ alkyl, aryloxy, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, $-C_1-C_6$ haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

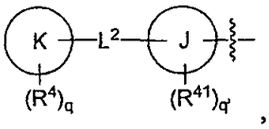
R^7 is –Z or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-OC(=O)-R^{11}$, or $-OC(=O)-N(R^{11})_2$;

R^{21} and R^3 are each independently hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

G is a group of the formula,



, wherein

J is aryl or heteroaryl;

K is aryl or heteroaryl;

each R^4 and R^{41} is independently halogen, heteroaryl, heterocyclyl, - G^1, -E- G^1, or –D-E- G^1, wherein

D is –O-;

E is -$[C(R^{15})_2]_m$- or -C_3-C_6cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -SOR^{11}, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11};

L^2 is a bond;

q is 1, 2, or 3; and

q' is 0, 1, 2 or 3;

each R^{10} is independently -R^{11}, -C(=O)R^{11}, -CO_2R^{11}, or -SO_2R^{11};

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_3-C_8 cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_8)cycloalkyl, -C_1-C_6 haloalkyl, -$N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, OR^{13}, $N(R^{13})_2$, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, C_0-C_6 alkyl, -$NR^{13}SO_2$ R^{13}, or -$OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$.

In one embodiment, the invention provides the compound according to formula IIa or IIb, wherein:

R^1 is -L^1-R^5, wherein

L^1 is a bond, L^5, L^6, $-L^5-L^6-L^5-$, or $-L^6-L^5-L^6-$, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

m is 0, 1, 2, 3, or 4; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

L^6 is -CO-, $-SO_2-$, -O-, $-CON(R^{11})-$, $-C_3-C_6$cycloalkyl-, or -heterocyclyl-,

wherein the cycloalkyl, or heterocyclyl is optionally substituted with one or more R^{14}; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C, wherein

B is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl-; and

C is halogen, $-C_1-C_6$alkyl, or $-C_1-C_6$haloalkyl;

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(C_3-C_8$ cycloalkyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkenyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, $-C_1-C_6$ alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, $-C_1-C_6$ haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 is-L^3-R^7, wherein

L^3 is a bond; and

R^7 is halogen, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, or $-C(=O)N(R^{11})(OR^{11})$;

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen, -Z', -Y'-Z', or –X'-Y'-Z', wherein

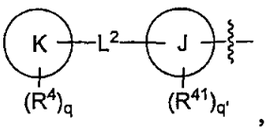
X' is –O-;

Y' is -[C(R^{15})$_2$]$_m$- or -C_3-C_6cycloalkyl; and

Z' is –H, halogen, –OR^{11}, -SR^{11}, -S(=O)$_2R^{11}$, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -N(R^{11})$_2$, -N(R^{11})C(=O)R^{11}, -CN, -S(=O)$_2$N(R^{11})$_2$, -C(=O)N(R^{11})(OR^{11}), or -N(R^{11})S(O=)$_2R^{11}$;

R^{21} is hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl; and

G is a group of the formula,



, wherein

J is aryl or heteroaryl;

K is aryl or heteroaryl;

each R^4 and R^{41} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, - G^1, -E- G^1, or –D-E- G^1, wherein

D is –O-;

E is -[C(R^{15})$_2$]$_m$- or -C_3-C_6cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -COR^{11}, -COOR^{11}, -CON(R^{11})$_2$, -C≡N, -OR^{11}, -OCON(R^{11})$_2$, -NR^{11}COR^{11}, -NR^{11}SO_2R^{11}, -N(R^{11})$_2$, -NR^{11}COOR^{11}, -SOR^{11}, -SO_2R^{11}, -SO_2NR^{11}COR^{11}, -SO_2N(R^{11})$_2$, or -SR^{11},

L^2 is a bond;

q is 1, 2, or 3; and

q' is 0, 1, 2, or 3;

each R^{10} is independently -R^{11}, -C(=O)R^{11}, -CO_2R^{11}, or -SO_2R^{11};

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_3-C_8 cycloalkyl, -C_1-C_6 haloalkyl, -N(R^{12})$_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_0-C_6alkylN(R^{13})$_2$, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkylCON(R^{13})$_2$, C_0-C_6 alkylCONR^{13}OR^{13}, C_0-C_6 alkylSO_2N(R^{13})$_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy,

aryloxyalkyl, C_{0-6}alkoxyaryl, arylC_{0-6} alkylcarboxy, C_0-C_6 alkyl, -$NR^{13}SO_2$ R^{13}, or -OC_{0-6} alkyl$COOR^{13}$;

each R^{13} is independently hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-; and

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$.

In one embodiment, the invention provides the compound according to formula IIa or IIb, wherein:

R^1 is -L^1-R^5, wherein

L^1 is a bond, -C_3-C_8 cycloalkyl-, or L^5, wherein

each L^5 is independently –$[C(R^{15})_2]_m$-, wherein

m is 0, 1, 2, or 3; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C, wherein

B is –$[C(R^{15})_2]_m$- or -C_3-C_6cycloalkyl-; and

C is –C_1-C_6alkyl or -C_1-C_6haloalkyl;

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, -C_1-C_6 alkyl, aryloxy, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, -C_1-C_6 haloalkyl, -SO_2R^{11}, -OR^{11}, -SR^{11}, -N_3, -SO_2R^{11}, -COR^{11}, -$SO_2N(R^{11})_2$, -$SO_2NR^{11}COR^{11}$, -C≡N, -$C(O)OR^{11}$, -$CON(R^{11})_2$, .$CON(R^{11})OR^{11}$, -$OCON(R^{11})_2$, -$NR^{11}COR^{11}$, -$NR^{11}CON(R^{11})_2$, -$NR^{11}COOR^{11}$, or -$N(R^{11})_2$;

R^2 is -L^3-R^7, wherein L^3 is a bond; and

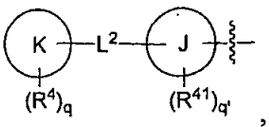
R^7 is –Z or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$- or -C_3-C_6cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-OC(=O)\text{-}R^{11}$, or $-OC(=O)\text{-}N(R^{11})_2$;

R^{21} is hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

G is a group of the formula,



, wherein

J is aryl or heteroaryl;

K is aryl or heteroaryl;

each R^4 and R^{41} is independently halogen, heteroaryl, heterocyclyl, - G^1, -E- G^1, or –D-E- G^1, wherein

D is –O-;

E is $-[C(R^{15})_2]_m$- or $-C_3$-C_6cycloalkyl; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$;

L^2 is a bond;

q is 1, 2, or 3; and

q' is 0, 1, 2 or 3;

each R^{10} is independently $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, or $-SO_2R^{11}$;

each R^{11} is independently -hydrogen, $-C_1$-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl–C_3-C_8 cycloalkyl, $-C_1$-C_6 haloalkyl, $-N(R^{12})_2$, aryl, $-(C_1$-$C_6)$alkyl-aryl, heteroaryl, $-(C_1$-$C_6)$alkyl-heteroaryl, heterocyclyl, or $-(C_1$-$C_6)$alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, OR^{13}, $N(R^{13})_2$, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, C_0-C_6 alkyl, $-NR^{13}SO_2$ R^{13}, or $-OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkylCON(R^{11})$_2$, C_0-C_6 alkylCONR^{11}OR^{11}, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkylCOOR^{11}.

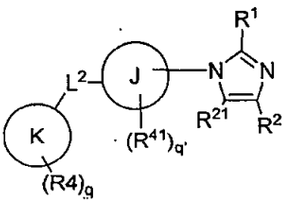
In one embodiment, the invention provides the compound according to formula IIa, IIb, IIc, and IId, wherein R^1 is L^1-R^5, wherein L^1 is a bond, and R^2, R^{21}, R^3, R^5, and G are as defined for formulas IIa-d; such compounds are hereafter designated formulas IIIa-d.

In another embodiment, the invention provides the compound according to formulas IIa-d, wherein R^1 is L^1-R^5,

wherein L^1 is a bond; and R^5 is aryl optionally substituted with one or more R^{5a},

and R^2, R^{21}, R^3, and G are as defined for formulas IIa-d; such compounds are hereafter designated formulas IVa-d.

In another embodiment, the invention provides the compound of formula IV,



(IV),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, J, K, L^2, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according of the formula IV, wherein L^2 is a bond.

In another embodiment, the invention provides the compound according of the formula IV, wherein K is phenyl.

In another embodiment, the invention provides the compound according of the formula IV, wherein L^2 is a bond and K is phenyl.

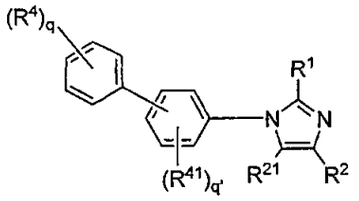
In another embodiment, the invention provides the compound according of the formula IV, wherein L^2 is a bond and J is phenyl.

In another embodiment, the invention provides the compound according of the formula IV, wherein J is phenyl.

In another embodiment, the invention provides the compound according of the formula IV, wherein J is phenyl, and K is phenyl.

In another embodiment, the invention provides the compound according of the formula IV, wherein J is phenyl, K is phenyl, and L^2 is a bond.

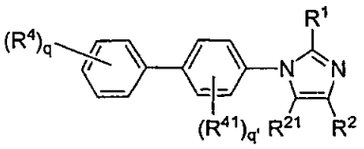
In another embodiment, the invention provides the compound of formula V,



(V),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound of formula VII,



(VII),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^{21} is –H, -halogen, -C_1-C_6alkyl, or –C_1-C_6haloalkyl; R^1 is as defined for formula IVa-d; and R^2, R^4, R^{41}, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^{41} is independently halogen, -G^1, -E-G^1, or –D-E-G^1, wherein

D is –O-;

E is -$[C(R^{15})_2]_m$-;

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$NR^{11}COR^{11}$, -$NR^{11}SO_2R^{11}$, -$N(R^{11})_2$, -SO_2R^{11}, or -$SO_2N(R^{11})_2$.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen,

such compounds are hereafter designated formula VIIa.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$N(R^{11})_2$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11}.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11},

such compounds are hereafter designated formula VIIb.

In another embodiment, the invention provides the compound according of the formula VII, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl;

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -$N(R^{11})_2$, -C(=N-OH)R^{11}, -C(=S)$N(R^{11})_2$, -CN, -$S(=O)_2N(R^{11})_2$, -C(=O)$N(R^{11})N(R^{11})_2$, -C(=O)$N(R^{11})(OR^{11})$, -OC(=O)-R^{11}, or -OC(=O)-$N(R^{11})_2$.

In another embodiment, the invention provides the compound according of the formula VII, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$,

such compounds are hereafter designated formula VIIc.

In another embodiment, the invention provides the compound according of the formula VIIa, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11},

such compounds are hereafter designated formula VIId.

In another embodiment, the invention provides the compound according of the formula VIIb, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$,

such compounds are hereafter designated formula VIIe.

In another embodiment, the invention provides the compound according of the formula VIIc, wherein each R^{41} is independently halogen, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, or halogen,

such compounds are hereafter designated formula VIIf.

In another embodiment, the invention provides the compound according of the formula VIId, wherein R^2 is $-L^3$-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3$-$C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or $(C_1$-$C_6)$alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$,

such compounds are hereafter designated formula VIIg.

In another embodiment, the invention provides the compound according of the formula VIIe, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8cycloalkyl, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, or $-N(R^{11})_2$.

In another embodiment, the invention provides the compound according of the formula VIIe, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8cycloalkyl, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, or $-N(R^{11})_2$; and R^{21} is –H.

In another embodiment, the invention provides the compound according of the formula VIIf, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according of the formula VIIf, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and R^{21} is –H.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8cycloalkyl, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, or $-N(R^{11})_2$.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according of the formula VII, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and R^{21} is –H.

In another embodiment, the invention provides the compound according of the formula VIIg, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according of the formula VIIg, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and R^{21} is –H.

In another embodiment, the invention provides the compound according to formula VII, wherein R^{21} is hydrogen, halogen, nitro, cyano, aryl, heteroaryl, heterocyclyl, -C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-heteroaryl, -C_1-C_6 alkyl-aryl, -Z, -Y-Z, or -X-Y-Z, wherein

X is -O-;

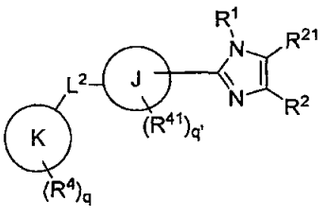
Y is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, or C_3-C_8 cycloalkyl; and

Z is -H, -CN, halogen, -OR^{11}, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -CN, -N_3, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, -$OC(=O)$-$R^{11}$, -$OC(=O)$-$N(R^{11})_2$, or -$N(R^{11})COOR^{11}$.

In another embodiment, the invention provides the compound according to formula VII, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to any of formulas VIIa-VIIg, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound of formula VIII,



(VIII),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, J, K, L^2, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula VIII wherein K is phenyl or pyridyl.

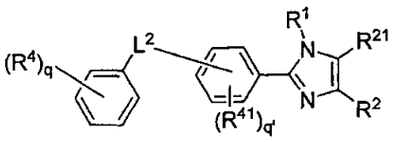
In another embodiment, the invention provides the compound according to formula VIII wherein K is phenyl.

In another embodiment, the invention provides the compound according to formula VIII wherein K is pyridyl.

In another embodiment, the invention provides the compound according to formula VIII wherein J is phenyl.

In another embodiment, the invention provides the compound according to formula VIII wherein J is phenyl and K is phenyl.

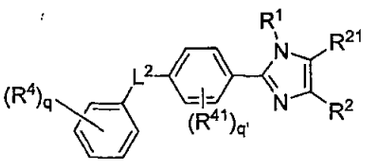
In another embodiment, the invention provides the compound of formula IX,



(IX),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as as defined for formula IIa-d.

In another embodiment, the invention provides the compound of formula X,



(X),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula X, wherein L^2 is a bond; such compounds are designated hereafter as formula XI.

In another embodiment, the invention provides the compound according to formula XI, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8cycloalkyl, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, or $-N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XI, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl,

such compounds are designated hereafter as formula XIa.

In another embodiment, the invention provides the compound according to formula XI, wherein R^2 is $-L^3$-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3$-$C_6)$cycloalkyl-, or C_2-C_6alkenyl;

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)\text{-}R^{11}$, or $-OC(=O)\text{-}N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XI, wherein R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl;

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$,

such compounds are designated hereafter as formula XIb.

In another embodiment, the invention provides the compound according to formula XI, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formula XI, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XIa, wherein R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl;

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$,

such compounds are designated hereafter as formula XId.

In another embodiment, the invention provides the compound according to formula XIb, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XId, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is -[C(R^{15})$_2$]$_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

In another embodiment, the invention provides the compound according to formula XI, wherein R^{21} is hydrogen, halogen, nitro, cyano, aryl, heteroaryl, heterocyclyl, -C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-heteroaryl, -C_1-C_6 alkyl-aryl, -Z, -Y-Z, or -X-Y-Z, wherein

X is -O-;

Y is -[C(R^{15})$_2$]$_m$-, -(C_3-C_6)cycloalkyl-, -C_2-C_6 alkenyl, or C_3-C_8 cycloalkyl; and

Z is -H, -CN, halogen, -OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -N(R^{11})$_2$, -CN, -N_3, -SO_2R^{11}, -S(=O)$_2$N(R^{11})$_2$, -C(=O)N(R^{11})N(R^{11})$_2$, -C(=O)N(R^{11})(OR^{11}), -OC(=O)-R^{11}, -OC(=O)-N(R^{11})$_2$, or -N(R^{11})COOR^{11}.

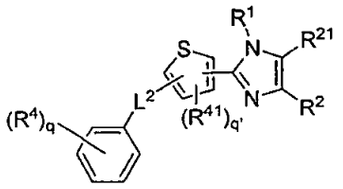
In another embodiment, the invention provides the compound according to formula XI, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to any of formulas XIa-XId, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula VIII, wherein J is thienyl.

In another embodiment, the invention provides the compound according to formula VIII, wherein J is thienyl and K is phenyl.

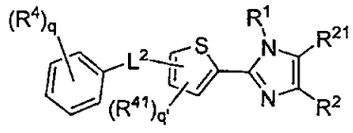
In another embodiment, the invention provides the compound of formula XII,



(XII),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as defined for formula IIa-d.

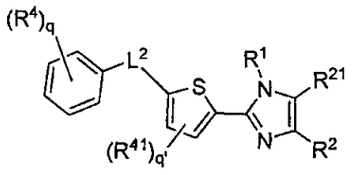
In another embodiment, the invention provides the compound of formula XIII,



(XIII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound of formula XIV,



(XIV)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XIV, wherein L^2 is a bond, such compounds are designated hereafter as formula XV.

In another embodiment, the invention provides the compound according to formula XV, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-C{\equiv}N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, or $-N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XV, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl, such compounds are designated hereafter as formula XVa.

In another embodiment, the invention provides the compound according to formula XV, wherein R^2 is $-L^3$-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3$-$C_6)$cycloalkyl-, or C_2-C_6alkenyl;

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)$-R^{11}, or $-OC(=O)$-$N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XV, wherein R^2 is $-L^3$-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3$-$C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or $(C_1$-$C_6)$alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$,

such compounds are designated hereafter as formula XVb.

In another embodiment, the invention provides the compound according to formula XV, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formula XV, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XVa,

R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$,

such compounds are designated hereafter as formula XVd.

In another embodiment, the invention provides the compound according to formula XVb, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XVd, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XV, wherein R^{21} is hydrogen, halogen, nitro, cyano, aryl, heteroaryl, heterocyclyl, $-C_1-C_6$ alkyl-heterocyclyl, $-C_1-C_6$ alkyl-heteroaryl, $-C_1-C_6$ alkyl-aryl, -Z, -Y-Z, or -X-Y-Z, wherein

X is -O-;

Y is $-[C(R^{15})_2]_m-$, $-C_2-C_6$ alkenyl, or C_3-C_8 cycloalkyl; and

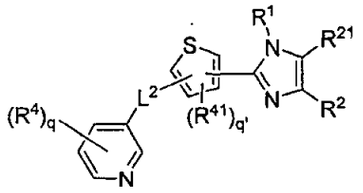
Z is -H, -CN, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, or $-N(R^{11})COOR^{11}$.

In another embodiment, the invention provides the compound according to formula XV, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to any of formulas XVa-XVd, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula VIII, wherein K is pyridinyl.

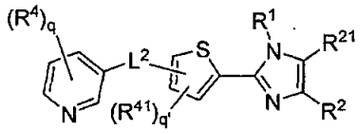
In another embodiment, the invention provides the compound according to formula XVI,



(XVI)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as defined for formula IIa-d.

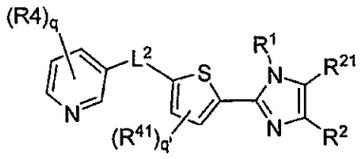
In another embodiment, the invention provides the compound according to formula XVII,



(XVII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XVIII,



(XVIII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where R^1 is as defined for formula IVa-d, and R^2, R^{21}, R^4, R^{41}, L^2, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XVIII, wherein L^2 is a bond, such compounds are designated hereafter as formula XIX.

In another embodiment, the invention provides the compound according to formula XIX, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, or $-N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XIX, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl, such compounds are designated hereafter as formula XIXa.

In another embodiment, the invention provides the compound according to formula XIX, wherein R^2 is $-L^3$-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)\text{-}R^{11}$, or $-OC(=O)\text{-}N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XIX, wherein R^2 is $-L^3$-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl; and

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$,

such compounds are designated hereafter as formula XIXb.

In another embodiment, the invention provides the compound according to formula XIX, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m$-; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formula XIX, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XIXa, wherein R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$

such compounds are designated hereafter as formula XIXd.

In another embodiment, the invention provides the compound according to formula XIXb, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XIXd, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XIX, wherein R^{21} is hydrogen, halogen, nitro, cyano, aryl, heteroaryl, heterocyclyl, $-C_1-C_6$ alkyl-heterocyclyl, $-C_1-C_6$ alkyl-heteroaryl, $-C_1-C_6$ alkyl-aryl, -Z, -Y-Z, or -X-Y-Z, wherein

X is -O-;

Y is $-[C(R^{15})_2]_m-$, $-C_2-C_6$ alkenyl, or C_3-C_8 cycloalkyl; and

Z is -H, -CN, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, or $-N(R^{11})COOR^{11}$.

In another embodiment, the invention provides the compound according to formula XIX, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to any of formulas XIXa-XIXd, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is heteroaryl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas IIIa-d, wherein R_1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a}; and J is phenyl.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a}; and K is phenyl.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a}; J is phenyl; and K is phenyl.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a}; J is phenyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with at least one or more R^{5a};

J is phenyl; K is phenyl; L^2 is a bond;

and R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a};

J is phenyl; K is phenyl; L^2 is a bond;

and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a};

J is phenyl; K is phenyl; L^2 is a bond;

and each R^{41} is independently halogen, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_{m'}-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula IIIa-d, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a};

J is phenyl; K is phenyl; L^2 is a bond;

and R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

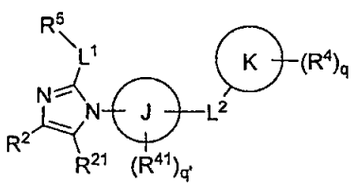
In another embodiment, the invention provides the compound according to formula IIa-d, wherein L^1 is $-[C(R^{15})_2]_{m'}-$ or $-C_3$-C_8 cycloalkyl, wherein

m' is any of 1 to 4; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl,

and R^2, R^{21}, R^3, R^5, and G are as defined for formulas IIa-d.

In another embodiment, the invention provides the compound of formula XX,



(XX),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein

L^1 is $-[C(R^{15})_2]_{m'}-$ or $-C_3$-C_8 cycloalkyl, wherein

m' is any of 1 to 3; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl,

and R^2, R^{21}, R^4, R^{41}, R^5, L^2, J, K, q, and q' are as defined for formula IIa-d.

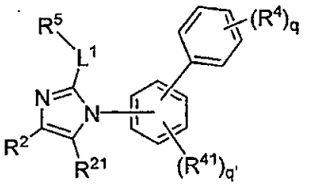
In another embodiment, the invention provides the compound according to formula XX, wherein J is phenyl.

In another embodiment, the invention provides the compound according to formula XX, wherein K is phenyl.

In another embodiment, the invention provides the compound according to formula XX, wherein J is phenyl and K is phenyl.

In another embodiment, the invention provides the compound according to formula XX, wherein J is phenyl; K is phenyl; and L^2 is a bond.

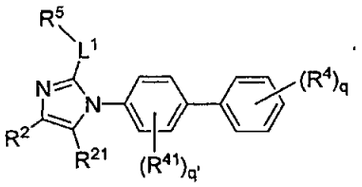
In another embodiment, the invention provides the compound of formula XXI,



(XXI)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where L^1 is as defined in formula XX, and R^2, R^{21},R^4, R^{41}, R^5, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XXII,



(XXII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where L^1 is as defined in formula XX, and R^2, R^{21}, R^4, R^{41}, R^5, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XXII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a},

such compounds are designated hereafter as formula XXIII.

In another embodiment, the invention provides the compound according to formula XXIII, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_{m'}$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, -(C_3-C_6)cycloalkyl-, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXIII, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E\text{-}G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XXIII, wherein each R^{41} is independently halogen, $-G^1$, or $-E\text{-}G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXIII, wherein R^{21} is hydrogen, halogen, nitro, cyano, $C_1\text{-}C_6$alkyl, or $C_1\text{-}C_6$haloalkyl.

In another embodiment, the invention provides the compound according to formula XXII, wherein R^{15} is –H; m is 1, 2, or 3; and R^5 is heterocyclyl optionally substituted with one or more R^{5a}, such compounds are designated hereafter as formula XXIV.

In another embodiment, the invention provides the compound according to formula XXIV, wherein R^2 is $-L^3\text{-}R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3\text{-}C_6)$cycloalkyl-, or $C_2\text{-}C_6$alkenyl,

wherein each R^{15} is independently H, halogen, $-(C_3\text{-}C_6)$cycloalkyl-, or $(C_1\text{-}C_6)$alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXIV, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E\text{-}G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XXIV, wherein each R^{41} is independently halogen, $-G^1$, or $-E\text{-}G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXIV, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula XXII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m is 1, 2, 3, or 4; and R^5 is heterocyclyl optionally substituted with one or more R^{5a}, such compounds are designated hereafter as formula XXIVa.

In another embodiment, the invention provides the compound according to formula XXIVa, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXIVa, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

In another embodiment, the invention provides the compound according to formula XXIVa, wherein each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

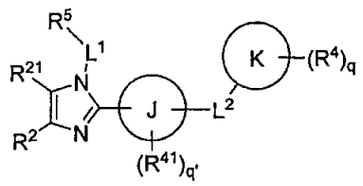
E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl or halogen.

In another embodiment, the invention provides the compound according to formula XXIVa, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound of formula XXVI,



(XXVI),

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein

L^1 is $-[C(R^{15})_2]_{m'}-$ or $-C_3$-C_8cycloalkyl, wherein

m' is any of 1 to 3; and

each R^{15} is independently hydrogen, halogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, or $(C_1$-$C_6)$haloalkyl,

and R^2, R^{21}, R^4, R^{41}, R^5, L^2, J, K, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XXVI, wherein J is aryl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein J is phenyl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein J is heteroaryl, such compounds are refered to hereafter as compounds of formula XXVIa.

In another embodiment, the invention provides the compound according to formula XXVIa wherein K is aryl.

In another embodiment, the invention provides the compound according to formula XXVIa wherein K is phenyl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein K is aryl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein K is heteroaryl, such compounds are refered to hereafter as compounds of formula XXVIb.In another embodiment, the invention provides the compound according to formula XXVIb wherein J is aryl.

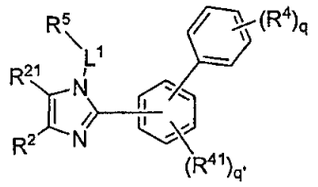
In another embodiment, the invention provides the compound according to formula XXVIb wherein J is phenyl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein K is phenyl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein J is phenyl and K is phenyl.

In another embodiment, the invention provides the compound according to formula XXVI, wherein J is phenyl; K is phenyl; and L^2 is a bond.

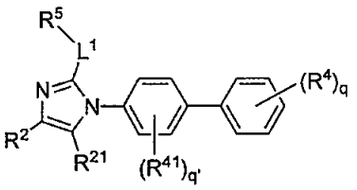
In another embodiment, the invention provides the compound of formula XXVII,



(XXVII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where L^1 is as defined in formula XXVI, and R^2, R^{21}, R^4, R^{41}, R^5, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XXVIII,



(XXVIII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, where L^1 is as defined in formula XXVI, and R^2, R^{21}, R^4, R^{41}, R^5, q, and q' are as defined for formula IIa-d.

In another embodiment, the invention provides the compound according to formula XXVIII, wherein R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, $-(C_3-C_6)$cycloalkyl-, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXVIII, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XXVIII, wherein each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXVII, wherein each R^{15} is independently –H, –(C_1-C_6)alkyl, or –(C_3-C_6)cycloalkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a}, such compounds are designated hereafter as formula XXIX.

In another embodiment, the invention provides the compound according to formula XXIX, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -[$C(R^{15})_2$]$_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, -(C_3-C_6)cycloalkyl-, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C(=N-OH)R^{11}, or -C(=S)N(R^{11})$_2$.

In another embodiment, the invention provides the compound according to formula XXIX, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein E is -[$C(R^{15})_2$]$_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

In another embodiment, the invention provides the compound according to formula XXIX, wherein each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -[$C(R^{15})_2$]$_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXIX, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula XXVIII, wherein R^{15} is –H; m is 1, 2, or 3; and R^5 is heterocyclyl optionally substituted with one or more R^{5a}, such compounds are designated hereafter as formula XXX.

In another embodiment, the invention provides the compound according to formula XXX, wherein R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -[$C(R^{15})_2$]$_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, -(C_3-C_6)cycloalkyl-, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXX, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E\text{-}G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XXX, wherein each R^{41} is independently halogen, $-G^1$, or $-E\text{-}G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXX, wherein R^{21} is hydrogen, halogen, nitro, cyano, $C_1\text{-}C_6$alkyl, or $C_1\text{-}C_6$haloalkyl.

In another embodiment, the invention provides the compound according to formula XXVIII, wherein each R^{15} is independently –H or $-(C_1\text{-}C_2)$alkyl; m is 1, 2, 3, or 4; and R^5 is heterocyclyl optionally substituted with one or more R^{5a}, such compounds are designated hereafter as formula XXXI.

In another embodiment, the invention provides the compound according to formula XXXI, wherein R^2 is $-L^3\text{-}R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3\text{-}C_6)$cycloalkyl-, or $C_2\text{-}C_6$alkenyl,

wherein each R^{15} is independently H, halogen, $-(C_3\text{-}C_6)$cycloalkyl-, or $(C_1\text{-}C_6)$alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXXI, wherein each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E\text{-}G^1$, wherein E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XXXI, wherein each R^{41} is independently halogen, $-G^1$, or $-E\text{-}G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl or halogen.

In another embodiment, the invention provides the compound according to formula XXXI, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula XXII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is heteroaryl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$- or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$C(=N\text{-}OH)R^{11}$, or -$C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2;

R^5 is heteroaryl optionally substituted with one or more R^{5a}; and

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

In another embodiment, the invention provides the compound according to formula XXII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXVII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is heteroaryl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formula XXVII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

In another embodiment, the invention provides the compound according to formula XXVII, wherein each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and

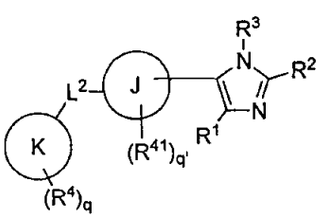
each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

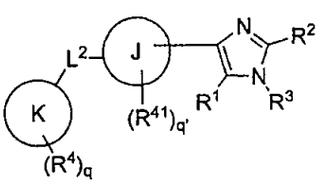
E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII,





(XXXII) (XXXIII)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^3 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl, and R^1, R^2, R^4, R^{41}, L^2, q, and q' are as defined for formulas IIa-d.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is aryl; K is aryl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is phenyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is phenyl; K is phenyl; L^2 is a bond; and R^1 is phenyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is phenyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is phenyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is phenyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and R^2 is $-L^3$-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3$-$C_6)$cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or $(C_1$-$C_6)$alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is phenyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is heteroaryl; K is aryl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is phenyl; L^2 is a bond; and R^1 is phenyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_{m'}-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is phenyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is heteroaryl; K is heteroaryl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is pyridyl, pyrimidyl, or pyrazinyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is pyridyl, pyrimidyl, or pyrazinyl; L^2 is a bond; and R^1 is phenyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is pyridyl, pyrimidyl, or pyrazinyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is pyridyl, pyrimidyl, or pyrazinyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is pyridyl, pyrimidyl, or pyrazinyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

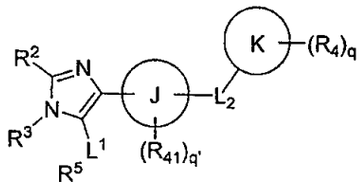
Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

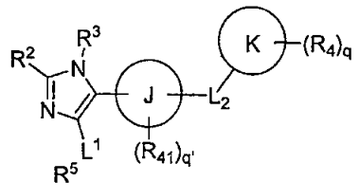
Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXXII and XXXIII, wherein J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; K is pyridyl, pyrimidyl, or pyrazinyl; L^2 is a bond; R^1 is phenyl optionally substituted with one or more R^{5a}; and each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV,



(XXXIV)



(XXXV)

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^3 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl, and R^1, R^2, R^4, R^{41}, L^2, q, and q' are as defined for formulas IIa-d.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is aryl; K is aryl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; and L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is heteroaryl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; and L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$- or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; and L^2 is a bond; each R^{15} is independently –H or –

(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -[$C(R^{15})_2$]$_{m'}$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; and L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; R^5 is heteroaryl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -[$C(R^{15})_2$]$_{m'}$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; and each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -[$C(R^{15})_2$]$_{m'}$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$N(R^{11})_2$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11}.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -[$C(R^{15})_2$]$_{m'}$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a}; and R^2 is -L^3-R^7, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; each R^{15} is independently –H or –(C_1-C_2)alkyl; m' is 1 or 2; and R^5 is phenyl optionally substituted with one or more R^{5a}; and each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; R^{15} is –H; m is 1, 2, or 3; and R^5 is heterocyclyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; R^{15} is –H; m is 1, 2, or 3;

R^5 is heterocyclyl optionally substituted with one or more R^{5a}; and each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; R^{15} is –H; m is 1, 2, or 3; R^5 is heterocyclyl optionally substituted with one or more R^{5a}; and each R^{41} is independently halogen, $-G^1$, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; R^{15} is –H; m is 1, 2, or 3;

R^5 is heterocyclyl optionally substituted with one or more R^{5a}; and R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXXIV and XXXV, wherein J is phenyl; K is phenyl; L^2 is a bond; R^{15} is –H; m is 1, 2, or 3; R^5 is heterocyclyl optionally substituted with one or more R^{5a}; and each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is aryl or heteroaryl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl, pyridyl, or thienyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is pyridyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is thienyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein K is aryl or heteroaryl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein K is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein K is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein K is phenyl or pyridyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein K is pyridyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein K is phenyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is aryl or heteroaryl; and K is aryl or heteroaryl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is aryl or heteroaryl; K is aryl or heteroaryl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein

J is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl;

K is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl; and

L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl; K is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl, pyridyl, or thienyl; K is phenyl or pyridyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is pyridyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is thienyl; K is phenyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is phenyl; K is pyridyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is pyridyl; K is pyridyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein J is thienyl; K is pyridyl; and L^2 is a bond.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein R^5 is aryl, heterocyclyl, or heteroaryl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein R^5 is aryl or heteroaryl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein R^5 is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein L^1 is a bond; and R^5 is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein L^1 is a bond; and R^5 is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein L^1 is a bond; and R^5 is phenyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, where in L^1 is a bond; and R^5 is pyridyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein L^1 is a bond; and R^5 is thienyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula IIa-d wherein R^{21} is hydrogen, halogen, nitro, cyano, aryl, heteroaryl, heterocyclyl, -C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-heteroaryl, -C_1-C_6 alkyl-aryl, -Z, -Y-Z, or -X-Y-Z, wherein

X is -O-;

Y is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, or C_3-C_8 cycloalkyl; and

Z is -H, -CN, halogen, -OR^{11}, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -CN, -N_3, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, -$OC(=O)$-$R^{11}$, -$OC(=O)$-$N(R^{11})_2$, or -$N(R^{11})COOR^{11}$.

In another embodiment, the invention provides the compound according to formula IIa-d wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula IIa-d wherein R^3 is hydrogen, aryl, heteroaryl, heterocyclyl, -C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-heteroaryl, -C_1-C_6 alkyl-aryl, -Z, or -Y-Z wherein

Y is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, or C_3-C_8 cycloalkyl; and

Z is -H, -CN, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, or $-N(R^{11})COOR^{11}$.

In another embodiment, the invention provides the compound according to formula IIa-d wherein R^3 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV wherein R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, or $-[C(R^{15})_2]-Z$, wherein

each R^{15} is independently H, halogen, or (C_1-C_2)alkyl; and

Z is –H, halogen, $–OR^{11"}$, $-C(=O)R^{11"}$, $-C(=O)OR^{11"}$, $-C(=O)N(R^{11"})_2$, $-C(=N-OH)R^{11"}$, or $-C(=S)N(R^{11"})_2$,

wherein $R^{11"}$ is –H or $–(C_1-C_6$ alkyl).

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein R^2 is -halogen, $–CF_3$, $-CH_2OH$, $–CH_2SO_2Me$, $-C(CH_3)_2OH$, or $–C(CH_3)_2SO_2Me$.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein R^2 is –halogen, $–CF_3$, $-CH_2OH$, or $-C(CH_3)_2OH$.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein R^2 is $-CF_3$ or $-C(CH_3)_2OH$.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein

each R^4 is independently halogen, -CH_2- G^1, -C(H)(F)- G^1, –CF_2- G^1, wherein

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -F, -$OR^{11'}$, or -$SO_2R^{11'}$

wherein $R^{11'}$ is –H or –C_1-C_6alkyl.

In another embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein each R^4 is independently -CH_3, -CF_3, -CF_2H, -CH_2F, -OH, -OMe, -CH_2OH, or -SO_2(C_1-C_3alkyl).

In one embodiment, the invention provides the compound according to any of the formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formulas IIa-d, IIIa-d, Iva-d, IV-XXIV, and XXVI-XXXV, wherein wherein each R^{41} is independently halogen, methyl or trifluoromethyl.

In another embodiment, the invention provides the compound according to formulas to formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein R^{21} is hydrogen, halogen, nitro, cyano, aryl, heteroaryl, heterocyclyl, -C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-heteroaryl, -C_1-C_6 alkyl-aryl, -Z, -Y-Z, or -X-Y-Z, wherein

X is -O-;

Y is -$[C(R^{15})_2]_m$-. -C_2-C_6 alkenyl, or C_3-C_8 cycloalkyl;

Z is -H, -CN, halogen, -OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -$N(R^{11})_2$, -CN, -N_3, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -C(=O)$N(R^{11})N(R^{11})_2$, -C(=O)$N(R^{11})(OR^{11})$, -OC(=O)-R^{11}, -OC(=O)-$N(R^{11})_2$, or -$N(R^{11})COOR^{11}$;

In another embodiment, the invention provides the compound according to formulas IIa-d, IIIa-d, IVa-d, IV-XXIV, and XXVI-XXXV, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

In another embodiment, the invention provides the compound according to formula IIa-d, wherein R^1 is -L^1-R^5, wherein L^1 is a bond, -$[C(R^{15})_2]_m$-, or -C_3-C_8 cycloalkyl-; and

R^5 is phenyl or pyridyl, each optionally substituted with one or two R^{5a}, wherein

each R^{5a} is independently –halogen, -C_1-C_6 alkoxy, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl;

R^2, R^{21}, and R^3 are each independently –H, –$[C(R^{15})_2]_m$-OH, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, halogen, -$C(O)N(R^{11})_2$, or -$COOR^{11}$;

L^2 is a bond;

J is phenyl, pyridyl, or thienyl;

K is phenyl, or pyridyl;

each R^{41} is -halogen, -C_1-C_6 alkyl, or C_1-C_6 -haloalkyl; and

each R^4 is -halogen, –$[C(R^{15})_2]_m$-OH, –SO_2R^{11}, –$SO_2N(R^{11})_2$, -$C(O)N(R^{11})_2$, -$COOR^{11}$, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl.

In another embodiment, the invention provides the compound according to formula IVa-d, wherein

R^1 is -L^1-R^5, wherein

L^1 is a bond, -$[C(R^{15})_2]_m$-, or -C_3-C_8 cycloalkyl-; and

R^5 is phenyl or pyridyl, each optionally substituted with one or two R^{5a}, wherein

each R^{5a} is independently –halogen, -C_1-C_6 alkoxy, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl;

R^2, R^{21}, and R^3 are each independently –H, –$[C(R^{15})_2]_m$-OH, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, halogen, -$C(O)N(R^{11})_2$, or -$COOR^{11}$;

L^2 is a bond;

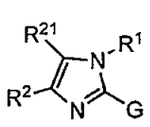
J is phenyl, pyridyl, or thienyl;

K is phenyl, or pyridyl;

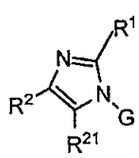
each R^{41} is -halogen, -C_1-C_6 alkyl, or C_1-C_6 -haloalkyl; and

each R^4 is -halogen, –$[C(R^{15})_2]_m$-OH, –SO_2R^{11}, –$SO_2N(R^{11})_2$, -$C(O)N(R^{11})_2$, -$COOR^{11}$, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl.

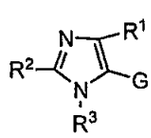
In a second aspect, the invention provides intermediate compounds according to one of the formulas XXVa-d,



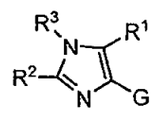
XXVa



XXVb



XXVc



XXVd

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein,

R^1 is $-L^1-R^5$, wherein

L^1 is a bond, L^5, L^6, $-L^5-L^6-L^5-$, or $-L^6-L^5-L^6-$, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

each L^6 is independently -CS-, -CO-, $-SO_2-$, -O-, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, or $-C(=NN(R^{11})_2)-$, -aryl-, $-C_3-C_8$cycloalkyl-, -heteroaryl-, or -heterocyclyl-;

wherein the aryl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more R^{14};

or each L^6 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, or $-SO_2N(R^{10})$; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C,

wherein

B is $-[C(R^{15})_2]_m-$ or $-C_3-C_8$ cycloalkyl-; and

C is halogen, $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, or $-N(R^{11})_2$,

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, $(C_3-C_8$ cycloalkyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkenyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$ $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, $-C_1-C_6$ alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, C_1-C_6 haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 and R^{21} are $-L^3-R^7$, wherein

each L^3 is independently a bond or $-(CH_2)_m-V^1-(CH_2)_n-$ wherein

n is 0-6; and

V^1 is $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-OCO-$, $-CO-$, $-CS-$, $-CONR^{10}-$, $-C(=N-R^{11})-$, $-C(=N-OR^{11})-$, $-C[=N-N(R^{11})_2]$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, C_3-C_6cyclo alkyl, or C_3-C_6 cyclohaloalkyl;

or each L^3 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, or $-SO_2N(R^{10})-$; and

each R^7 is independently hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, -Y-Z, or –X-Y-Z, wherein

X is –O-;

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl, $-C_3$-C_8cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, or $-OC(=O)-N(R^{11})_2$,

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen, haloaryl, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, $C(R^{11})=C(R^{11})$-COOH, aryl, heteroaryl, heterocyclyl, heterocyclyloxy, heteroaryloxy, -Z', -Y'-Z', or –X'-Y'-Z', wherein

X' is –O-;

Y' is $-[C(R^{15})_2]_m-$ or $-C_3$-C_8cycloalkyl; and

Z' is –H, halogen, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)\ R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-OR^{11}$, $-N(R^{11})C(=O)-R^{11}$, or $-N(R^{11})S(O=)_2R^{11}$,

wherein each R^{7a} is optionally substituted with one or more R^8,

wherein each R^8 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyl(OR^{11}), C_0-C_6 alkylOR^{11}, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, or C_0-C_6 alkylSO_2R^{11},

provided that R^2 and R^{21} are not simultaneously hydrogen

R^3 is –L-R^6, wherein

L is a bond, –X^3-$(CH_2)_n$-X^3-, -$(CH_2)_m$-X^3-$(CH_2)_n$- or -$(CH_2)_{1+w}$-Y^3-$(CH_2)_w$- wherein

n is 0-6; each w is independently 0 – 5; and

each X^3 is independently a bond, -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -C≡C-, -CO-, -CS-, -$CONR^{10}$-, -C(=N)(R^{11})-, -C(=N-OR^{11})-, -C[=N-$N(R^{11})_2$], -CO_2-, -SO_2-, or -$SO_2N(R^{10})$-; and

Y^3 is -O-, -S-, -NR^7-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -OCO-,-OC(=O)$N(R^{10})$-, -$NR^{10}CONR^{10}$-, -$N(R^{10})SO_2$-, or -$NR^{10}CSNR^{10}$-;

or L is C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$; and

R^6 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, -CN, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -$N(R^{11})_2$, -SO_2R^{11}, -S(=O)$_2N(R^{11})_2$, -C(=O)$N(R^{11})N(R^{11})_2$, or -C(=O)$N(R^{11})(OR^{11})$, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with with one or more R^{6a}, wherein

each R^{6a} is independently -Z", –Y"-Z", or–X"-Y"-Z", wherein

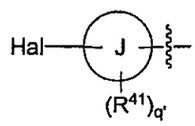
X" is –O-;

Y" is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with at least one group which is each independently Z";

Z" is -H, -CN, halogen, -OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -$N(R^{11})_2$, -N_3, -SO_2R^{11}, -S(=O)$_2N(R^{11})_2$, -C(=O)$N(R^{11})N(R^{11})_2$, -$N(R^{11})C(=O)N(R^{11})_2$, -OC(=O)-$OR^{11}$, -C(=O)$N(R^{11})(OR^{11})$, -OC(=O)-$R^{11}$, -OC(=O)-$N(R^{11})_2$, or -$N(R^{11})COOR^{11}$; and

G is a group of the formula,



wherein

Hal is halogen;

J is aryl or heteroaryl;

each R^{41} is independently -halogen, nitro, $CR^{11}=CR^{11}COOR^{11}$, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, -G^1, -E-G^1, or –D-E-G^1, wherein

D is –O-;

E is -$[C(R^{15})_2]_m$- or -C_3-C_8cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$OCON(R^{11})_2$, -$OCOOR^{11}$, -N_3, -$NR^{11}COR^{11}$, -$NR^{11}SO_2R^{11}$, -$N(R^{11})_2$, -$NR^{11}COOR^{11}$, -SOR^{11}, -SO_2R^{11}, -$SO_2NR^{11}COR^{11}$, -$SO_2N(R^{11})_2$, or -SR^{11};

wherein each R^4 is optionally substituted with one or more R^{4a},

wherein each R^{4a} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, C_1-C_6 alkoxyaryl, arylC_0-C_6 alkylcarboxy, -G', -E'-G', or –D'-E'-G', wherein

D' is –O-;

E' is -$[C(R^{15})_2]_m$- or -C_3-C_8cycloalkyl-; and

G' is –H, -halogen, -COR^{11}, -$COOR^{11}$, -C≡N, -OR^{11}, -$NR^{11}SO_2R^{11}$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11};

each m is 0, 1, 2, 3, 4, 5, or 6; and

q' is 0, 1, 2, 3, or 4,

each R^{10} is independently -R^{11}, -C(=O)R^{11}, -CO_2R^{11}, or -SO_2R^{11};

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_1-C_6 haloalkyl, -$N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, -C_0-C_6 alkyl$N(R^{13})_2$, -$NR^{13}SO_2R^{13}$, or -$OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein Hal is –Cl, -Br, or –I.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein Hal is –Cl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein Hal is -Br.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein Hal is –I.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is aryl or heteroaryl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is phenyl, pyridyl, or thienyl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is phenyl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is pyridyl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein J is thienyl.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein R^5 is aryl, heterocyclyl, or heteroaryl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein R^5 is aryl or heteroaryl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein R^5 is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein L^1 is a bond.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein L^1 is a bond; and R^5 is phenyl, pyridyl, thienyl, pyrrolyl, furanyl, pyrimidinyl, pyrazinyl, imidazoyl, pyrazoyl, oxazoyl, thiazoyl, isoxazoyl, isothiazoyl, triazoyl, triazinyl, tetrazoyl, or tetrazinyl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein L^1 is a bond; and R^5 is phenyl, pyridyl, thienyl, pyrrolyl, or furanyl, wherein R^5 is optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein L^1 is a bond; and R^5 is phenyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein L^1 is a bond; and R^5 is pyridyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein L^1 is a bond; and R^5 is thienyl optionally substituted with one or more R^{5a}.

In another embodiment, the invention provides the compound according to formulas XXVa-d, wherein R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

In another embodiment, the invention provides the compound according to formulas XXVa-d, wherein R^2 is $-L^3-R^7$, wherein L^3 is a bond; and

R^7 is hydrogen, halogen, or $-[C(R^{15})_2]-Z$, wherein

each R^{15} is independently H, halogen, or (C1-C2)alkyl; and

Z is –H, halogen, $-OR^{11"}$, $-C(=O)R^{11"}$, $-C(=O)OR^{11"}$, $-C(=O)N(R^{11"})_2$, $-C(=N-OH)R^{11"}$, or $-C(=S)N(R^{11"})_2$,

wherein $R^{11"}$ is –H or $-(C_1-C_6$ alkyl).

In another embodiment, the invention provides the compound according to formulas XXVa-d, wherein R^2 is -halogen, $-CF_3$, $-CH_2OH$, $-CH_2SO_2Me$, $-C(CH_3)_2OH$, or $-C(CH_3)_2SO_2Me$.

In another embodiment, the invention provides the compound according to formulas XXVa-d, wherein R^2 is –halogen, $-CF_3$, $-CH_2OH$, or $-C(CH_3)_2OH$.

In another embodiment, the invention provides the compound according to formulas XXVa-d, wherein R^2 is $-CF_3$ or $-C(CH_3)_2OH$.

In one embodiment, the invention provides the compound according to formulas XXVa-d, wherein each R^{41} is independently halogen, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, or halogen.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein R^1 is L^1-R^5, wherein L^1 is a bond; and

R^5 is phenyl or pyridyl, each optionally substituted with one or two R^{5a}, wherein

each R^{5a} is independently –halogen, $-CH_3$, or $-CF_3$;

R^2 is –H, $-C(R^{20})_2OH$, $-CH_3$, $-CF_3$, or halogen, wherein

each R^{20} is independently –H, -F, $-CH_3$, or $-CF_3$;

J is phenyl, pyridyl, or thienyl; and

each R^{41} is -halogen, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2CF_3$, or $-CH_2CF_3$.

In another embodiment, the invention provides the compound according to formula XXVa-d, wherein q' is 0 or 1; R^1 is L^1-R^5, wherein L^1 is a bond; and

R^5 is phenyl optionally substituted with one or two R^{5a}, wherein

each R^{5a} is independently –halogen, $-CH_3$, or $-CF_3$;

each R^2 is –H, $-C(R^{20})_2OH$, $-CH_3$, $-CF_3$, or halogen, wherein

each R^{20} is independently –H, -F, $-CH_3$, or $-CF_3$; and

R^{41} is -halogen, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2CF_3$, or $-CH_2CF_3$.

In another embodiment, the invention provides the compound according to formulas XXVa-d, wherein wherein each R^{41} is independently halogen, methyl or trifluoromethyl.In another embodiment, the invention provides the compound according any of the previous embodiments wherein R^{21} is hydrogen.

In a third aspect, the invention provides a pharmaceutical composition comprising a compound of any of formulas IIa-d, IIIa-d, IVa-d, XXVa-d, or IV-XXXV, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula IV, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula V, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula VI, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula VII, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of formula IIa-d, or a pharmaceutically acceptable derivative thereof, in a pharmaceutically acceptable carrier.

In a fourth aspect, the invention provides a kit, comprising a packaging material and a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV, or a pharmaceutically acceptable derivative thereof, which is effective for modulating the activity of a nuclear receptor or for treatment, prevention, inhibition, or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders.

In another embodiment, the invention provides a kit, comprising a packaging material, and a compound of formula IIa-d, or a pharmaceutically acceptable derivative thereof, which is effective for modulating the activity of a nuclear receptor or for treatment, prevention, inhibition, or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders.

In another embodiment, the invention provides a kit, comprising a packaging material, a compound of formula IIa-d, or a pharmaceutically acceptable derivative thereof, which is effective for modulating the activity of a nuclear receptor or for treatment, prevention, inhibition, or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, further comprising a label that indicates that the compound of formula IIa-d, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity is implicated.

In a sixth aspect, the invention provides a method of treating, preventing, inhibiting, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the sixth aspect, the invention provides a method of treating, preventing, inhibiting, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated,

comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to part (A) of formulas IIa-d.

When part (A) of formulas IIa-d is referenced herein with respect to methods of using compounds of the invention, such as for treatment, prevention, inhibition, or amelioration of disease, or for use in preparation of a medicament for the treatment, prevention, or amelioration of disease, it is meant that all compounds defined by part (A) are included and the provisos of part (B) of the same formulas are not to be considered when determining the scope of the compounds defined for the uses therein.

In a preferred embodiment of the sixth aspect, the invention provides the method wherein the disease or disorder is hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane,or cardiovascular disorders.

In a seventh aspect, the invention provides a method of reducing cholesterol levels in a subject in need thereof, comprising administering an effective cholesterol level-reducing amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the seventh aspect, the invention provides a method of reducing cholesterol levels in a subject in need thereof, comprising administering an effective cholesterol level-reducing amount of a compound according to part (A) of formulas IIa-d.

In an eighth aspect, the invention provides a method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the eighth aspect, the invention provides a method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to part (A) of formulas IIa-d.

In a ninth aspect, the invention provides a method of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the ninth aspect, the invention provides a method of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound according to part (A) of formulas IIa-d.

In an embodiment of the ninth aspect, the invention provides the method wherein the nuclear receptor is an orphan nuclear receptor.

In an embodiment of the ninth aspect, the invention provides the method wherein the nuclear receptor is a liver X receptor.

In a preferred embodiment of the ninth aspect, the invention provides the method wherein the nuclear receptor is a liver X receptor, wherein the liver X receptor is LXRα or LXRβ.

In an eleventh aspect, the invention provides a method of modulating cholesterol metabolism, comprising administering an effective cholesterol metabolism-modulating amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the eleventh aspect, the invention provides a method of modulating cholesterol metabolism, comprising administering an effective cholesterol metabolism-modulating amount of a compound according to part (A) of formulas IIa-d.

In a twelfth aspect, the invention provides a method of treating, preventing or ameliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the twelfth aspect, the invention provides a method of treating, preventing or ameliorating one or more symptoms of hypocholesterolemia in a subject in need thereof, comprising administering a therapeutically effective amount of a compound according to part (A) of formulas IIa-d.

In a thirteenth aspect, the invention provides a method of increasing cholesterol efflux from cells of a subject, comprising administering an effective cholesterol efflux-increasing amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In a preferred embodiment of the thirteenth aspect, the invention provides a method of increasing cholesterol efflux from cells of a subject, comprising administering an effective cholesterol efflux-increasing amount of a compound according to part (A) of formulas IIa-d.

In a fourteenth aspect, the invention provides a method of increasing the expression of ATP-Binding Cassette (ABC1) in the cells of a subject, comprising administering an effective ABC1 expression-increasng amount of a compound of any of formula IIa-d, IIIa-d, IVa-d, XXVa-d,or IV-XXXV.

In the following embodiments of the first aspect, it is understood that the following provisos apply:

(i) when L^2 is a bond, both J and K are not absent;

(ii) if the compound if defined by formula IIaa, then

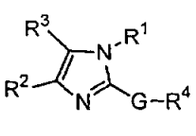
a. if J is phenyl and K is thienyl, furyl, or thiazoyl and q is 0, then R^1 is not 4-(NH_2SO_2)phenyl, 4-(NH_2SO_2)-3-fluorophenyl, p-(CH_3SO_2)phenyl-, or 4p-(CH_3SO_2)-3-fluorophenyl-; and

b. if R^5 is pyridyl or phenyl optionally substituted with one or more R^{5a} and L^1 is a bond, then G is not p-(NH_2SO_2)phenyl or p-(CH_3SO_2)phenyl-;

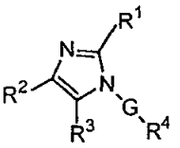
(iii) if the compound if defined by formula IIcc or IIdd, then G is not p-(NH_2SO_2)phenyl or p-(CH_3SO_2)phenyl-

(iv) the compound is not 1-(biphenyl-4-yl)-2,5-diphenyl-1H-imidazole.

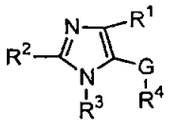
One embodiment of the invention relates to compounds represented by formulae IIaa, IIbb, IIcc or IIdd:



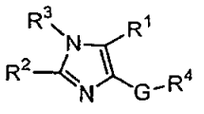
IIaa



IIbb



IIcc



IIdd

as an isomer, a mixture of stereoisomers, a racemic mixture thereof of stereoisomers, or as a tautomer; or as a pharmaceutically acceptable salt, prodrug, solvate or polymorph thereof.

Each R^1 substitutent is independently selected from the group consisting of R^5 and -L_1-R^5.

Another embodiment is that R^1 substitutent is R^5; Preferred R^5 is selected from the group consisting of 5-12 membered aromatic or non-aromatic ring, 5-12 membered heterocyclyl or heteroaryl having one or more heteroatoms N, O or S; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a}. R^5 is preferably thienyl, furanyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiazolyl, indolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, imidazolyl and phenyl.

Examples of R^{5a} groups include halogen, C_{1-6} haloalkyl, hydroxy, nitro, C_{1-6} aliphatic group, C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, $OCOR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl SR^{11}, C_{0-6} alkyl $SO_2N(R^{11})_2$; arylalkyl, aryloxyaryl, aryl C_{1-6} alkoxy, OC_{1-6} alkylCOR^{11}, OC_{1-6} alkyl$N(R^{11})_2$, C_{0-6} alkyl$N(R^{11})_2$; C_{0-6} alkylOR^{11}, C_{0-6} alkyl$N(R^{11})_2$, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkyl $COON(R^{11})_2$, C_{0-6} alkyl$CON(R^{11})_2$; C_{0-6} alkylC≡N, OC_{0-6} alkyl$COOR^{11}$, C_{0-6} alkyl$OCON(R^{11})_2$, or C_{1-6} alkylOC_{1-6} alkyl. R^{5a} is optionally substituted at substitutable position with SO_2R^{11}, C_{0-6} alkoxyaryl, 5-12 membered aromatic or non-aromatic ring, or 5-12 membered heterocyclyl or heteroaryl having one or more heteroatoms N, O or S. Preferably, R^{5a} is Cl, Br, F, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, OC_{0-6}

alkylCOOR^{11}, NR^{11}COR^{11}, C_{0-6} alkylCON(R^{11})$_2$, NO_2, and OC_{1-6} alkylCON(R^{11})$_2$. Examples of R^{5a} include $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, $OCOCH(CH_3)_2$, $OCOC(CH_3)_3$, $NHCOCH_3$, $OCON(CH_3)_2$, $OCONHCH_3$, OCON $(CH_2)_2CH_3$, $OCONHCH(CH_3)_2$, $O(CH_2)_2$, $CONH_2$, $O(CH)(CH_3)_2$, C_{1-6} alkyl, OCH_2COOH, $OCH_2COOC(CH_3)_3$, $O(CH_2)_2N(CH_2CH_3)_2$, $OC(CH_3)_2COOC(CH_3)_3$, or OCH_2CH_2OH. More preferably, R^{5a} is Cl, F, or CF_3,

Another embodiment is that R^1 substitutent is -L_1-R^5. Preferred R^5 is selected from the group consisting of 5-12 membered aromatic or non-aromatic ring, 5-12 membered heterocyclyl or heteroaryl having one or more heteroatoms N, O or S; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a}. Examples of preferred R^5 include phenyl, pyridinyl, oxazolyl, thienyl, thiazolyl, morpholinyl, furanyl, imidazolyl, piperazinyl, pyrimidinyl, isoxazolyl or piperidinyl, more preferably, oxazolyl, pyridinyl, phenyl, furanyl, thienyl or thiazolyl.

Embodiments for L_1 include a direct bond, C_{1-6}alkoxy, carbonyl, SO_2, CS, CON(R^{11})$_2$, CONR^{11}OR^{11}, CONR^{11}N(R^{11})$_2$, -C(=NR^{11})-, -C(=NOR^{11})-, -C(=NN(R^{11})$_2$)-, 5-12 membered aromatic or non-aromatic ring, 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms N, O, or S which is optionally substituted at a substitutable position with one or more radicals of R^{14}. Another embodiment for L_1 is -$(CH_2)_m$-V-$(CH_2)_n$-;or V-$(CH_2)_n$–V; m is 0-6; n is 0-6; V is independently –C(R^{11})$_2$-, -C(R^{11})$_2$C(R^{11})$_2$-, -C(R^{11})=C(R^{11})-, –C(R^{11})$_2$O-, -C(R^{11})$_2$NR^{11}-, -C≡C-, -O-, -S-, -N(R^{10})CO-, -N(R^{10})CO_2 -, -CON(R^{10})-, -CO-, -CO_2-, -OC(=O), -OC(=O)N(R^{10})-, -CONR^{11}OR^{11}-, -CONR^{11}NR^{11}-, -CONR^{11}-, -SO_2-, -N(R^{10})SO_2-, -SO_2N(R^{10})-, cycloC_{3-6} alkyl, -NR^{10}CSNR^{10}-, cycloC_{3-6}haloalkyl or -NR^{10}CONR^{10}-. A preferred L_1 is selected from the group consisting of CONH, C_{1-6} alidiyl, CO, SO_2, CH_2, CH_2O, CH_2CH_2, C=O, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, OCH_2CH_2, OCH_2CO, $OCH_2CH_2N(CH_3)_2$, and $CONHCH_2CH_2N(CH_3)_2$. More preferred L_1 is selected from the group consisting of CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, $CONHCH_2CH_2N(CH_3)_2$; OCH_2 and OCH_2CH_2. Preferred R^5 is selected from the group consisting of phenyl, pyridinyl, oxazolyl, thienyl, thiazolyl, furanyl, morpholinyl, imidazolyl, piperazinyl, pyrimidinyl, isoxazolyl and piperidinyl. Other preferred R^{5a} includes halogen, haloalkyl, $OCH_2CON(CH_3)_2$, $OCH_2COOC(CH_3)_3$, $OCH_2CH_2N(CH_2CH_3)_2$, OCH_2COOH, $OC(CH_3)_2COOC(CH_3)_2$, $OCON(CH_3)_2$, $OCONHCH_3$, OCH_2CH_2OH, $OCONHCH_2CHCH_3$, or $NHCOCH_3$.

Another embodiment is that R^2 is independently selected from the group consisting of R^{7}and L_3-R^7; Each R^7 is independently selected from hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkylOR^{11}, C_{0-6} alkylCOOR^{11}, C_{0-6} alkylCON(R^{11})$_2$, C_{0-6} alkylN(R^{11})$_2$, C_{0-6} alkylOR^{11}, C_{0-6} alkylC≡N, cycloC_{3-6} alkylC≡N, C_{0-6} alkyl CONR^{11}N(R^{11})$_2$, C_{0-6} alkylCONR^{11}OR^{11}, C_{0-6} alkylOCOR^{11},

C_{0-6} alkyl$SO_2N(R^{11})_2$, cycloC_{3-6} alkyl, cycloC_{3-6} alkylOR^{11}, C_{0-6} alkylCOR^{11}; 5-12 membered aromatic or non-aromatic ring; or 5-12 membered heteroaryl and heterocyclyl having one or more heteroatoms N, O or S; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

Another embodiment is that R^2 is R^7, selected from the group consisting of 5-12 membered aromatic or non-aromatic ring; 5-12 membered heteroaryl and heterocyclyl having one or more heteroatoms N, O or S. R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

Preferred R^7 is phenyl, pyridinyl, thienyl, furanyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, isoxazolyl, pyrimidinyl, naphthyl, hydrogen, CF_3, C_{1-6} alkylC≡N, CH_2OH, $COOCH_3$, $COON(R^{11})_2$ or $COOR^{11}$. Other examples of R^7 include trifluoromethyl, $CH_2C{\equiv}N$, $C(CH_3)_2C{\equiv}N$, $COOCH_3$, CH_2OH, $CONHCH_2CH_3$, $CONHOCH_2CH(OH)CH_2OH$, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2CH_2OCH_3$, CH_2COOCH_3, $CON(CH_3)_2$, $COOCH(CH_3)_2$, $CONHCH_2CH_2CH_2OCH_3$, $OCOCH(CH_3)_2$, $OCH_2CON(CH_3)_2$, $CH_2CONHCH_2(CH_3)$, $C(CH_3)_2OH$, COOH, nitro, cycloC_{3-6} alkyl, cycloC_{3-6} alkylOR^{11}, cycloC_{3-6} alkylC≡N, or $COOCH(CH_3)_2$. More preferably, R^7 is CF_3, $COOCH_3$, COOH, or $CONHCH_2CH_3$. When R^7 is phenyl or pyridinyl, preferred R^{7a} is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl. Examples of R^{7a} include halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, and $OCH(CH_3)_2$.

Another embodiment is that R^2 is L_3-R^7. A preferred L_3 is independently selected from a direct bond, -CS-, -CO-, -CONH-, $-CONR^{11}$-, $-C(=NR^{11})$-, $-C(=NOR^{11})$-, $-C(=NN(R^{11})_2)$-; $(CH_2)_m$-V_1-$(CH_2)_n$- or -V_1-$(CH_2)_n$-V_1-; m is 0-6; n is 0-6; V_1 is independently $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, $-NR^{11}$-, $-CR^{11}NR^{11}$-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$, $-CON(R^{10})$-, -OCO-, -CO-, $-CO_2$-, $-OC(=O)$-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, $-NR^{10}CONR^{10}$-, cycloC_{3-6} alkyl, $-NR^{10}CSNR^{10}$-, cycloC_{3-6}haloalkyl or $-SO_2N(R^{10})$. More preferably, L_3 is CH_2, CO, OCH_2, CH_2OCH_2, CONH, CH_2OCOH_2, CH_2NHCH_2, $CH_2NC(CH_3)_2$, $CH_2N(CH_3)CH_2$, CH_2COCH_3, $CH_2N(CH_3)_2CH_2$, cyclohexamine or cyclopropanamine.

Each R^{7a} is independently a halogen, C_{1-6} alkyl, $CR^{11}{=}CR^{11}COOR^{11}$, C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, C_{0-6} alkyl$OCOOR^{11}$, C_{0-6} alkyl$NR^{11}COR^{11}$, C_{0-6} alkyl SO_2NCOR^{11}, C_{0-6} alkyl$SO_2N(R^{11})_2$; C_{0-6} alkylSR^{11}, (C_{0-6} alkyl)C=O(OR^{11}), $OVOR^{11}$,C_{1-6} haloalkyl, OC_{1-6} haloalkyl, haloaryl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, arylC_{0-6} alkylcarboxy, $NR^{11}SO_2$ R^{11}, OC_{1-6} alkyl, OC_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyheteroaryl, C_{0-6}alkoxyheterocyclyl, cycloC_{3-6}alkyl$COOR^{11}$,

cycloC_{3-6}alkylamine; 5-12 membered aromatic or non-aromatic ring, or 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms N, O or S; Examples of R^{7a} is selected from the group consisting of halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, and $OCH(CH_3)_2$.

Each R^{7a} may be substituted at a substitutable position with one or more radicals of R^8; Each R^8 is independently C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylOR^{11}, C_{0-6} alkylOR^{11}, C_{0-6} alkyl$CON(R^{11})_2$, C_{0-6} alkylCOR^{11}, C_{0-6} alkyl$COOR^{11}$, $NR^{11}COOR^{11}$, or C_{0-6} alkylSO_2R^{11}.

Examples of R^{7a} are selected from the group consisting of halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, and $OCH(CH_3)_2$.

Each R^3 is independently selected from the group consisting of R^6 and -L-R^6. One embodiment is that R^3 is R^6 and is independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{0-6} haloalkylOR^{11}, C_{0-6} alkylOR^{11}, C_{0-6} alkyl$CON(R^{11})_2$, $OCON(R^{11})_2$, C_{0-6} alkylCOR^{11}, $CONR^{11}OR^{11}$, C_{0-6} alkyl$COOR^{11}$; 5-12 membered aromatic or non-aromatic ring; 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms N, O or S; Each R^6 may be substituted at a substitutable position with one or more radicals of R^{6a}; Preferred R^6 is hydrogen or optionally substituted phenyl.

Each R^{6a} is independently halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{0-6} haloalkylOR^{11}, $CON(R^{11})_2$, $CONR^{11}OR^{11}$, C_{0-6} alkyl$COOR^{11}$, CR^{11}=$CR^{11}COOR^{11}$, C_{0-6} alkylOR^{11}, C_{0-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$OCOOR^{11}$, C_{0-6} alkyl$NR^{11}OR^{11}$, C_{0-6} alkyl $SO_2NR^{11}COR^{11}$, C_{0-6} alkyl $SO_2N(R^{11})_2$; C_{0-6} alkylSR^{11}, (C_{0-6} alkyl)C=O(OR^{11}), $OVOR^{11}$, OC_{1-6} haloalkyl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, arylC_{0-6} alkylcarboxy, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, OC_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyheteroaryl,C_{0-6}alkoxyheterocyclyl, cycloalkyl$COOR^{11}$.

Another embodiment is that R^3 is L-R^6, L is independently selected from direct bond, -CO-, -CONH-, $-CONR^{11}$-, $-C(=NR^{11})$-, $-C(=NOR^{11})$-, -CS-, $-C(=NN(R^{11})_2)$-; C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})$=$C(R^{11})$-, -C≡C-, -O-, -S-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$, $-NR^{11}$-, $-OR^{11}$-, $-CON(R^{10})$-, -CO-, $-CO_2$-, -OC(=O)-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, or $-SO_2N(R^{10})$-; $-(CH_2)_m$-V_0-$(CH_2)_n$- or -V_0-$(CH_2)_n$-V_0-; m is 0-6; n is 0-6; V_0 is independently $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})$=$C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, $-NR^{11}$-, $-CR^{11}NR^{11}$-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, $-CON(R^{10})$-, -OCO-, $-COR^{11}$-, - $COOR^{11}$-, -CO-, $-CO_2$, -OC(=O), $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, $-NR^{10}COR^{10}$-, $-NR^{10}CSNR^{10}$-,

cycloC_{3-6}haloalkyl or -$SO_2N(R^{10})$-. Examples of L include O, CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, $CONHCH_2CH_2N(CH_3)_2$ or OCH_2CH_2.

Each R^4 is independently selected from C_{1-6} alkyl, $CR^{11}=CR^{11}COOH$, C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, C_{0-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$OCOOR^{11}$, C_{0-6} alkyl$NR^{11}COR^{11}$, C_{0-6} alkyl$SO_2NR^{11}COR^{11}$, C_{0-6} alkyl$SO_2N(R^{11})_2$, C_{0-6} alkylSR^{11}, (C_{0-6} alkyl)C=O(OR^{11}), $OVOR^{11}$, halogen, C_{1-6}haloalkyl, C_{0-6} alkylC≡N, OC_{1-6} haloalkyl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, arylC_{0-6} alkyl$COOR^{11}$, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, OC_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyheteroaryl,C_{0-6}alkoxyheterocyclyl, cycloalkyl$COOR^{11}$, a 5-12 membered aromatic ring or non-aromatic ring, or 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms N, O or S. Preferred R^4 is selected from the group consisting of OH, CN, $C(CH_3)_2OH$, SO_2CH_3, $SO_2C(CH_3)_3$, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, cyclobutane-COOH, $OC(CH_3)_2COOH$, CF_3, $C(CH_3)_2COOH$, CH_2COOCH_3, CH_2CH_2COOH, OCH_2COOCH_3, and $COCH_3$. More preferably, R^4 is SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, or SCH_3.

Each R^4 is optionally substituted at a substitutable position with one or more radicals of R^{4a}. Each R^{4a} is independently selected from C_{1-6} alkyl, (C_{1-6} alkyl)C=O(OR^{11}); C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, C_{0-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl $SO_2N(R^{11})_2$; C_{0-6} alkylSR^{11}, (C_{0-6} alkyl)C=O(OR^{11}), halogen, C_{1-6} haloalkyl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, arylC_{0-6} alkyl$COOR^{11}$, C_{0-6} alkylC≡N, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, or OC_{0-6} alkyl$COOR^{11}$.

Each R^{10} is independently selected from R^{11}, C(=O)R^{11}, CO_2R^{11}, SO_2R^{11}.

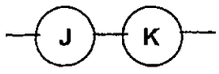
Each R^{11} is independently selected from hydrogen or substituted or unsubstituted C_{1-8} aliphatic group; C_{1-6}haloalkyl; $N(R^{12})_2$; 5-12 membered aromatic or non-aromatic ring, or 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms, N, S or O; which is optionally substituted at a substitutable position with one or more radicals of R^{12}.

Each R^{12} is independently halogen, C_{1-6}haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)C=O(OR^{13}); C_{0-6} alkylCOR^{13}, C_{0-6} alkylSO_2R^{13}, C_{0-6} alkyl$CON(R^{13})_2$, C_{0-6} alkyl$CONR^{13}OR^{13}$, C_{0-6} alkylOR^{13}, C_{0-6} alkyl $SO_2N(R^{13})_2$, C_{0-6} alkylSR^{13}, (C_{0-6} alkyl)C=O(OR^{13}), C_{0-6} haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, C_{0-6} alkoxyaryl, arylC_{0-6} alkylcarboxy, C_{0-6} alkyl$NR^{13}SO_2R^{13}$, OC_{1-6} alkyl, or OC_{1-6} alkylCOOH.

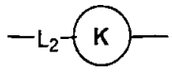
Each R^{13} is independently hydrogen or substituted or unsubstituted C_{1-8} aliphatic group.

Each R^{14} is independently C_{1-6} alkyl, C_{1-6} alkoxy, halogen, C_{1-6} haloalkyl, C_{0-6} alkyl$CON(R^{11})_2$, C_{0-6} alkyl $CONR^{11}OR^{11}$, C_{0-6} alkylOR^{11}, or C_{0-6} alkyl$COOR^{11}$.

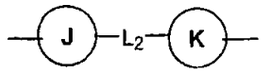
Another embodiment of the invention is that G is independently G1, G2 or G3;



G1



G2



G3

Each Ring J or Ring K may be independently absent, same or different and is independently selected from a 5-12 membered aromatic or non-aromatic ring, or 5-12 membered heterocyclyl or heteroaryl having one or more hetero atoms, N, S or O.

Each Ring J or Ring K independently is optionally substituted at a substitutable position with one or more radicals of R^4. Ring J is preferably a phenyl ring or a 5-6 membered heteroaryl ring. Examples of Ring J include phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, biphenyl, naphthyl, piperidinyl, piperazinyl, or imidazolyl. A preferred Ring J is thienyl or phenyl. Ring J is optionally substituted at a substitutable position with one or more radicals of R^4. Suitable Ring J substituents designated as R^4 include methylsulfonyl, or C_{1-6} aliphatic group or substituents selected from the group consisting of $CR^{11}=CR^{11}COOR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{0-6}alkylOR^{11}, C_{1-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkylOCOOR^{11}, C_{0-6} alkylCON$(R^{11})_2$,OC_{1-6} alkylCON$(R^{11})_2$, C_{0-6} alkylC≡N, C_{0-6} alkyl$NR^{11}COR^{11}$, C_{0-6} alkyl$SO_2NR^{11}COR^{11}$, C_{0-6} alkyl $SO_2N(R^{11})_2$, C_{0-6} alkylSR^{11}, (C_{0-6} alkyl) C=O(OR^{11}), OVOR^{11}, halogen, C_{1-6}haloalkyl, OC_{1-6} haloalkyl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, arylC_{0-6} alkylCOOR^{11}, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, OC_{0-6} alkylCOOR^{11}, C_{0-6} alkoxyheteroaryl,C_{0-6}alkoxyheterocyclyl, cycloalkylCOOR^{11}, a 5-12 membered aromatic ring or non-aromatic ring, and 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms N, O or S. Examples of preferred R^4 include OH, CN, $C(CH_3)_2OH$, SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, $SO_2C(CH_3)_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $C(CH_2CH_3)_2COOH$, CH_2COOCH_3, $C(CH_3)_2COOCH_3$, CH_2CH_2COOH, CH=CHCOOH, OCH_2COOCH_3, $COCH_3$, OCH_3, $COOC(CH_3)_3$, cyclobutane-COOH, $OC(CH_3)_2COOH$, CH_2CH_3, CH_3, $CH(CH_3)_2$, CH_2COOCH_3, $OCON(CH_2CH_3)_2$, $NHCOCH_3$, or CF_3.

Examples of Ring K include phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, biphenyl, naphthyl, piperidinyl, piperazinyl, isoxazolyl, pyrimidinyl, or imidazolyl. Ring K is optionally substituted at a substitutable position with one or more radicals of R^4. Suitable Ring K substituents designated as R^4 include methylsulfonyl, or C_{1-6} aliphatic group or substituents selected from the group consisting of $CR^{11}=CR^{11}COOR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, C_{1-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkylOCOOR^{11}, C_{0-6} alkyl$NR^{11}COR^{11}$, C_{0-6} alkyl$SO_2NR^{11}COR^{11}$, C_{0-6} alkyl$SO_2N(R^{11})_2$, C_{0-6} alkylSR^{11}, (C_{0-6} alkyl)C=O(OR^{11}), OVOR^{11}, halogen, C_{1-6}haloalkyl, OC_{1-6} haloalkyl, C_{0-6} alkylC≡N, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, arylC_{0-6} alkylcarboxy, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, OC_{0-6} alkylCOOR^{11}, C_{0-6} alkoxyheteroaryl,C_{0-6}alkoxyheterocyclyl, cycloalkyl COOR^{11}, a 5-12 membered aromatic ring or non-aromatic ring, and 5-12 membered heteroaryl or

heterocyclyl having one or more heteroatoms N, O or S. Preferably, Ring K is phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, biphenyl, naphthyl, piperidinyl, piperazinyl, isoxazolyl, pyrimidinyl, or imidazolyl. When Ring K is a phenyl or pyridinyl, it is preferably substituted by methylsulfonyl.

Examples of preferred R^4 groups include include OH, CN, $C(CH_3)_2OH$, SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, $SO_2C(CH_3)_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $C(CH_2CH_3)_2COOH$, CH_2COOCH_3, $C(CH_3)_2COOCH_3$, CH_2CH_2COOH, CH=CHCOOH, OCH_2COOCH_3, $COCH_3$, OCH_3, $COOC(CH_3)_3$, cyclobutane-COOH, $OC(CH_3)_2COOH$, CH_2CH_3, CH_3, $CH(CH_3)_2$, CH_2COOCH_3, $OCON(CH_2CH_3)_2$, $NHCOCH_3$, or CF_3.

,-L_2 is -$(CH_2)_m$-V_2-$(CH_2)_n$- or -V_2-$(CH_2)_m$-V_2-; m is 0-6; n is 0-6; V_2 is independently -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -$CON(R^{11})$-, -$CON(R^{11})O$-, -CO-, -CO_2-, -$OR^{11}N$-, -$OR^{11}COO$-, -OC(=O)-, -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, -$NR^{10}CONR^{10}$-, cycloC_{3-6} alkyl, -$NR^{10}CSNR^{10}$-, cycloC_{3-6}haloalkyl or -$SO_2N(R^{10})$-; C_{0-6} alidiyl chain wherein alidiyl chain is optionally interrupted by –$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -$CON(R^{11})$-, -$CON(R^{11})O$-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, cycloC_{3-6}alkyl or -$SO_2N(R^{10})$-; 5-12 membered aromatic or non-aromatic ring, 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms, N, S or O which is optionally substituted at a substitutable position with one or more radicals of R^9. Alternatively, L_2 is a direct bond, -CS-, $-C_{1-6}$ alkyl-, $-C_{1-6}$ alkoxy-, $-C_{0-6}$ alkylCOO-, -CH=CHCOO-, $-C_{0-6}$ alkylCONR^{11}-, $-OC_{0-6}$alkylCOO-, $-C_{0-6}$alkylSO$_2$-, $-C_{0-6}$alkyN(R^{11})-, $-C_{0-6}$ alkylN(R^{11})-, $-C_{0-6}$ alkylCO-, -cycloalkylamine-, -C(=NR^{11})-, -C(=NOR^{11})-, -C(=NN(R^{11})$_2$)-; 5-12 membered aromatic or non-aromatic ring, or 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms, N, S or O which is optionally substituted at a substitutable position with one or more radicals of R^9. A preferred L_2 is selected from the group consisting of -CONH-, $-CONHCH_2$-, $-CH_2O$-, $-OCH_2COOCH_2$-, $-CONHCH_2$-, and -C≡C-.

Another embodiment is that G is G1, R^1 is R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G1, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, isoxazolyl, pyrimidinyl, or imidazolyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^{5a} is halogen, trifluoromethyl, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH_2CH_2N(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, or $OCH(CH_3)_2$;

c) R^2 is trifluoromethyl, $COOCH_3$, CH_2OH, $CONHCH_2CH_3$, $CONHOCH_2CH(OH)$ CH_2OH, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2CH_2OCH_3$, CH_2COOCH_3, $CON(CH_3)_2$, $COOCH(CH_3)_2$, $CONHCH_2CH_2CH_2OCH_3$, $OCOCH(CH_3)_2$, $OCH_2CON(CH_3)_2$, $CH_2CONHCH_2(CH_3)$, $C(CH_3)_2OH$, COOH, nitro or $COOCH(CH_3)_2$;

d) R^3 is hydrogen or optionally substituted phenyl;

e) Ring J is thienyl, thiazolyl, furanyl, pyridinyl or phenyl;

a) Ring K is optionally substituted phenyl or pyridinyl; and

b) R^4 is OH, CN, $C(CH_3)_2OH$, SO_2CH_3, $SO_2C(CH_3)_3$, CH_3, SO_2NH_2, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, CF_3, OCF_3, CH_2CF_3, $C_{1\text{-}6}$ alkyl, halogen or CH_2COOH.

Another embodiment is that G is G1, R^1 is R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G1, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, imidazolyl, isoxazolyl, pyrimidinyl or phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^{5a} is halogen, trifluoromethyl, $OCONH(CH_2)_2CH_3$, $OCONH(CH_2CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, or $OCH(CH_3)_2$;

c) R^2 is R^7 independently selected from $CH_2C{\equiv}N$, $C(CH_3)_2C{\equiv}N$, $cycloC_{3\text{-}6}$ $alkylC{\equiv}N$, thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, imidazolyl, isoxazolyl, pyrimidinyl or phenyl; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

d) R^{7a} is selected from the group consisting of halogen, trifluoromethyl, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $CH{=}CHCOOH$, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, and $OCH(CH_3)_2$;

e) R^3 is hydrogen or optionally substituted phenyl;

f) Ring J is thienyl, thiazolyl, furanyl, pyridinyl, or phenyl;

g) Ring K is optionally substituted phenyl or pyridinyl; and

h) R^4 is OH, CN, $C(CH_3)_2OH$, CH=CHCOOH, SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, SCH_2CH_3, $SO_2C(CH_3)_3$, SCH_3, OCH_3, C_{1-6} alkyl, CF_3, F, Cl, or Br.

Another embodiment is that G is G1, R^1 is L_1-R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G1, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is L_1-R^5; R^5 is phenyl, pyridinyl, morpholinyl, oxazolyl, furanyl, thiazolyl or thienyl; R^5 is optionally substituted with R^{5a};

b) R^{5a} is halogen or trifluoromethyl;

c) L_1 is CS, CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, OCH_2, OCH_2CO, or OCH_2CH_2;

d) R^2 is trifluoromethyl, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2CH_2N(CH_3)_2$, or $CONHCH_2CH_2CH_2OCH_3$.

e) R^3 is hydrogen or phenyl optionally substituted with R^{6a};

f) Ring J is thienyl, pyridinyl, furanyl, thiazolyl or phenyl; Ring K is substituted phenyl or pyridinyl; and

g) R^4 is SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, halogen or CH_2COOH.

Another embodiment is that G is G1, R^1 is R^5 and R^2 is L_3R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G1, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is R^5 selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, imidazolyl, isoxazolyl, pyrimidinyl and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^{5a} is $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, $OCOCH(CH_3)_2$, $NHCOCH_3$, $OCONHCH(CH_3)_2$, $O(CH_2)_2$, $CONH_2$, $O(CH)(CH_3)_2$, C_{1-6} alkyl, OCH_2COOH, $OCH_2COOC(CH_3)_3$, $O(CH_2)_2N(CH_2CH_3)_2$, $OCOC(CH_3)_3$, $OC(CH_2)_2COOH$, $OCONH(CH_3)_2$, $OCONCH_3$, $OCONHCH_2CH_2CH_3$, $OC(CH_3)_2COOC(CH_3)_3$, and $O(CH_2)_2OH$.

c) R^2 is L_3-R^7; R^7 is phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, piperidinyl, imidazolyl, piperazinyl, or pyridinyl;

d) L_3 is –CO-, -C_{1-6} alidiyl-, -CONH-, -$CONR^{11}$-, -$CONR^{11}NR^{11}$-, -CH_2OCH_2-, -$CH_2OCH_2CH_2$-, -OCH_2-, -$CH_2N(CH_3)_2$-, -CH_2NHCH_2-, -$CONR^{11}O$-, -CH_2OCOCH_2-, -$CH_3N(CH_3)(CH_2)$-, -CH_2N(cyclopropane)CH_2-, -$CH_2NC(CH_3)_2CH_2$-, -CH_2N(cyclohexane)CH_2-, -$CH_2NCH(CH_3)_2CH_2$-, -$CH_2N(CF_3)(CH_2)_2$-,

$-CH_2N(CH_3)(CH_2)CH_2OCOCH_2CH_2-$, $-CONHCH_2CH_2N(CH_3)_2-$, or $-CH_2N(CH_2C{\equiv}N)CH_2-$, -CS-;

e) R^{7a} is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6} alkoxy, CF_3, OCH_2CH_2COOH, CH_2COOH, $COOCH_3$, CH_2OH and OCH_3.

f) R^3 is hydrogen or phenyl optionally substituted with R^{6a};

g) Ring J is thienyl, pyridinyl, thiazolyl or phenyl;

h) Ring K is substituted phenyl or pyridinyl; and

i) R^4 is SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, SO_2NH_2, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, CF_3 or $COCH_3$;

Another embodiment is that G is G1, R^1 is L_1-R^5 and R^2 is L_3-R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G1, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^5 is L_1-R^5; R^5 is selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, imidazolyl, piperazinyl, piperidinyl, oxazolyl, pyridinyl, isoxazolyl, pyrimidinyl, imidazolyl and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^{5a} is C_{1-6} alkyl, C_{1-6} alkoxy, COOH, halogen or trifluoromethyl;

c) L_1 is CS, CH_2, CH_2O, CH_2CH_2, OCH_2CH_2, OCH_2CO, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, or $CONHCH_2CHN(CH_3)_2$;

d) R^2 is L_3-R^7; R^7 is selected from the group consisting of phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, pyridinyl, isoxazolyl, pyrimidinyl, imidazolyl, CF_3, cycloC_{3-6} alkylC≡N, C_{0-6} alkylC≡N and $COOCH_3$; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

e) L_3 is CH_2, CS, CH_2OCH_2, $NC(CH_3)_2$, $CH_2NH(CH_2)_2$, CONH, CO, $CONR^{11}$, OCH_2, $CH_2N(CH_3)_2CH_2$, CH_2OCOCH_2, $CH_2CONHCH_2$, $CH_2CONHCH_2CH_2$, cycloalkylamine, $CH_2N(CH_3)CH_2$, or $CH_2NCH(CH_3)_2CH_2$;

f) R^{7a} is selected from the group consisting of halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, $CH_2N(CH_2)CH_2CF_3$, and $OCH(CH_3)_2$;

g) R^3 is hydrogen or phenyl optionally substituted with R^{6a};

h) Ring J is thienyl, thiazolyl, pyridinyl, furanyl or phenyl; Ring K is optionally substituted phenyl or pyridinyl; and

i) R^4 is SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, or Br.

Another embodiment is that G is G2 and R^1 is R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G2, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is is R^5 selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, isoxazolyl, pyrimidinyl, imidazolyl and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^2 is R^7 selected from the group consisting of phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, pyridinyl, isoxazolyl, pyrimidinyl, imidazolyl, CF_3, cycloC_{3-6} alkylC≡N, C_{0-6} alkylC≡N, and $COOCH_3$; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

c) R^3 is hydrogen or optionally substituted phenyl;

d) L_2 is selected from the group consisting of -CONH-, $-CONHCH_2-$, $-CH_2O-$, $-OCH_2COOCH_2-$, -O-, C≡C-, $-OCH_2CH_2-$,and $-CONHOCH_2CH(OH)CH_2O-$, -CS-;

e) Ring J or K is substituted phenyl, biphenyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, furanyl, thienyl, or naphthyl; and

f) R^4 is selected from the group consisting of OH, CN, $C(CH_3)_2OH$, SO_2CH_3, $SO_2CH_2CH_3$, SO_2CH_2 CH_2CH_3, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $C(CH_3)_2COOH$, CH_2COOCH_3, $C(CH_3)_2COOCH_3$, CH_2CH_2COOH, $OCH_2CON(R^{11})_2$, $OCH_2CH_2N(CH_3)_2$, OCH_2COOH, OCH_2COOCH_3, CH_2OH, $COCH_3$, $COOC(CH_3)_3$, cyclobutane-COOH, $OC(CH_3)_2COOH$ and CF_3.

Another embodiment is that G is G2, R^1 is L_1-R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G2, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is L_1-R^5; R^5 is substituted phenyl or pyridinyl;

b) R^{5a} is halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} haloalkyl, nitro, C_{1-6} alkoxy, or OCON(C_{1-6} alkyl)$_2$;

c) L_1 is CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, $CONHCH_2CH_2N(CH_3)_2$ or OCH_2CH_2, -CS-;

d) R^2 is R^7 is selected from the group consisting of phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, pyridinyl, CF_3, cycloC_{3-6} alkylC≡N, C_{0-6} alkylC≡N or $COOCH_3$;

e) R^3 is hydrogen or phenyl optionally substituted with R^{6a};

f) Ring J or K is substituted phenyl, thienyl, furanyl, piperazinyl, piperidinyl or pyridinyl;

g) L_2 is CONH, $CONHCH_2$, CH_2O, OCH_2COOCH_2, O, C≡C, -CS-, OCH_2CH_2 or $CONHOCH_2CH(OH)CH_2O$; and

h) R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{1-6} alkyl$COOR^{11}$, and methyl sulfonyl.

Another embodiment is that G is G2, R^1 is R^5 and R^2 is L_3R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G2, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is R^5 selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, imidazolyl, isoxazolyl, pyrimidinyl and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^{5a} is halogen or trifluoromethyl;

c) R^2 is L_3-R^7;R^7 is selected from the group consisting of phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, pyridinyl, phenyl, imidazolyl, isoxazole, pyrimidinyl, CF_3, cycloC_{3-6} alkylC≡N, C_{0-6} alkylC≡N and $COOCH_3$; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

d) L_3 is –CS-, CH_2, CH_2OCH_2, NCH_2 $(CH_2)_2$, $CH_2N(CH_2)_2$, CH_2CN, CONH, CO, or $CONHCH_2$;

e) R^3 is hydrogen or optionally substituted phenyl;

f) Ring J or K is substituted phenyl, furanyl, thienyl, pyridinyl, biphenyl or naphthyl;

g) L_2 is CONH, CS, $CONHCH_2$, CH_2O, OCH_2COOCH_2, OCH_2CH_2, or

or OCH_2;and

h) R^4 is SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, SCH_3, OCH_3, C_{1-6} alkyl, $COOCH_2CO$, OCH_3, CH_2COOH, CH_2COOCH_3, $CH(CH_3)_2COOH$, $OC(CH_3)_2COOH$, $COOC(CH_3)_3$, cyclobutane-COOH, $C(CH_3)_2COOH$, OCH_2COOCH_3, and CF_3.

Another embodiment is that G is G3, R^1 is R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G3, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is is R^5 selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, imidazolyl, isoxazole, pyrimidinyl and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^2 is R^7 selected from the group consisting of phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, pyridinyl, imidazolyl, isoxazole, pyrimidinyl, CF_3, halogen, cycloC_{3-6} alkylC≡N, C_{0-6} alkylC≡N and $COOCH_3$; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

c) R^3 is hydrogen or optionally substituted phenyl;

d) L_2 is selected from the group consisting of -CONH-, -$CONHCH_2$-, -CS-, -CH_2O-, -OCH_2COOCH_2-, -$COOCH_2$-, -CO-, -OCH_2-, -OCO-, -NHCON-, -O-, -OCH_2CH_2-, -OCON-, and -SO_2-;

e) Ring J or K is substituted phenyl, biphenyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thienyl, pyrimidinyl or naphthyl;

f) R^4 is methylsulfonyl, halogen, haloalkyl, CH_2COOH, OCH_2-phenyl, CH_2COO-phenyl, OCH_2COOH, or $OCH_2CHN(CH_3)_2$; and

g) R^{5a} is $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, $OCOCH(CH_3)_2$, $NHCOCH_3$, $OCONHCH(CH_3)_2$, $O(CH_2)_2$, $CONH_2$, $O(CH)(CH_3)_2$, C_{1-6} alkyl, OCH_2COOH, $OCH_2COOC(CH_3)_3$, $O(CH_2)_2N(CH_2CH_3)_2$, $OCOC(CH_3)_3$, $OC(CH_2)_2COOH$, $OCONH(CH_3)_2$, $OCONCH_3$, $OCONHCH_2CH_2CH_3$, $OC(CH_3)_2COOC(CH_3)_3$, and $O(CH_2)_2OH$.

Another embodiment is that G is G3, R^1 is L_1-R^5 and R^2 is R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G3, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is L_1-R^5; R^5 is substituted phenyl or pyridinyl;

b) R^{5a} is halogen or trifluoromethyl;

c) L_1 is CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, CS, $CONH(CH_2)_3OCH_2$, $CONHCH_2CH_2N(CH_3)_2$ or OCH_2CH_2;

d) R^2 is halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} carboxyalkyl, or CF_3;

e) R^3 is hydrogen or phenyl optionally substituted with R^{6a};

f) Ring J or K is phenyl, pyridinyl, thienyl, furanyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiazolyl, indolyl, oxazolyl, isoxazolyl, pyrimidinyl, imidazolyl, or biphenyl; and

g) L_2 is CS, CONH, $CONHCH_2$, CH_2O, OCH_2COOCH_2, OCH_2 or OCH_2CH_2;

h) R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{1-6} alkyl$COOR^{11}$, and methyl sulfonyl.

Another embodiment is that G is G3, R^1 is R^5 and R^2 is L_3R^7. When G of formulae IIaa, IIbb, IIcc, or IIdd is G3, a more preferred embodiment of this invention relates to a compound having one or more features selected from the group consisting of:

a) R^1 is selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, isoxazolyl, imidazolyl, pyrimidinyl and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a};

b) R^2 is L_3-R^7; $R^7$is phenyl, pyridinyl, thienyl, furanyl, morpholinyl, thiazolyl, oxazolyl, piperidinyl, imidazolyl, piperazinyl, pyridinyl, isoxazolyl, imidazolyl, pyrimidinyl, CF_3, cycloC_{3-6} alkylC≡N, C_{0-6} alkylC≡N and $COOCH_3$; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a};

c) L_3 is –CO-, -CS-, -C_{1-6} alidiyl-, -CONH-, -$CONR^{11}$-, -$CONR^{11}NR^{11}$-, -CH_2OCH_2-, -$CH_2OCH_2CH_2$-, -OCH_2-, -$CH_2N(CH_3)_2$-, -CH_2NHCH_2-, -$CONR^{11}O$-, -CH_2OCOCH_2-, -$CH_3N(CH_3)(CH_2)$-, -CH_2N(cyclopropane)CH_2-, -$CH_2NC(CH_3)_2CH_2$-, -CH_2N(cyclohexane)CH_2-, -$CH_2NCH(CH_3)_2CH_2$-, -$CH_2N(CF_3)(CH_2)_2$-, -$CH_2N(CH_3)(CH_2)CH_2OCOCH_2CH_2$-, -$CONHCH_2CH_2N(CH_3)_2$-, or -$CH_2N(CH_2C{\equiv}N)CH_2$-;

d) R^3 is hydrogen or optionally substituted phenyl;

e) Ring J or K is substituted phenyl, furanyl, thienyl, pyridinyl, biphenyl or naphthyl; and

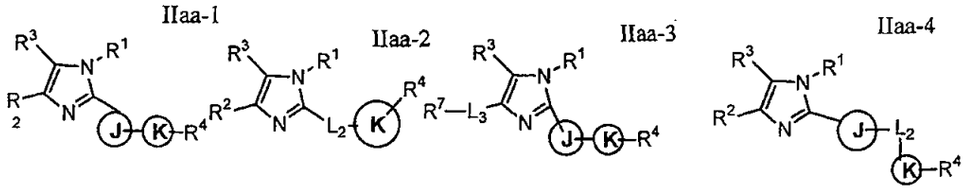
f) L_2 is CONH, $CONHCH_2$, CH_2O, OCH_2COOCH_2, CS or $CONHCH_2$;

g) R^4 is SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, SO_2NH_2, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, CF_3 or $COCH_3$.

Another embodiment of this invention relates to a composition comprising a compound of the present invention or a tautomer or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. It will be appreciated that the compounds of this invention may be derivatized at functional groups to provide prodrug derivatives which are capable of conversion back to the parent compounds *in vivo*. Examples of such prodrugs include the physiologically acceptable and metabolically labile ester derivatives, such as methoxymethyl esters, methylthiomethyl esters, or pivaloyloxymethyl esters derived from a hydroxyl group of the compound or a carbamoyl moiety derived from an amino group of the compound. Additionally, any physiologically acceptable equivalents of the compounds of the present invention, similar to metabolically labile esters or carbamates, which are capable of producing the parent compounds of the present invention *in vivo*, are within the scope of this invention.

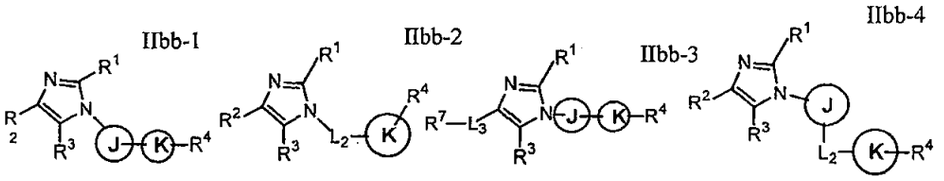
Another embodiment of this invention relates to compounds represented by formulae IIaa-1, IIaa-2, IIaa-3 or IIaa-4 (Embodiment IIaa):

IIaa-1 IIaa-2 IIaa-3 IIaa-4



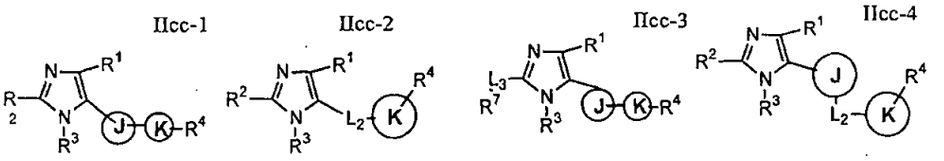
Another embodiment of this invention relates to compounds represented by formulae IIbb-1, IIbb-2, IIbb-3, or IIbb-4 (Embodiment IIb):

IIbb-1 IIbb-2 IIbb-3 IIbb-4



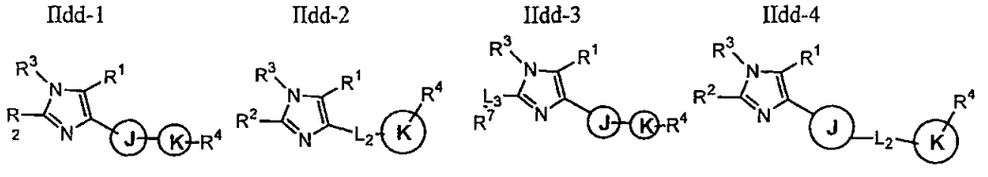
Another embodiment of this invention relates to compounds represented by formulae IIc-1, IIcc-2, IIcc-3, or IIcc-4 (Embodiment IIcc):

IIcc-1 IIcc-2 IIcc-3 IIcc-4



Another embodiment of this invention relates to compounds represented by formulae IIdd-1, IIdd-2, IIdd-3, or IIdd-4 (Embodiment IIdd):

IIdd-1 IIdd-2 IIdd-3 IIdd-4



Of the above embodiments IIaa-IIdd, R^1 is R^5 selected from the group consisting of thienyl, furanyl, morpholinyl, thiazolyl, indolyl, oxazolyl, pyridinyl, isoxazolyl, pyrimidinyl, imidazolyl, and phenyl; R^5 is optionally substituted at a substitutable position with one or more radicals of R^{5a}. Preferred R^5 is phenyl or pyridinyl optionally substituted with R^{5a}.

R^2 is R^7 selected from the group consisting of trifluoromethyl, $COOCH_3$, CH_2OH, $CONHCH_2CH_3$, $CONHOCH_2CH(OH)CH_2OH$, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2CH_2OCH_3$, CH_2COOCH_3, $CON(CH_3)_2$, $COOCH(CH_3)_2$, $CONHCH_2CH_2CH_2OCH_3$, $OCOCH(CH_3)_2$, $OCH_2CON(CH_3)_2$, $CH_2CONHCH_2(CH_3)$, $C(CH_3)_2OH$, COOH, nitro or $COOCH(CH_3)_2$, $CH_2C{\equiv}N$, $C(CH_3)_2C{\equiv}N$, cycloC_{3-6} alkyl$C{\equiv}N$, thienyl, furanyl, morpholinyl, thiazolyl,

indolyl, oxazolyl, pyridinyl, imidazolyl, isoxazolyl, pyrimidinyl and phenyl; R^7 is optionally substituted at a substitutable position with one or more radicals of R^{7a}.

L_1 is independently selected from direct bond, -CO-, -CONH-, -$CONR^{11}$-, -$C(=NR^{11})$-, -$C(=NOR^{11})$-, -$C(=NN(R^{11})_2)$-; C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})=C(R^{11})$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$, -NR^{11}-, -OR^{11}-, -$CON(R^{10})$-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$-; -$(CH_2)_m$-V_0-$(CH_2)_n$- or -V_0-$(CH_2)_n$-V_0-; m is 0-6; n is 0-6; V_0 is independently –$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})=C(R^{11})$-, –$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -NR^{11}-, -$CR^{11}NR^{11}$-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -OCO-, -COR^{11}-, -$COOR^{11}$-, -CO-, -CO_2, -OC(=O), -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, -$NR^{10}COR^{10}$-, -$NR^{10}CSNR^{10}$-, cycloC_{3-6}haloalkyl or -$SO_2N(R^{10})$-; More specifically, L_1 is selected from the group consisting of –CONH-, -C_{1-6} alkyl-, -C_{1-6} alkoxy-, -CO-, -SO_2-, -CH_2-, -CH_2O-, -CH_2CH_2-, -C=O-, -CONH-, -$CONHC(CH_3)_2$-, -$CONH(CH_2)_3OCH_2$-, -OCH_2CH_2-, -$OCH_2CH_2N(CH_3)_2$-, and -$CONHCH_2CH_2N(CH_3)_2$-.

L_3 is independently selected from direct bond, -CO-, -CONH-, -$CONR^{11}$-, -$C(=NR^{11})$-, -$C(=NOR^{11})$-, -$C(=NN(R^{11})_2)$-; C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})=C(R^{11})$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$, -NR^{11}-, -OR^{11}-, -$CON(R^{10})$-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$-; -$(CH_2)_m$-V_0-$(CH_2)_n$- or -V_0-$(CH_2)_n$-V_0-; m is 0-6; n is 0-6; V_0 is independently –$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})=C(R^{11})$-, –$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -NR^{11}-, -$CR^{11}NR^{11}$-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -OCO-, -COR^{11}-, -$COOR^{11}$-, -CO-, -CO_2, -OC(=O), -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, -$NR^{10}COR^{10}$-, -$NR^{10}CSNR^{10}$-, cycloC_{3-6}haloalkyl or -$SO_2N(R^{10})$-. More specifically, L_3 is –CO-, -C_{1-6} alidiyl-, -CONH-, -$CONR^{11}$-, -$CONR^{11}NR^{11}$-, -CH_2OCH_2-, -$CH_2OCH_2CH_2$-, -OCH_2-, -$CH_2N(CH_3)_2$-, -CH_2NHCH_2-, -$CONR^{11}O$-, -CH_2OCOCH_2-, -$CH_3N(CH_3)(CH_2)$-, -CH_2N(cyclopropane)CH_2-, -$CH_2NC(CH_3)_2CH_2$-, -CH_2N(cyclohexane)CH_2-, -$CH_2NCH(CH_3)_2CH_2$-, -$CH_2N(CF_3)(CH_2)_2$-, -$CH_2N(CH_3)(CH_2)CH_2OCOCH_2CH_2$-, -$CONHCH_2CH_2N(CH_3)_2$-, or -$CH_2N(CH_2C{\equiv}N)CH_2$-.

R^{7a} is selected from the group consisting of halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, or $OCH(CH_3)_2$.

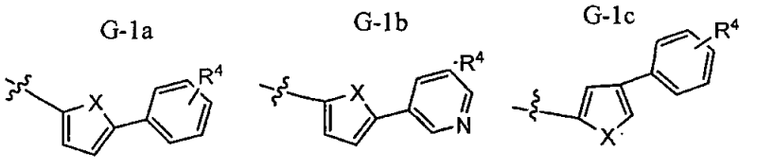
L_2 is independently selected from direct bond, -CO-, -CONH-, -$CONR^{11}$-, -$C(=NR^{11})$-, -$C(=NOR^{11})$-, -$C(=NN(R^{11})_2)$-; C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})=C(R^{11})$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$, -NR^{11}-, -OR^{11}-,

-CON(R^{10})-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)N(R^{10})-, -SO_2-, -N(R^{10})SO_2-, or -SO_2N(R^{10})-; -$(CH_2)_m$-V_0-$(CH_2)_n$- or -V_0-$(CH_2)_n$-V_0-; m is 0-6; n is 0-6; V_0 is independently –C(R^{11})$_2$-, -C(R^{11})$_2$C(R^{11})$_2$-, -C(R^{11})=C(R^{11})-, –C(R^{11})$_2$O-, -C(R^{11})$_2$NR^{11}-, -C≡C-, -O-, -S-, -NR^{11}-, -CR^{11}NR^{11}-, -N(R^{10})CO-, -N(R^{10})CO_2-, -CON(R^{10})-, -OCO-, -COR^{11}-, - COOR^{11}-, -CO-, -CO_2, -OC(=O), -OC(=O)N(R^{10})-, -SO_2-, -N(R^{10})SO_2-, -NR^{10}COR^{10}-, -NR^{10}CSNR^{10}-, cycloC_{3-6}haloalkyl or -SO_2N(R^{10})-. More specifically, L_2 is selected from the group consisting of -CONH-, -CONHCH_2-, -CH_2O-, -OCH_2COOCH_2-, -O-, C≡C-, -OCH_2CH_2, and -CONHOCH_2CH(OH)CH_2O-.

R^{5a} is independently selected from the group consisting of OCH_2C$(CH_3)_3$, Cl, F,Br, OCH_2C$H(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, OCOC$H(CH_3)_2$, OCOC$(CH_3)_3$, NHCOCH_3, OCON$(CH_3)_2$, OCONHCH_3, OCON $(CH_2)_2CH_3$, OCONHC$H(CH_3)_2$, O$(CH_2)_2$, $CONH_2$, O$CH(CH_3)_2$, C_{1-6} alkyl, OCH_2COOH, OCH_2COOC$(CH_3)_3$, O$(CH_2)_2$N$(CH_2CH_3)_2$, OC$(CH_3)_2$COOC$(CH_3)_3$, and OCH_2CH_2OH. R^4 is selected from the group consisting of SO_2CH_3, $SO_2C(CH_3)_3$, SO_2NH_2, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $C(CH_3)_2COOH$, CH_2COOCH_3, $C(CH_3)_2COOCH_3$, CH_2CH_2COOH, OCH_2COOCH_3, $COCH_3$, $COOC(CH_3)_3$, cyclobutane-COOH, $OC(CH_3)_2COOH$, $COOCH_2CH_3$, OCF_3, and CF_3.

Another embodiment of this invention relates to compounds as described above wherein G is selected from the group consisting of:

G-1a G-1b G-1c



G-1d G-1e G-1f

Of the above compounds, R is selected from the group consisting of C_{0-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by –C(R^{11})$_2$-, -C(R^{11})$_2$C(R^{11})$_2$-, -C(R^{11})=C(R^{11})-, –C(R^{11})$_2$O-, -C(R^{11})$_2$NR^{11}-, -C≡C-, -O-, -S-, -N(R^{10})CO-, -N(R^{10})CO_2-, -CON(R^{10})-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)N(R^{10})-, -SO_2-, -N(R^{10})SO_2-, or -SO_2N(R^{10})-.

Each R^4 is independently selected from, C_{1-6} alkyl, CR^{11}=CR^{11}COOR^{11}, C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, C_{0-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkylOCOOR^{11}, C_{0-6} alkylNR^{11}COR^{11}, C_{0-6} alkylSO_2NR^{11}COR^{11}, C_{0-6} alkyl SO_2N(R^{11})$_2$, C_{0-6} alkylSR^{11}, (C_{0-6} alkyl)C=O(OR^{11}), OVOR^{11}, halogen, C_{1-6}haloalkyl, C_{1-6}haloalkylOR^{11}, OC_{1-6}haloalkyl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl,

$arylC_{0-6}$ alkylcarboxy, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, OC_{0-6} alkyl$COOR^{11}$, C_{0-6} alkylC≡N, C_{0-6} alkoxyheteroaryl,C_{0-6}alkoxyheterocyclyl, cycloalkyl$COOR^{11}$, a 5-12 membered aromatic ring or non-aromatic ring, or 5-12 membered heteroaryl or heterocyclyl having one or more heteroatoms N, O or S. Preferred R^4 is selected from the group consisting of SO_2CH_3, $SO_2C(CH_3)_3$, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, C_{1-6} alkyl, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, cyclobutane-COOH, $OC(CH_3)_2COOH$, CF_3, $C(CH_3)_2COOH$, CH_2COOCH_3, CH_2CH_2COOH, OCH_2COOCH_3, and $COCH_3$. More preferably, R^4 is SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, or SCH_3.

X is selected from the group consisting of S, NR^{11} and O.

Each R^4 is optionally substituted at a substitutable position with one or more radicals of R^{4a};

Each R^{4a} is independently selected from, C_{1-6} alkyl, $(C_{1-6}$ alkyl)C=O(OR^{11}); C_{1-6} alkoxy, C_{0-6} alkylOR^{11}, C_{0-6} alkylCOR^{11}, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$SO_2N(R^{11})_2$; C_{0-6} alkylSR^{11}, $(C_{0-6}$ alkyl)OC=O(OR^{11}), halogen, C_{1-6} haloalkyl, aryloxy, aralkyloxy, aryloxyalkyl, C_{1-6} alkoxyaryl, $arylC_{0-6}$ alkylcarboxy, $NR^{11}SO_2R^{11}$, OC_{1-6} alkyl, C_{0-6} alkylC≡N, or OC_{0-6} alkyl$COOR^{11}$.

Definitions

The following definitions apply to the terms used herein, unless expressly stated to the contrary. So, for example, "alkyl" is defined hereinbelow as containing from 1 to 12 carbon atoms, but a substituent defined as C_{1-6}alkyl is limited to an alkyl moiety of from 1 to 6 carbons. All selections of any variables in connection with any of the general structures or formulas herein are understood to be proper only when said selection yields a stable chemical structure as recognized by one skilled in the art.

When particular embodiments are referred to by structure only, all otherwise unnamed chemical groups making up that structure are as defined in each individual embodiment of that structure. So, for example, when it is stated, "In another embodiment, the invention provides the compound according to any one of formulas Ia-d, wherein K is phenyl or pyridyl," it is meant that another embodiment of the invention comprises each embodiment of any one of formulas Ia-d described in the specification in which K is phenyl or pyridyl and all other moieties are as defined in the particular embodiments.

For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.* CH_3-CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent

moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-. Similarly, $C_{0\text{-}6}$ alkylOR^{11} includes both –OR^{11} and C_1-C_6-OR^{11}, and -$[C(R^{15})_2]_m$- is a bond when m is 0. In the instances when a moiety is a divalent radical, there is no implied limitation on the location of the two bonds connecting the linking radical to its two supporting chemical units. For example, for a divalent cyclohexyl radical, the cyclohexyl can be connected either through two separate chemical bonds to two distinct carbons atoms within the ring; or the two bonds can be connected to the same carbon atom in the ring. In an illustrative example, if a divalent cyclopropyl radical connects two phenyl rings together, this definition encompasses both 1,2-diphenylcyclopropyl and 1,1-diphenylcyclopropyl units.

As used herein the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. For example, "a compound" refers to one or more of such compounds, while "the enzyme" includes a particular enzyme as well as other family members and equivalents thereof as known to those skilled in the art. As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated.

The term "absent" as used herein means the group is replaced by a single bond. If replacing the group with a bond results in two connected moieties both defined as bonds, then –bond-bond- groups are understood to reduce to a single bond.

The term "interrupted by" as used herein means the group specified is inserted at any point within the specified chain, but not at the termini. For example, if a C_3-alkyl chain, as defined herein, is interrupted by –O-, then the following groups would be encompassed: -CH_2-O-CH_2CH_2-, -CH_2CH_2-O-CH_2, -$CH(CH_3)$-O-CH_2-, and -CH_2-O-$CH(CH_3)$-.

The terms "aliphatic" and "aliphatic group" as used herein means straight-chain, branched or cyclic C_1-C_{12} (unless stated otherwise) hydrocarbon radicals which are completely saturated or which contain one or more units of unsaturation but which are not aromatic. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of a larger moiety include both straight and branched chains containing one to twelve carbon atoms.

The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety include both straight and branched chains containing two to twelve carbon atoms.

The term "alkoxy" refers to an -O-alkyl radical, where alkyl is defined herein.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (iso-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like. Unless stated otherwise specifically in the specification, the alkyl radical is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and R^{11} are as defined above in the First aspect of the invention. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkyl group that the substitution can occur on any carbon of the alkyl group.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to eight carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, the alkenyl radical is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and R^{11} are as defined above in the First aspect of the invention. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkenyl group that the substitution can occur on any carbon of the alkenyl group.

"Aryl" refers to aromatic monocyclic or multicyclic ring system containing from 6 to 19 carbon atoms, where the ring system is optionally partially or fully saturated. Aryl groups include, but are not limited to groups such as fluorenyl, phenyl and naphthyl. Unless stated otherwise specifically in the specification, the term "aryl" is meant to include aryl radicals optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halogen, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, R^0-OR^{11}, R^0 -$N(R^{11})_2$-, R^0 -COR^{11}, R^0-$COOR^{11}$, R^0-$CON(R^{11})_2$, R^0-$N(R^{11})COOR^{10}$, R^0-$N(R^{11})COR^{11}$, R^0-NSO_2R^{11}, R^0-$N(R^{11})SO_2R^{11}$, R^0-SO_2OR^{11}, R^0-SO_2R^{11}, and R^0-$SO_2N(R^{11})_2$ where each R^0 is independently selected from a substituted or an unsubstituted aliphatic group, an unsubstituted heteroaryl or heterocyclic ring, phenyl (Ph), substituted Ph, -OPh, substituted –OPh, or substituted –CH_2Ph. Examples of substitutents on the aliphatic group or phenyl ring of R^0 include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl,

alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy or haloalkyl.

An aliphatic group or non-aromatic heterocyclic ring may contain one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group or of non-aromatic heterocyclic ring include those listed above for unsaturated carbon of an aryl or heteroaryl group and including the following:=O, =S, =NNHR^0, =NN(R^0)$_2$, =N-, =NNHC(O)R^0, =NNHCO$_2$ (alkyl), =NNHSO$_2$(alkyl), or =NR^0, where R^0 is independently selected from hydrogen, unsubstituted or substituted aliphatic group, an unsubstituted heteroaryl or heterocyclic ring, phenyl (Ph), substituted Ph, -OPh, substituted –OPh, –CH$_2$Ph or substituted -CH$_2$Ph. Examples of substitutents on the aliphatic group include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy or haloalkyl.

Suitable substituents on the nitrogen of a non-aromatic heterocyclic ring include -R^0, -N(R^0)$_2$, -C(O)R^0, CO2R^0, -C(O)C(O)R^0, -SO$_2$R, -SO$_2$N(R^0)$_2$, -C(=S)N(R^0)$_2$, -C(=NH)-N(R^0)$_2$, and NR^{0}RSO$_2$R^0 wherein each R^0 is independently selected from hydrogen, unsubstituted or substituted aliphatic group, an unsubstituted heteroaryl or heterocyclic ring, phenyl (Ph), substituted Ph, -OPh, substituted –OPh, or substituted –CH$_2$Ph. Examples of substitutents on the aliphatic group or the phenyl ring include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy or haloalkyl.

The term "alkoxyaryl" as used herein means an aryl group, as defined herein, substituted with one or more alkoxy groups, as defined herein. Examples of alkoxyaryl groups include, but are not limited to, methoxyphenyl, butyloxyphenyl, and dimethoxynaphthyl.

"Aralkyl" or "arylalkyl" refers to a radical of the formula -RaRb where Ra is an alkyl radical as defined above and Rb is one or more aryl radicals as defined above, *e.g.*, benzyl, diphenylmethyl and the like. The aryl radical(s) and the alkyl radical is optionally substituted as described above.

The term "aralkyloxy" or "arylalkoxy" as used herein, means an aralkyl group, as defined herein, appended to the parent molecule through a oxygen atom. Examples of aralkyloxy include, but are not limited to, benzyloxy, 2-phenylethoxy, 4-phenylbutoxy, 9-fluorenylmethoxy, and the like.

The term "arylalkylcarboxy" as used herein, means an arylakyl group, as defined herein, appended to the parent molecule through a carboxy group, as defined herein. The carboxy group can be bonded in either sense; either with the carbonyl carbon bonded to the arylalkyl group and the oxygen bonded to the parent molecule; or the carbonyl bonded to the parent molecule and the oxygen bonded to

the arylalkyl group. Examples of arylalkylcarboxy groups include, but are not limited to, benzylacetoxy, (benzyloxy)carbonyl, (2-phenylethoxy)carbonyl, phenyl-acetyloxy, and 1-oxo-5-phenyl-pentyloxy.

The term "aryloxy" as used herein, means an aryl group, as defined herein, appended to a parent molecule through an oxygen atom. Examples of "aryloxy" groups include, but are not limited to phenoxy, 1-naphthyloxy, and 2-naphthyloxy.

"Alkylene" and "alkylene chain" refer to a straight or branched divalent hydrocarbon chain, linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, preferably having from one to eight carbons, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain may be attached to the rest of the molecule and to the radical group through one carbon within the chain or through any two carbons within the chain. The alkylene chain is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and R^{11} are as defined above in the First aspect of the invention. The alkylene chain may be attached to the rest of the molecule through any two carbons within the chain.

"Alkenylene" and "alkenylene chain" refer to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, *e.g.*, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. The alkenylene chain is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and R^{11} are as defined above in the First aspect of the invention.

The term "aryloxyalkyl" as used herein, means an alkyl group appended to the parent molecule, wherein the alkyl group is substituted with one aryloxy group, as defined herein. Examples of aryloxyalkyl groups include, but are not limited to phenoxymethyl, naphthyloxybutyl, and phenoxyhexyl.

The term "aryloxyaryl" as used herein, means an aryl group appended to the parent molecule, wherein the aryl group is substituted with one aryloxy group, as defined herein. Examples of aryloxyaryl groups include, but are not limited to phenoxyphenyl, naphthyloxyphenyl, and phenoxynaphthyl.

The term "carbonyl" as used herein, means a –C(=O)- group.

The term "carboxy" as used herein, means a –C(=O)O- group.

"Cycloalkyl" refers to a stable monovalent monocyclic or bicyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms (unless stated otherwise), and which is saturated or includes one more unsaturated units (but is not aromatic) and is attached to the rest of the molecule by a single bond, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cylcopent-1-enyl, cyclohexyl, cyclohex-2,4-dienyl, decalinyl and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and R^{11} are as defined above in the first aspect of the invention.

"Cycloalkylalkyl" refers to a radical of the formula -RaRd where Ra is an alkyl radical as defined above and Rd is a cycloalkyl radical as defined above. The alkyl radical and the cycloalkyl radical may be optionally substituted as defined above.

The term "cyclohaloalkyl" as used herein means a cycloalkyl group, as defined herein which is substituted by one or more halo groups, as defined herein. Examples of "cyclohaloalkyl" groups include, but are not limited to, bromocyclohexyl, trifluorocyclopentyl, dichlorocyclohexyl and the like.

"Halo" or "Halogen" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 2-bromoethenyl, 3-bromoprop-1-enyl, and the like.

The term "haloaryl" as used herein, means an aryl group, as defined herein, substituted with one or more halo groups. Examples of haloaryl groups include, but are not limited to, bromophenyl, fluorophenyl, pentafluorophenyl, chloronaphthyl, chloro-iodophenyl, and the like.

"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical is optionally oxidized; the nitrogen atom is optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, decahydroisoquinolyl, imidazolinyl,

imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuranyl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-OR^{11}$, $-N(R^{11})_2$-, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and R^{11} are as defined above in the First aspect of the invention.

"Heterocyclylalkyl" refers to a radical of the formula -RaRe where Ra is an alkyl radical as defined above and Re is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. The heterocyclyl radical and the alkyl radical are optionally substituted as defined above.

The term "heterocyclyloxy" as used herein, means a heterocyclyl group, as defined herein, appended to a parent molecule through an oxygen atom. Examples of "heterocyclyloxy" groups include, but are not limited to piperidinyloxy, tetrahydrofuranyloxy, tetrahydrotheinyloxy tetrahydropyranyloxy, dihydropyranyloxy, pyrrolidinyloxy, oxetanyloxy, and oxiranyloxy.

"Heteroaryl" refers to a 3- to 18-membered aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical is optionally oxidized; the nitrogen atom is optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, phthalimidyl pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are

optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-OR^{11}$, $-N(R^{11})_2$-, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, and $-SO_2N(R^{11})_2$ where each R^{10} and $R^{11}$are as defined above in the First aspect of the invention. For purposes of this invention, the tem "*N*-heteroaryl" refers to heteroaryl radicals as defined above containing at least one nitrogen atom in ring.

The term "heteroaryloxy" as used herein, means a heteroaryl group, as defined herein, appended to a parent molecule through an oxygen atom. Examples of "heteroaryloxy" groups include, but are not limited to pyridyloxy, indolyloxy, and quinolyloxy.

"Heteroarylalkyl" refers to a radical of the formula $-R_aR_f$ where R_a is an alkyl radical as defined above and R_f is a heteroaryl radical as defined above, and if the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkyl radical at the nitrogen atom. The heteroaryl radical and the alkyl radical are optionally substituted as defined above.

The term "linker group" or "linker" means an organic moiety that connects two parts of a compound. Linkers are typically comprised of an atom such as oxygen or sulfur, a unit such as -NH-, $-CH_2$-, -CO-, -CONH-, or a chain of atoms, such as an alidiyl chain. The molecular mass of a linker is typically in the range of about 14 to 200, preferably in the range of 14 to 96 with a length of up to about six atoms. Examples of linkers include a saturated or unsaturated C_{1-6} alidiyl chain which is optionally substituted, and wherein one or two saturated carbons of the chain are optionally replaced by -CO-, -COCO-, -CONH-, -CONHNH-, $-CO_2$-, $-NHCO_2$-, -O-, -NHCONH-, -OCONH-, -NHNH-, -NHCO-, -S-, -SO-, $-SO_2$-, -NH-, $-SO_2NH$-, or $-NHSO_2$-.

The term "alidyl" or "alidiyl chain" refers to an optionally substituted, straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation. The optional substituents are as described above for an aliphatic group. Alidiyl chain used herein may include alidiyl chains containing 0-4 fluorine substituents.An "agonist for a nuclear receptor" is an agent that, when bound to the nuclear receptor, activates nuclear receptor activity to activate or repress gene function. In some cases, nuclear receptors can act through second messenger signaling pathways, and the invention would apply to these actions as well. The activation can be similar in degree to that provided by a natural hormone for the receptor, or can be stronger (optionally referred to as a "strong agonist"), or can be weaker (optionally referred to as a "weak agonist" or "partial agonist"). An example of a hormone for a nuclear receptor is thyroid hormone, which is a natural hormone for the thyroid receptor. A "putative agonist" is an agent to be tested for agonist activity.

Partial agonists or partial antagonists bind to receptors and yield a response less than that of a full agonist at saturating ligand concentrations. A partial agonist will block binding of a full agonist and suppress receptor activity to the level induced by the partial agonist alone. For example, partial agonists bind to receptors and induce only part of the changes in the receptors that are induced by agonists. The differences can be qualitative or quantitative. Thus, a partial agonist can induce some of the conformation changes induced by agonists, but not others, or it may only induce certain changes to a limited extent. Some of these compounds are naturally produced. For example, many plant estrogens (phytoestrogens), such as genistein, can behave as partial estrogen receptor agonists.

An "antagonist for a nuclear receptor" is an agent that reduces or blocks activity mediated by the receptor in response to an agonist of the receptor. The activity of the antagonist can be mediated, *e.g.*, by blocking binding of the agonist to the receptor, or by altering receptor configuration and/or activity of the receptor. A "putative antagonist" is an agent to be tested for antagonist activity.

A "nuclear receptor" is a receptor that activates or represses transcription of one or more genes in the nucleus (but can also have second messenger signaling actions), typically in conjunction with other transcription factors. The nuclear receptor is activated by the natural cognate ligand for the receptor. Nuclear receptors are ordinarily found in the cytoplasm or nucleus, rather than being membrane-bound. Nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in repsonse to a ligand therefor. Nuclear receptors may be classified based on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors is LXR.

As used herein, an orphan nuclear receptor is a nuclear receptor for which the natural ligand is unknown.

As used herein, liver X receptor or LXR refers to a nuclear receptor implicated in cholesterol biosynthesis. As used herein, the term LXR refers to both LXRα and LXRβ, two forms of the protein found in mammals. Liver X receptor-α. or LXRα refers to the receptor described in U.S. Pat. Nos. 5,571,696, 5,696,233 and 5,710,004, and Willy et al. (1995) Gene Dev. 9(9):1033-1045. Liver X receptor-β or LXRβ refers to the receptor described in Peet et al. (1998) Curr. Opin. Genet. Dev.

8(5):571-575; Song et al. (1995) Ann. N.Y. Acad. Sci. 761:38-49; Alberti et al. (2000) Gene 243(1-2):93-103; and references cited therein; and in U.S. Pat. Nos. 5,571,696, 5,696,233 and 5,710,004.

As used herein, compounds which are "commercially available" may be obtained from standard commercial sources including Acros Organics (Pittsburgh PA), Aldrich Chemical (Milwaukee WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park UK), Avocado Research (Lancashire U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester PA), Crescent Chemical Co. (Hauppauge NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester NY), Fisher Scientific Co. (Pittsburgh PA), Fisons Chemicals (Leicestershire UK), Frontier Scientific (Logan UT), ICN Biomedicals, Inc. (Costa Mesa CA), Key Organics (Cornwall U.K.), Lancaster Synthesis (Windham NH), Maybridge Chemical Co. Ltd. (Cornwall U.K.), Parish Chemical Co. (Orem UT), Pfaltz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Riedel de Haen AG (Hannover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland OR), Trans World Chemicals, Inc. (Rockville MD), and Wako Chemicals USA, Inc. (Richmond VA).

As used herein, "suitable conditions" for carrying out a synthetic step are explicitly provided herein or may be discerned by reference to publications directed to methods used in synthetic organic chemistry. The reference books and treatise set forth above that detail the synthesis of reactants useful in the preparation of compounds of the present invention, will also provide suitable conditions for carrying out a synthetic step according to the present invention.

As used herein, "methods known to one of ordinary skill in the art" may be identified though various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds of the present invention, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler *et al.*, "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C. may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services.

"Prodrugs" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., *et al.*, "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. The term "prodrug" is also meant to include any covalently bonded carriers which release the active compound of the invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392). Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention and the like.

"Polymorph" refers to the different crystal forms of a compound, resulting from the possibility of at least two different arrangements of the molecules of the compound in the solid state. Polymorphs of a given compound will be different in crystal structure but identical in liquid or vapor states. Different polymorphic forms of a given substance may differ from each other with respect to one or more physical properties, such as solubility and dissociation, true density, crystal shape, compaction behavior, flow properties, and/or solid state stability.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and domestic animals, such as cats, dogs, swine, cattle, sheep, goats, horses, rabbits, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals as defined herein and aryl radicals having no substitution.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Pharmaceutically acceptable derivative" refers to pharmaceutically acceptable salts as defined herein and also includes esters, prodrugs, solvates and polymorphs of the compounds of the invention.

"Therapeutically effective amount" refers to that amount of a compoundof the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, for a disease-state associated with nuclear receptor activity. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Modulating" or "modulate" refers to the treating, prevention, suppression, enhancement or induction of a function or condition. For example, the compounds of the present invention can modulate hyperlipidemia by lowering cholesterol in a human, thereby suppressing hyperlipidemia.

"Treating" or "treatment" as used herein covers the treatment of a disease or condition associated with the nuclear receptor activity as disclosed herein, in a mammal, preferably a human, and includes:

i. Preventing a disease or condition associated with the nuclear receptor activity from occurring in a mammal, in particular, when such mammal is predisposed to the disease or condition but has not yet been diagnosed as having it;

ii. inhibiting a disease or condition associated with the nuclear receptor activity, *i.e.*, arresting its development; or

iii. relieving a disease or condition associated with the nuclear receptor activity, *i.e.*, causing regression of the condition.

The compounds of formulae IIaa, IIbb, IIcc, or IIdd or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; *i.e.*, the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and

diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The chemical naming protocol and structure diagrams used herein employ and rely on the chemical naming features as utilized by the ChemDraw program (available from Cambridgesoft Corp., Cambridge, MA). In particular, the compound names were derived from the structures using the Autonom program as utilized by Chemdraw Ultra or ISIS base (MDL Corp.).

The term "atherosclerosis" refers to process whereby atherosclerotic plaques form within the inner lining of the artery wall leading to atherosclerotic cardiovascular diseases. Atherosclerotic cardiovascular diseases can be recognized and understood by physicians practicing in the relevant fields of medicine, and include without limitation, restenosis, coronary heart disease (also known as coronary artery heart disease or ischemic heart disease), cerebrovascular disease including ischemic stroke, multi-infarct dementia, and peripheral vessel disease, including intermittent claudication, and erectile dysfunction.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (*e.g.*, elevated levels of Low Density Lipoprotein, (LDL), Very Low Density Lipoprotein (VLDL) and depressed levels of High Density Lipoprotein (HDL) (less than 40 mg/dL)).

As used herein, "EC_{50}" refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

The term "cholesterol" refers to a steroid alcohol that is an essential component of cell membranes and myelin sheaths and, as used herein, incorporates its common usage. Cholesterol also serves as a precursor for steroid hormones and bile acids.

The term "triglyceride(s)" ("TGs"), as used herein, incorporates its common usage. TGs consist of three fatty acid molecules esterified to a glycerol molecule and serve to store fatty acids which are used by muscle cells for energy production or are taken up and stored in adipose tissue.

The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forMS (ES): (1) hypercholesterolemia, *i.e.*, an elevated LDL cholesterol level (120 mg/dL and above); (2) hypertriglyceridemia, *i.e.*, an elevated triglyceride level; (150 mg/dL and above) and (3) combined hyperlipidemia, *i.e.*, a combination of hypercholesterolemia and hypertriglyceridemia.

Exemplary Primary Hyperlipidemia include, but are not limited to, the following:

(1) Familial Hyperchylomicronemia, a rare genetic disorder which causes a deficiency in an enzyme, LP lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood;

(2) Familial Hypercholesterolemia, a relatively common genetic disorder caused where the underlying defect is a series of mutations in the LDL receptor gene that result in malfunctioning LDL receptors and/or absence of the LDL receptors. This brings about ineffective clearance of LDL by the LDL receptors resulting in elevated LDL and total cholesterol levels in the plasma;

(3) Familial Combined Hyperlipidemia, also known as multiple lipoprotein-type hyperlipidemia; an inherited disorder where patients and their affected first-degree relatives can at various times manifest high cholesterol and high triglycerides. Levels of HDL cholesterol are often moderately decreased;

(4) Familial Defective Apolipoprotein B-100 is a relatively common autosomal dominant genetic abnormality. The defect is caused by a single nucleotide mutation that produces a substitution of glutamine for arginine which can cause reduced affinity of LDL particles for the LDL receptor. Consequently, this can cause high plasma LDL and total cholesterol levels;

Familial Dysbetalipoproteinemia, also referred to as Type III Hyperlipoproteinemia, is an uncommon inherited disorder resulting in moderate to severe elevations of serum triglyceride (TG) and cholesterol levels with abnormal apolipoprotein E function. HDL levels are usually normal; and

Familial Hypertriglyceridemia, is a common inherited disorder in which the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not cholesterol levels) and can often be associated with low plasma HDL levels.

Risk factors in exemplary Secondary Hyperlipidemia include, but are not limited to, the following: (1) disease risk factors, such as a history of type 1 diabetes, type 2 diabetes, Cushing's syndrome, hypothyroidism and certain types of renal failure; (2) drug risk factors, which include, birth control pills; hormones, such as estrogen, and corticosteroids; certain diuretics; and various beta. blockers; (3) dietary risk factors include dietary fat intake per total calories greater than 40%; saturated fat intake per total calories greater than 10%; cholesterol intake greater than 300 mg per day; habitual and excessive alcohol use; and obesity; and (4) non-genetic dyslipidemias.

The methods of the present invention can be used effectively in combination with one or more additional active diabetes agents depending on the desired target therapy (see, *e.g.*, Turner, N. et al. Prog. Drug Res. (1998) 51:33-94; Haffner, S. Diabetes Care (1998) 21: 160178; and DeFronzo, R. et al. (eds.), Diabetes Reviews (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of

combination therapies with oral agents (see, *e.g.*, Mahler, R., J. Clin. Endocrinol. Metab. (1999)84:1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998)21:87-92; Bardin, C.W.(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby--Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. et al., Clin.Ther. (1997) 19: 16-26; Coniff, R. et al., Am. J. Med. (1995) 98: 443-451; and Iwamoto, Y. et al, Diabet. Med. (1996)13: 365-370; Kwiterovich, P. Am. J. Cardiol (1998) 82(12A):3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.As used herein, "IC_{50}" refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of nuclear receptor, including the LXRα or LXRβ activity, in an assay that measures such response.

As used herein, "LXRα" (LXR alpha) refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms. Representative LXRα species include, without limitation the rat (Genbank Accession NM_031627), mouse (Genbank Accession BC012646), and human (GenBank Accession No. U22662) forms of the receptor.

As used herein, "LXRβ" (LXR beta) refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms. Representative LXRβ species include, without limitation the rat (GenBank Accession NM_031626), mouse (Genbank Accession NM_009473), and human (GenBank Accession No. U07132) forms of the receptor.

As used herein "LXR" or "LXRs" refers to both LXRα and LXRβ.

The terms "obese" and "obesity" refers to a Body Mass Index (BMI) greater than 27.8 kg/m^2 for men and 27.3 kg/m^2 for women (BMI equals weight (kg)/(height)^2(m^2).

Use of the Compounds of the Invention

The compounds of the invention exhibit valuable pharmacological properties in mammals, and are particularly useful as selective LXR agonists, antagonists, inverse agonists, partial agonists and antagonists, for the treatment, or prevention of diseases associated with, or symptoms arising from the complications of, altered cholesterol transport, cholesterol reverse transport, fatty acid metabolism, cholesterol absorption, cholesterol re-absorption, cholesterol secretion, cholesterol excretion, or cholesterol metabolism.

These diseases include, for example, hyperlipidemia, dyslipidemia, hypercholesterolemia, atherosclerosis, atherosclerotic cardiovascular diseases, hyperlipoproteinemia, (see, *e.g.*, Patent Application Publication Nos. WO 00/57915 and WO 00/37077), hyperglycemia, insulin resistance,

diabetes, lipodystrophy, obesity, syndrome X (US Patent Application No. 20030073614, International Patent Application Publication No. WO 01/82917), excess lipid deposition in peripheral tissues such as skin (xanthomas) (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814), stroke, peripheral occlusive disease, memory loss (*Brain Research* (1997), Vol. 752, pp. 189-196), optic nerve and retinal pathologies (*i.e.*, macular degeneration, retintis pigmentosa), repair of traumatic damage to the central or peripheral nervous system (*Trends in Neurosciences* (1994), Vol. 17, pp. 525-530), prevention of the degenerative process due to aging (*American Journal of Pathology* (1997), Vol. 151, pp. 1371-1377), Parkinson's disease or Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334; *Trends in Neurosciences* (1994), Vol. 17, pp. 525-530), prevention of degenerative neuropathies occurring in diseases such as diabetic neuropathies (see, *e.g.*, International Patent Application Publication No. WO 01/82917), multiple sclerosis (*Annals of Clinical Biochem.* (1996), Vol. 33, No. 2, pp. 148-150), and autoimmune diseases (*J. Lipid Res.* (1998), Vol. 39, pp. 1740-1743).

Also provided, are methods of increasing the expression of ATP-Binding Cassette (ABCA1), (see, *e.g.*, International Patent Application Publication No. WO 00/78972) thereby increasing reverse cholesterol transport in mammalian cells using the claimed compounds and compositions.

Accordingly in another aspect, the invention also includes methods to remove cholesterol from tissue deposits such as atherosclerotic plaques or xanthomas in a patient with atherosclerosis or atherosclerotic cardiovascular disease manifest by clinical signs of such disease, wherein the methods comprise administering to the patient a therapeutically effective amount of a compound or composition of the present invention. Additionally, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic cardiovascular disease event including ischemic heart disease, ischemic stroke, multi-infarct dementia, and intermittent claudication comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event. The patient may already have atherosclerotic cardiovascular disease at the time of administration, or may be at risk for developing it. Risk factors for developing atherosclerotic cardiovascular disease events include increasing age (65 and over), male gender, a family history of atherosclerotic cardiovascular disease events, high blood cholesterol (especially LDL or "bad" cholesterol over 100 mg/dL), cigarette smoking and exposure to tobacco smoke, high blood pressure, diabetes, obesity and physical inactivity.

Also contemplated herein is the use of a compound of the invention, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following therapeutic agents in treating atherosclerosis: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-

coenzyme A:cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin or fibric acid derivatives.

In one embodiment compounds of the invention are used in combination with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester, free acid and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope of this invention. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; *see,* U.S. Patent No. 4,231,938); simvastatin (ZOCOR®; *see,* U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; *see,* U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; *see,* U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; *see,* U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; *see*, U.S. Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in combination with the compounds of the invention are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry,* pp. 85-89 (5 February 1996). In presently preferred embodiments, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

The compounds of the present invention can also be used in methods for decreasing hyperglycemia and insulin resistance, *i.e.*, in methods for treating diabetes (International Patent Application Publication No. WO 01/82917), and in methods of treatment, prevention, or amelioration of disorders related to, or arising as complications of diabetes, hyperglycemia or insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" (See US Patent Application 20030073614) comprising the administration of a therapeutically effective amount of a compound or composition of the present invention to a patient in need of such treatment. Additionally, the instant invention also provides a method for preventing or reducing the risk of developing hyperglycemia, insulin resistance, diabetes or syndrome X in a patient, comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. See, *e.g.*, LeRoith, D. et al., (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996). According to the American Diabetes Association, diabetes mellitus is estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for macrovascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

There are two major forms of diabetes: type 1 diabetes (formerly referred to as insulin-dependent diabetes or IDEM); and type 2 diabetes (formerly referred to as noninsulin dependent diabetes or NIDDM).

Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequate control of glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids, *e.g.*, cholesterol and triglyceride, in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease. For a review of disorders of lipid metabolism, see, *e.g.*, Wilson, J. et al., (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally

caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, *e.g.*, Joslin, E. Ann. Chim. Med. (1927), Vol. 5, pp. 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with non-diabetic subjects (see, *e.g.*, Garcia, M. J. et al., Diabetes (1974), Vol. 23, pp. 105-11 (1974); and Laakso, M. and Lehto, S., Diabetes Reviews (1997), Vol. 5, No. 4, pp. 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., et al., Arteriosclerosis (1978), Vol. 30, pp. 153-162).

The compounds of the invention can also be used effectively in combination with one or more additional active diabetes agents depending on the desired target therapy (see, *e.g.*, Turner, N. et al., Prog. Drug Res. (1998), Vol. 51, pp.33-94; Haffner, S., Diabetes Care (1998), Vol. 21, pp. 160-178; and DeFronzo, R. et al. (eds.), Diabetes Reviews (1997), Vol. 5, No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, *e.g.*, Mahler, R., J. Clin. Endocrinol. Metab. (1999), Vol. 84, pp. 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998), Vol. 21, pp. 87-92; Bardin, C. W.(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby--Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., Ann. Intern. Med. (1994), Vol. 121, pp. 928-935; Coniff, R. et al., Clin. Ther. (1997), Vol.19, pp. 16-26; Coniff, R. et al., Am. J. Med. (1995), Vol. 98, pp. 443-451; Iwamoto, Y. et al., Diabet. Med. (1996), Vol. 13, pp. 365-370; Kwiterovich, P., Am. J. Cardiol (1998), Vol. 82 (12A), pp. 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

Accordingly, the compounds of the invention may be used in combination with one or more of the following therapeutic agents in treating diabetes: sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone), and related insulin sensitizers, such as selective and non-selective activators of PPARα, PPARβ and PPARγ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester,

DHEA-SO4); antiglucocorticoids; TNFαinhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the therapeutic agents discussed above for treating atherosclerosis.

Further provided by this invention are methods of using the compounds of the invention to treat obesity, as well as the complications of obesity. Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of type 2 diabetes (See, *e.g.*, Barrett-Conner, E., Epidemol. Rev. (1989), Vol. 11, pp. 172-181; and Knowler, et al., Am. J Clin. Nutr. (1991), Vol. 53, pp. 1543-1551).

In addition, the compounds of the invention can be used in combination with agents used in treated obesity or obesity-related disorders. Such agents, include, but are not limited to, phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptor modulators, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

Evaluation of the Use of the Compounds of the Invention

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear receptors, including the LXRs (LXRα and LXRβ). Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see, generally, Glickman et al., J. Biomolecular Screening (2002), Vol. 7, No. 1, pp. 3-10, as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays, (see, Lehmann. et al., J. Biol Chem. (1997), Vol. 272, No. 6, pp. 3137-3140.

High throughput screening systems are commercially available (see, *e.g.*, Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for

various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see, for example, Owicki, J., Biomol. Screen (2000 October), Vol. 5, No. 5, pp. 297), scintillation proximity assays (SPA) (see, for example, Carpenter et al., Methods Mol. Biol. (2002), Vol 190, pp. 31-49) and fluorescence resonance energy transfer energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee et al., J. Steroid Biochem. Mol. Biol. (2002 July); Vol. 81, No. 3, pp. 217-25; (Zhou et al., Mol. Endocrinol. (1998 October), Vol. 12, No. 10, pp. 1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of LXRα, the LBD comprises amino acids 188-447, for LXRβ the LDB comprises amino acids 198-461, and for FXR, the LBD comprises amino acids 244 to 472 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound (for example, [^{3}H] 24,25 Epoxycholesterol) generates an optical signal when it is brought into close proximity to a scintillant such as a YSI-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of LXR with RXRα can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to monitor the ability of the compounds provided herein to bind to LXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in

close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXRα is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-*S*-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequenced derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, IC_{50}) the activity of an agonist for the nuclear receptor

In addition, a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds of the present invention. These approaches include the co-transfection assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand

binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor (see, for example, US Patents Nos. 5,071,773; 5,298,429 and 6,416,957). Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as the LXRs, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Typically, the expression plasmid comprises: (1) a promoter, such as an SV40 early region promoter, HSV tk promoter or phosphoglycerate kinase (pgk) promoter, CMV promoter, Srα promoter or other suitable control elements known in the art, (2) a cloned polynucleotide sequence, such as a cDNA encoding a receptor, co-factor, or fragment thereof, ligated to the promoter in sense orientation so that transcription from the promoter will produce a RNA that encodes a functional protein, and (3) a polyadenylation sequence. For example and not limitation, an expression cassette of the invention may comprise the cDNA expression cloning vectors, or other preferred expression vectors known and commercially available from vendors such as Invitrogen, (CA), Stratagene, (CA) or Clontech, (CA). Alternatively expression vectors developed by academic groups such as the pCMX vectors originally developed in the Evans lab (Willey et al. Genes & Development 9 1033-1045 (1995)) may also be used.

The transcriptional regulatory sequences in an expression cassette are selected by the practitioner based on the intended application; depending upon the specific use, transcription regulation can employ inducible, repressible, constitutive, cell-type specific, developmental stage-specific, sex-specific, or other desired type of promoter or control sequence.

Alternatively, the expression plasmid may comprise an activation sequence to activate or increase the expression of an endogenous chromosomal sequence. Such activation sequences include for example, a synthetic zinc finger motif (for example, see US Patents 6,534,261 and 6,503,7171) or a strong promoter or enhancer sequence together with a targeting sequence to enable homologous or non-homologous recombination of the activating sequence upstream of the gene of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include human LXRα (accession U22662), human LXRβ (accession U07132), rat FXR (accession U18374), human FXR (accession NM_005123), human RXRα (accession NM_002957), human RXRβ (accession XM_042579), human RXRγ (accession XM_053680), human PPARα (accession X57638) and human PPARδ (accession U10375). All accession numbers in this application refer to GenBank accession numbers.

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase (typically with SV40 small t intron and poly-A tail, (de Wet et al., (1987) Mol. Cell. Biol. 7 725-735) down stream from the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence, obtained for example, from the plasmid pBLCAT2 (Luckow & Schutz (1987) Nucl. Acid. Res.15 5490-5494)) which is linked in turn to the appropriate response element (RE).

The choice of hormone response element is dependent upon the type of assay to be used. In the case of the use of the full-length LXRα or LXRβ a reporter plasmid comprising a known LXR RE would typically be used, such as for example in a reporter plasmid such as LXREx1-tk-luciferase, (see U.S. patent No. 5,747,661, which is hereby incorporated by reference). In the case of a LXRα or LXRβ-LBD-Gal4 fusion, GAL4 Upstream Activating Sequences (UAS) would be used. Typically the GAL4 UAS would comprise the sequence 5'CGGRNNRCYNYNCNCCG-3', where Y = C or T, R =A or G, and N = A, C, T or G, and would be present as a tandem repeat of 4 copies.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase (see, Berger, J., et al., Gene (1988), Vol. 66, pp. 1-10; and Kain, S.R., Methods. Mol. Biol. (1997), Vol. 63, pp. 49-60), β-galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan et al., and Bronstein, I., et al., J. Chemilum. Biolum. (1989), Vol. 4, pp. 99-111), chloramphenicol acetyltransferase (See, Gorman et al., Mol. Cell Biol. (1982), Vol. 2, pp. 1044-51), β-glucuronidase, peroxidase, β-lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases

(U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; and 5,843,746) and naturally fluorescent proteins (Tsien, R.Y., Annu. Rev. Biochem. (1998), Vol. 67, pp. 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full length nuclear receptor. As with the full length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A / Umud super families are used.

A third cell based assay of utility for screening compounds of the present invention is a mammalian two-hybrid assay that measures the ability of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand (see, for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the reporter gene. This interaction significantly enhances the transcription of the reporter gene which can be measured for various reporter genes as described above.

Transcription of the reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of LXRα or LXRβ may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by LXRα or LXRβ and other nuclear receptors *in vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by LXR target genes. Genes that are known to be regulated by the LXRs include the ATP binding cassette transporters ABCA1, ABCG1, ABCG5, ABCG8, the sterol response element binding protein 1c (SREBP1c) gene, stearoyl CoA desaturase 1 (SCD-1) and the apolipoprotein apoE gene (ApoE).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice ($ApoE^{-/-}$), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice ($LDLR^{-/-}$) and atherosclerosis using both the Apo $E(^{-/-})$ and $LDLR(^{-/-})$ mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally LXR or FXR animal models (*e.g.*, knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (see, for example, Peet, et al., Cell (1998), Vol. 93, pp. 693-704, and Sinal, et al., Cell (2000), Vol. 102, pp. 731-744).

Administration of the Compounds of the Invention

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate

pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state associated with the activity of a nuclear receptor in accordance with the teachings of this invention.

A pharmaceutical composition of the invention may be in the form of a solid or liquid. In one aspect, the carrier(s) are particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup, injectable liquid or an aerosol, which is useful in, *e.g.*, inhalatory administration.

When intended for oral administration, the pharmaceutical composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the pharmaceutical composition may be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following may be present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; a flavoring agent such as peppermint, methyl salicylate or orange flavoring; and a coloring agent.

When the pharmaceutical composition is in the form of a capsule, *e.g.*, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or oil.

The pharmaceutical composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the present compounds, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid pharmaceutical composition of the invention intended for either parenteral or oral administration should contain an amount of a compound of the invention such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred oral pharmaceutical compositions contain between about 4% and about 50% of the compound of the invention. Preferred pharmaceutical compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 1% by weight of the compound of the invention.

The pharmaceutical composition of the invention may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the compound of the invention from about 0.1 to about 10% w/v (weight per unit volume).

The pharmaceutical composition of the invention may be intended for rectal administration, in the form, *e.g.*, of a suppository, which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol.

The pharmaceutical composition of the invention may include various materials, which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials that form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule.

The pharmaceutical composition of the invention in solid or liquid form may include an agent that binds to the compound of the invention and thereby assists in the delivery of the compound. Suitable agents that may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

The pharmaceutical composition of the invention may consist of dosage units that can be administered as an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. One skilled in the art, without undue experimentation may determine preferred aerosols.

The pharmaceutical compositions of the invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. Generally, a therapeutically effective daily dose is from

about 0.1 mg to about 20 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.1 mg to about 10 mg/kg of body weight per day; and most preferably, from about 0.1 mg to about 7.5 mg/kg of body weight per day.

Compounds of the invention, or pharmaceutically acceptable derivatives thereof, may also be administered simultaneously with, prior to, or after administration of one or more of the therapeutic agents described above in the Utility of the Compounds of the Invention. Such combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of the invention and one or more additional active agents, as well as administration of the compound of the invention and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of the invention and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compounds of the invention and one or more additional active agents can be administered at essentially the same time, *i.e.*, concurrently, or at separately staggered times, *i.e.*, sequentially; combination therapy is understood to include all these regimens.

Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the Physicians' Desk Reference (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day and, more preferably, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg and, more particularly, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

Preparation of the Compounds of the Invention

It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

It will also be appreciated by those skilled in the art that in the processes described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for 1,2-dihydroxys include ketal- and acetal-forming groups. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, Protective Groups in Organic Synthesis (1991), 2nd Ed., Wiley-Interscience. The protecting group may also be a polymer resin such as a Wang resin or a 2-chlorotrityl chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of the invention, as described above in the First aspect of the invention, may not possess pharmacological activity as such, they may be administered to a mammal having a disease associated with defects in cholesterol transport, glucose metabolism, fatty acid metabolism and cholesterol metabolism, and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of the invention are included within the scope of the invention.

It is understood that one of ordinary skill in the art would be able to make the compounds of the invention not specifically prepared herein in light of the following disclosure, including the Preparations and Examples, and information known to those of ordinary skill in the chemical synthesis field.

Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures or by methods disclosed herein. All commercially available compounds were used without further purification unless otherwise indicated. Deuterated solvents such as DMSO or $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) were used in all experiments as indicated. ^1H NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Mass spectra were

recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid) and electrospray (ES) ionization. Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, CH_2Cl_2 (dichloromethane), C_6H_6 (benzene), TFA (trifluoroacetic acid), EtOAc (Ethyl Acetate), Et_2O (diethyl ether), DMAP (4-dimethylaminopyridine), DMF (N,N-dimethylformamide) and THF (tetrahydrofuran). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

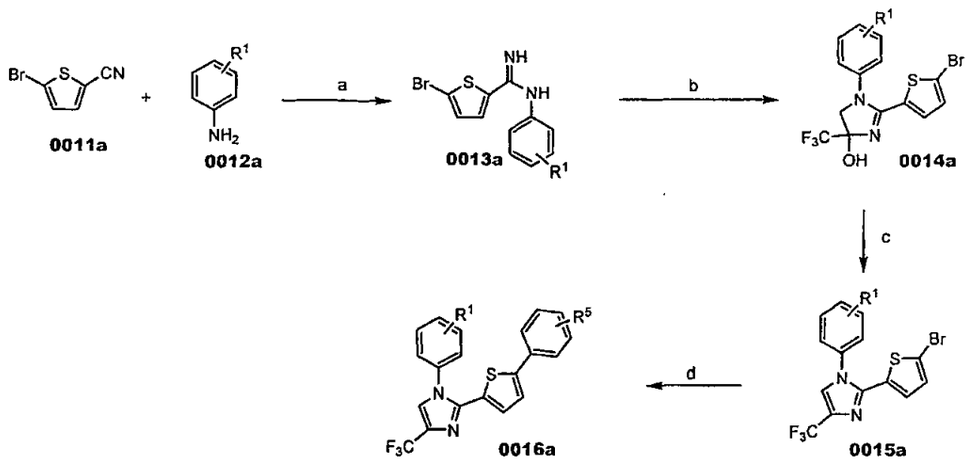
For purposes of illustration only, most of the formulae in the following Reaction Schemes are directed to specific embodiments of the compounds of invention. However, one of ordinary skill in the art, in view of the teachings of this specification would reasonably be expected to be able to prepare all the compounds of the invention in the First aspect of the invention utilizing the appropriately-substituted starting materials and methods known to one skilled in the art.

In the general descriptions immediately following each Reaction Scheme, the phrase "standard isolation procedures" is meant to include one or more of the following techniques familiar to one schooled in the art of organic chemistry: organic extraction, washing of organic solutions with dilute aqueous acid or base, use of drying agents, filtration, concentration *in vacuo*, followed by purification using distillation, crystallization, or solid-liquid phase chromatography. The phrase "elevated temperature" refers to a temperature above ambient temperature and the phrase "reduced temperature" refers to a temperature below ambient temperature.

The following specific Preparations (for intermediates) and Examples (for compounds, pharmaceutical compositions and methods of use of the invention) are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention. Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to one of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

Unless otherwise indicated, all compounds associated with NMR and/or mass spectra data were prepared and the NMR and mass spectra measured.

Scheme 1



Reaction and conditions: (a) NaHMDS, THF; 0°C- rt; (b) 3-bromo-1,1,1-trifluoroacetone, $NaHCO_3$, 2-PrOH, 80°C; (c) TSA, toluene, reflux; (d) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

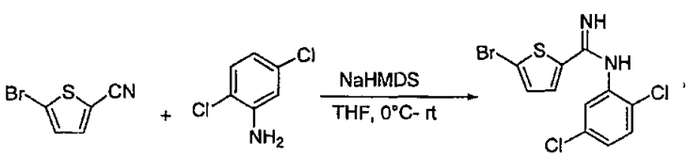
In general, compounds of formula (**0016a**) are prepared by first reacting an aniline of formula (**0012a**) with aryl nitriles (**0011a**), such as 5-bromo-thiophene-2-carbonitrile, in the presence of base to give compounds of formula (**0013a**) after standard isolation procedures. In a subsequent step, exposure of amidine (**0013a**) to haloketone, such as 1-bromo-3,3,3-trifluoroacetone, under basic condition at elevated temperature provides 1*H*-imidazol-4-ol of formula (**0014a**) after standard isolation procedures. Conversion of compounds of formula (**0014a**) to compounds of formula (**0015a**) is then accomplished by treating the compounds of formula (**0014a**) with a catalyst acid such as *p*-toluenesulfonic acid at reflux. In a palladium-mediated coupling reaction, for example, a Suzuki reaction, compounds of formula (**0015a**) are then reacted with a boronate or boronic acid reagent to give compounds of formula (**0016a**) after standard isolation procedures.

Example 1

1-(2,5-Dichloro-phenyl)-2-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1H-imidazole

Example 1a

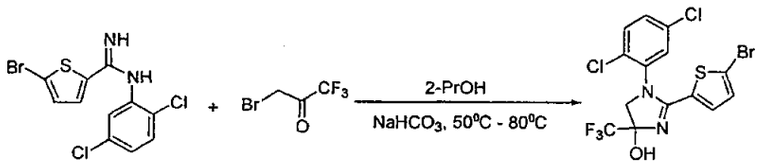
Preparation of 5-Bromo-N-(2,5-dichloro-phenyl)-thiophene-2-carboxamidine



Under N_2 atmosphere, to a solution of 2,5-dichloroaniline (341 mg, 2.1 mmol) in 2mL dry THF was added sodium bis(trimethylsilyl)amide (2.1 mL, 1M solution in THF, 2.1 mmol). After the mixture was stirred at ambient temperature for 40 min, a solution of 5-bromo-thiophene-2-carbonitrile (376 mg, 2 mmol) in 2 mL dry THF was added dropwise. The reaction mixture was stirred overnight, and then poured into 100 mL ice water. The orange precipitate was collected by filtration, washed with a solution of ether and hexane (3/7, v/v), and air dried to give a light orange solid (653 mg, 94% yield). ^{1}H-NMR (400MHz, MeOH-d_4): δ 6.94 (d, 1H), 6.99 (dd, 1H), 7.06 (d, 1H), 7.32 (d, 1H), 7.37 (d, 1H).

Example 1b

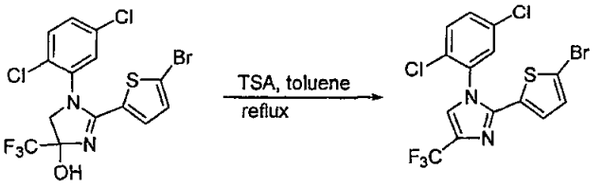
Preparation of 2-(5-Bromo-thiophen-2-yl)-1-(2,5-dichloro-phenyl)-4-trifluoromethyl-4,5-dihydro-1H-imidazol-4-ol



To a suspension of 5-bromo-N-(2,5-dichloro-phenyl)-thiophene-2-carboxamidine (634 mg, 1.8 mmol) and sodium bicarbonate (227 mg, 2.7 mmol) in 8 mL 2-proponal was added 3-bromo-1,1,1-trifluoroacetone (520 mg, 2.7 mmol). The reaction mixture was heated at 50°C for 1.5 hrs, then at 80°C for 4 hrs. After cooling to room temperature, the residue was filtered out and washed with dichloromethane. The filtrate and washings were combined together and concentrated under vacuum to give a light pink solid that was used directly for the next step (820 mg, 99% yield). ^{1}H-NMR (400MHz, DMSO-d_6): δ 3.09 (d, 1H), 3.95 (dd, 1H), 6.31 (d, 1H), 6.91 (d, 1H), 7.15 (m, 1H), 7.33 (dd, 1H), 7.44 (m, 2H).

Example 1c

Preparation of 2-(5-Bromo-thiophen-2-yl)-1-(2,5-dichloro-phenyl)-4-trifluoromethyl-1H-imidazole

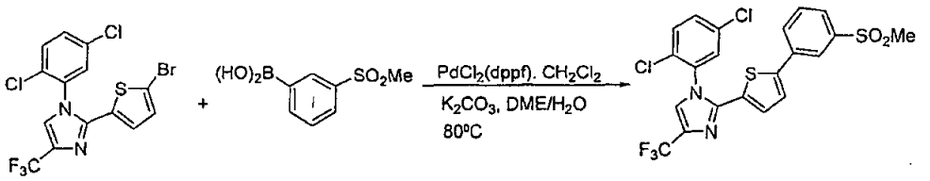


The mixture of 2-(5-bromo-thiophen-2-yl)-1-(2,5-dichloro-phenyl)-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-ol (822 mg, 1.8 mmol) and *p*-toluenesulfonic acid monohydrate (172 mg, 0.9 mmol) in 10 mL toluene was heated at 120°C for 6 hrs. The solvent was removed, and the residue was redissolved into dichloromethane, then washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel

(hexane/EtOAc 85/15) to give an off-white solid (512 mg, 64% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.68 (d, 1H), 6.89 (d, 1H), 7.31 (dd, 1H), 7.47 (dd, 1H), 7.55 (d, 1H), 7.56 (s, 1H).

Example 1d

Preparation of 1-(2,5-Dichloro-phenyl)-2-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-4-trifluoromethyl-1H-imidazole



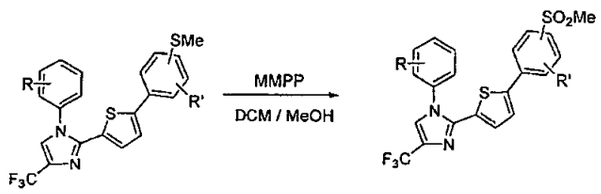
2-(5-Bromo-thiophen-2-yl)-1-(2,5-dichloro-phenyl)-4-trifluoromethyl-1*H*-imidazole (90 mg, 0.2 mmol), (3-methylsulfonyl)phenylboronic acid (60 mg, 0.3 mmol), potassium carbonate (110 mg, 0.8 mmol), and $PdCl_2(dppf).CH_2Cl_2$ (16 mg, 0.02 mmol) were mixed with 2 mL 9:1 DME/H_2O (v/v), then heated at 80^{0}C overnight. All solvent was removed *in vacuo*. The crude product was purified by chromatography on silica gel (Hexane/EtOAc, 6/4) to give a white solid (76 mg, 74% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 3.08 (s, 3H), 6.79 (d, 1H), 7.22 (d, 1H), 7.36 (d, 1H), 7.52 (d, 1H), 7.58 (m, 3H), 7.78 (m, 1H), 7.86 (m, 1H), 8.10 (t, 1H).

All the following compounds were prepared in similar manner as described in Scheme 1 and mass and NMR spectra measured.The boronic acid or boronate reagents for Suzuki coupling, if not commercially available, were made using standard techniques that are readily apparent to one skilled in the art.

- 1-(2,5-dichlorophenyl)-2-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1H-imidazole; MS (ES): 517.3 $[M+H]^+$;
- 5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methyl-2-(methylthio)pyridine; MS (ES): 500.4 $[M+H]^+$;
- 5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylthio)-3-methylpyridine; MS (ES): 514.2 $[M+H]^+$;
- 4-(5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}pyridin-2-yl)morpholine; MS (ES): 525.4,527.3 $[M+H]^+$;
- 1,1-dimethylethyl 4-(5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}pyridin-2-yl)piperazine-1-carboxylate; MS (ES): 624.5, 626.3 $[M+H]^+$;
- 1-(2-chlorophenyl)-2-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1H-imidazole; MS (ES): 483.2 $[M+H]^+$;

- 5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methyl-2-(methylthio)pyridine; MS (ES): 466.2 $[M+H]^+$;
- 5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylthio)-3-methylpyridine; MS (ES): 480.2 $[M+H]^+$;
- methyl (4-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methylphenyl)acetate; MS (ES): 491.2 $[M+H]^+$;
- 3-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}benzenesulfonamide; MS (ES): 484.0 $[M+H]^+$;
- 4-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}benzenesulfonamide; MS (ES): 484.1 $[M+H]^+$;

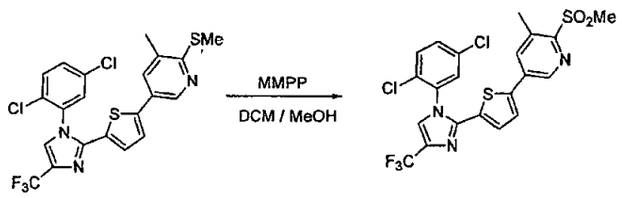
Scheme 2



The starting materials were prepared in similar manner as Scheme 1, followed by further transformations to make the final products as described in Scheme 2.

Example 2

Preparation of 5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(methylsulfonyl)-3-methylpyridine



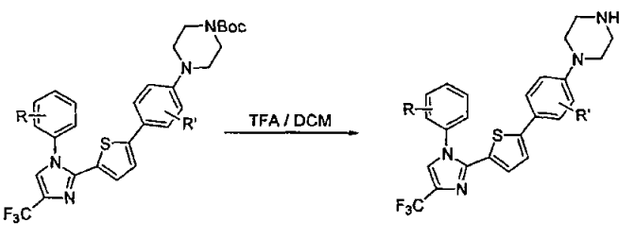
5-{5-[1-(2,5-Dichloro-phenyl)-4-trifluoromethyl-1*H*-imidazol-2-yl]-thiophen-2-yl}-3-methyl-2-methylsulfanyl-pyridine (80 mg, 0.16 mmol) was dissolved in 8 mL mixture of dichloromethane and methanol (5:1, V/V). MMPP (magnesium monoperoxyphthalate hexahydrate, 200 mg, 0.35 mmol, 80% tech.) was added then. The mixture was stirred at room temperature for 2 hrs, then diluted with dichloromethane, and filtered. The filtrate was washed with saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (15 → 60% EtOAc/Hexane) to give a white solid (52 mg, 61% yield). 1H-NMR (400MHz,

DMSO-d_6): δ 2.61 (s, 3H), 3.37 (s, 3H), 6.58 (d, J = 4.0, 1H), 7.63 (d, J = 4.0, 1H), 7.86 – 7.79 (m, 2H), 8.20 – 8.17 (m, 2H), 8.31 - 8.30 (m, 1H), 8.80 (m, 1H). MS (ES): 532.2, 536.2 $[M+H]^+$

The following compounds were made in similar manner by oxidation of appropriate sulfides.

- 5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylsulfonyl)-3-methylpyridine; MS (ES): 546.2 $[M+H]^+$
- 5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methyl-2-(methylsulfonyl)pyridine; MS (ES): 532.2 $[M+H]^+$
- 5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methyl-2-(methylsulfonyl)pyridine; MS (ES): 498.4 $[M+H]^+$
- 5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylsulfonyl)-3-methylpyridine; MS (ES): 512.2 $[M+H]^+$

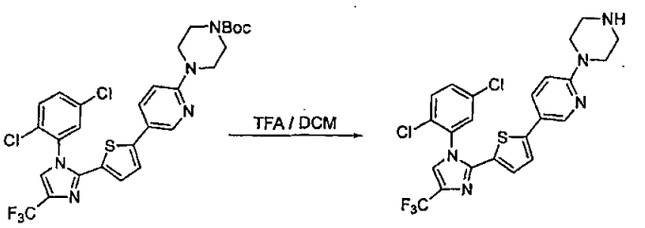
Scheme 3



The starting materials were prepared in similar manner as Scheme 1, followed by further transformations to make the final products as described in Scheme 3.

Example 3

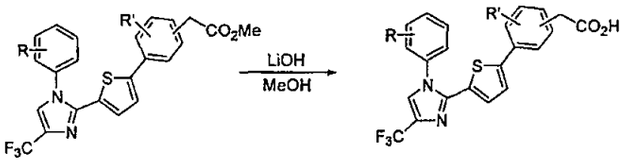
1-(5-{5-[1-(2,5-Dichloro-phenyl)-4-trifluoromethyl-1H-imidazol-2-yl]-thiophen-2-yl}-pyridin-2-yl)-piperazine



4-(5-{5-[1-(2,5-Dichloro-phenyl)-4-trifluoromethyl-1H-imidazol-2-yl]-thiophen-2-yl}-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (104 mg, 0.17 mmol) was mixed with 4 mL 50% trifluoromethylacetic acid in dichloromethane, and stirred at room temperature for 2 hrs. All solvent was removed; the residue was redissolved in dichloromethane and neutralized to pH 7 by saturated $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was precipitated from dichloromethane / Hexane mixture, then filtered and washed several

times with dichloromethane to give yellow solid (50 mg, 57% yield). 1H-NMR (400MHz, $CDCl_3$): δ 3.30 – 2.97 (m, 4H), 3.57 – 3.54 (m, 4H), 6.63 (d, J = 8.7, 1H), 6.78 (d, J = 4.0, 1H), 6.96 (d, J = 4.0, 1H), 7.31(s, 1H), 7.60 – 7.50 (m, 4H), 8.37 (m, 1H). MS (ES): 524.3, 526.5, $[M+H]^+$

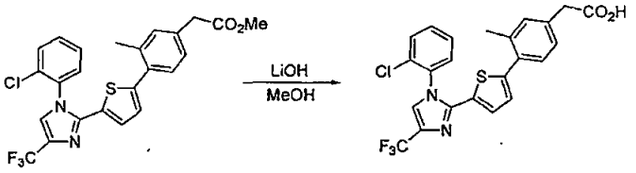
Scheme 4



The starting materials were prepared in similar manner as Scheme 1, followed by further transformations to make the final products as described in Scheme 4.

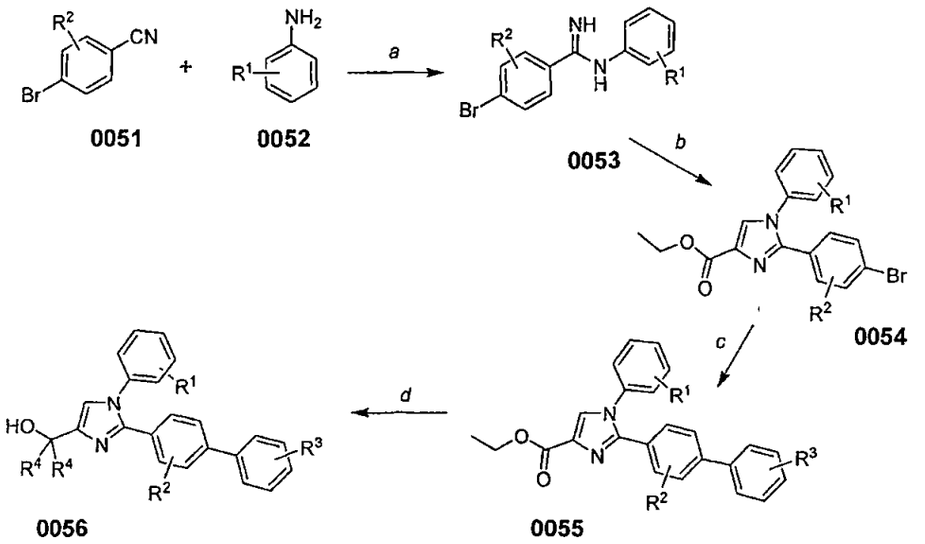
Example 4

(4-{5-[1-(2-Chloro-phenyl)-4-trifluoromethyl-1H-imidazol-2-yl]-thiophen-2-yl}-3-methyl-phenyl)-acetic acid



(4-{5-[1-(2-Chloro-phenyl)-4-trifluoromethyl-1*H*-imidazol-2-yl]-thiophen-2-yl}-3-methyl-phenyl)-acetic acid methyl ester (123 mg, 0.25 mmol) was dissolved in 6 mL mixture of THF and water (3:1, V/V). Lithium hydroxide monohydrate (2.3 mg, 0.55 mmol) was added then. The mixture was stirred at room temperature for 3 hrs. The mixture was neutralized to pH 7 by 1N HCl, and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (0 → 5% MeOH/DCM) to give a white solid (47 mg, 39% yield). 1H-NMR (400MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.64 (s, 2H), 6.83 (s, 2H), 7.13 – 7.10 (m, 1H), 7.16 (m, 1H), 7.29 – 7.27 (m, 1H), 7.35 (m, 1H), 7.47 - 7.46 (m, 2H), 7.57 - 7.52 (m, 1H), 7.64 – 7.62 (m, 1H). MS (ES): 477.1, $[M+H]^+$

Scheme 5



(a) Me_3Al, PhMe, 90°C; (b) ethyl bromopyruvate, $NaHCO_3$, 2-PrOH, 95°C; (c) $ArB(OH)_2$, $Cl_2Pd(dppf)$, K_2CO_3, H_2O/DME, 80°C; (d) R^4MgBr, THF, 0°C-rt.

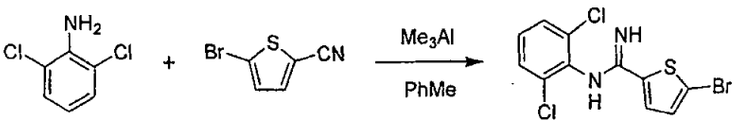
In general, compounds of formula (**0056**) can be prepared as depicted in Scheme 5. An arylnitrile (**0051**) and an arylamine (**0052**) can react in the presence of a Lewis acid, such as trimethylaluminum, to give the corresponding amidine (**0053**). Heteroarylnitriles **0051** and/or heteroarylamines **0052** also can be utilized for the syntheses of their respective amidines **0053**. Intermediate **0053** then can react with ethyl bromopyruvate in the presence of a weak base, such as sodium bicarbonate, followed by dehydration at elevated temperature to yield the corresponding imidazole (**0054**). This intermediate **0054** can undergo cross-coupling reactions, such as with an arylboronic acid under typical Suzuki conditions, to afford the corresponding 2-biaryl-imidazole (**0055**). **0055** can react with a Grignard reagent, such as an alkylmagnesium bromide, to afford the desired product **0056**.

Example 5

2-{1-(2,6-dichlorophenyl)-2-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-1H-imidazol-4-yl}-propan-2-ol

Example 5a

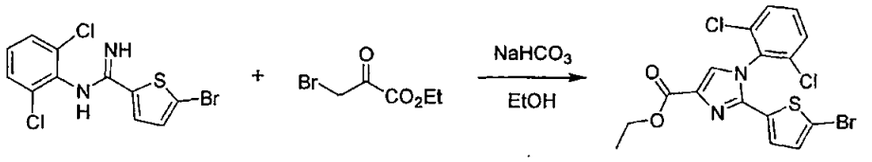
Preparation of 5-bromo-N-(2,6-dichlorophenyl)-thiophene-2-carboxamidine



To a stirred solution of 2,6-dichloroaniline (1.75 g, 10.8 mmol) in toluene (25 mL, anhyd) was added dropwise a 2.0M solution of trimethylaluminum in toluene (8.0 mL, 16 mmol). After 90 min the reaction mixture was charged with a solution of 5-bromothiophene-2-carbonitrile (3.00 g, 16 mmol) in toluene (20 mL, anhyd) and then heated at 90°C. After 5 h the reaction mixture was allowed to cool to ambient temperature and quenched by addition to a stirred slurry of silica (25 g) in 3:1 $CHCl_3$/MeOH (100 mL). After 30 min the resulting mixture was filtered and the solids rinsed with MeOH and DCM. The combined filtrates were concentrated to afford the title compound (3.9 g, quant) as a pale yellow solid, which was used in the next step without purification. GC-MS(EI): 348, 350, 352.

Example 5b

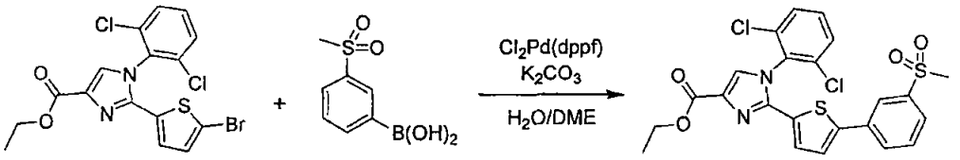
Preparation of 2-(5-bromothiophen-2-yl)-1-(2,6-dichlorophenyl)-1H-imidazole-4-carboxylic acid ethyl ester



A stirred mixture of 5-bromo-N-(2,6-dichlorophenyl)-thiophene-2-carboxamidine (3.9 g, 11 mmol) and sodium bicarbonate (1.85 g, 22 mmol) in isopropanol (55 mL) was charged with ethyl bromopyruvate (2.5 mL, 20 mmol) and then heated at 95°C. After 17 h the reaction mixture was allowed to cool to ambient temperature, filtered and the solids rinsed with EtOAc. The combined filtrates were concentrated under reduced pressure and purified by chromatography (silica, EtOAc/Hex, 15:85 to 65:35) to give the title compound (3.3 g, 67%) as a tacky yellow solid, which was used in the next step without further purification. ^{1}H-NMR (DCM-d_2): δ 7.60 (s, 1H), 7.49-7.59 (m, 3H), 6.89 (d, 1H), 6.56 (d, 1H), 4.37 (q, 2H), 1.38 (t, 3H).

Example 5c

Preparation of 1-(2,6-dichlorophenyl)-2-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-1H-imidazole-4-carboxylic acid ethyl ester

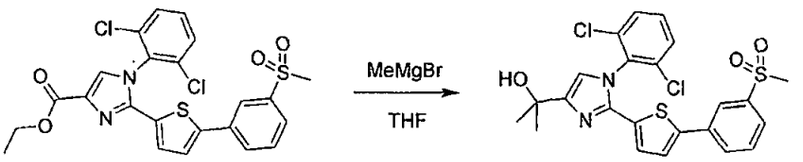


A mixture of 2-(5-bromothiophen-2-yl)-1-(2,6-dichlorophenyl)-1H-imidazole-4-carboxylic acid ethyl ester (335 mg, 0.75 mmol), 3-methanesulfonyl-phenylboronic acid (180 mg, 0.90 mmol), K_2CO_3 (0.32 g, 2.3 mmol), $Cl_2Pd(dppf)\cdot DCM$ (30 mg, 5 mol%) and H_2O (0.4 mL) in DME (4 mL) was sparged with Argon for 5 min and then heated at 80°C as a sealed flask. After 2 h the reaction mixture

was allowed to cool to ambient temperature, filtered (Celite™) and the filter agent rinsed with EtOAc. The combined filtrates were concentrated under reduced pressure and purified by chromatography (silica, EtOAc/Hex, 30:70 to 80:20) to give the title compound (313 mg, 80%) as a pale yellow solid, which was used in the next step without further purification. ^{1}H-NMR (DCM-d_2): δ 8.08 (m, 1H), 7.82 (m, 2H), 7.64 (s, 1H), 7.51-7.62 (m, 4H), 7.24 (d, 1H), 6.72 (d, 1H), 4.38 (q, 2H), 3.05 (s, 3H), 1.40 (t, 3H).

Example 5d

Preparation of 2-{1-(2,6-dichlorophenyl)-2-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-1H-imidazol-4-yl}-propan-2-ol



To a stirred solution of 1-(2,6-dichlorophenyl)-2-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-1H-imidazole-4-carboxylic acid ethyl ester (300 mg, 0.58 mmol) in THF (3 mL) at 0°C was added a 3.0M solution of methylmagnesium bromide in Et_2O (0.80 mL, 2.4 mmol). After addition was completed the flask was removed from the ice-water bath and allowed to warm to ambient temperature. At 40 min the reaction mixture was quenched by addition of satd NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), concentrated and purified by chromatography (silica, EtOAc/Hex, 40:60 to 90:10) to give the title compound (0.17 g, 59%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 8.07 (m, 1H), 7.81 (m, 2H), 7.46-7.60 (m, 4H), 7.21 (d, 1H), 6.85 (s, 1H), 6.62 (d, 1H), 3.05 (s, 3H), 2.68 (br s, 1H), 1.61 (s, 6H); MS(ES): 507, 509 $[M+H]^+$.

In a similar manner, the following imidazoles were prepared from appropriate reagents. Optionally the order of Suzuki cross-coupling and addition of Grignard reagent was switched.

- 2-(1-(2,6-dichlorophenyl)-2-(5-(3-(ethylsulfonyl)phenyl)thiophen-2-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 521, 523 $[M+H]^+$
- 2-(1-(2,6-dichlorophenyl)-2-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$
- 2-(1-(2,6-dichlorophenyl)-2-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 529, 531 $[M+H]^+$
- 2-(1-(2-isopropyl-6-methylphenyl)-2-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 503 $[M+H]^+$
- 2-(2-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1-(2-isopropyl-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 517 $[M+H]^+$

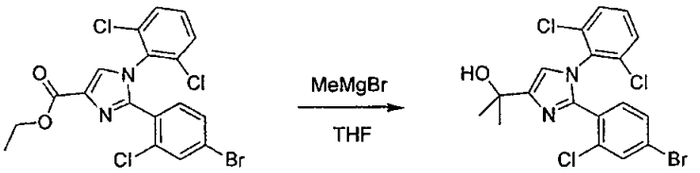
- 2-(1-(2-isopropylphenyl)-2-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 489 $[M+H]^+$
- 2-(2-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 503 $[M+H]^+$
- 2-(1-(2,6-dichlorophenyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 501, 503 $[M+H]^+$
- 2-(1-(2,6-dichlorophenyl)-2-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$
- 2-(2-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 535, 537 $[M+H]^+$
- 2-(2-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 549, 551 $[M+H]^+$

Example 6

2-[5-chloro-2-(3-chloro-3'-methanesulfonyl-biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-propan-2-ol

Example 6a

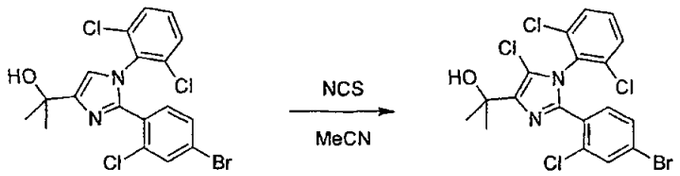
Preparation of 2-[2-(4-bromo-2-chlorophenyl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-propan-2-ol



To a 3.0 M solution of MeMgBr in Et_2O (7.0 mL, 21.0 mmol) at 0°C added slowly a solution of 2-(4-bromo-2-chlorophenyl)-1-(2,6-dichlorophenyl)-1H-imidazole-4-carboxylic acid ethyl ester (2.80 g, 5.90 mmol) in THF (30 mL, anhyd). After addition was completed the flask was removed from the ice-water bath and allowed to warm to ambient temperature. At 50 min the reaction mixture was quenched by addition of satd NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), concentrated and purified by chromatography (silica, EtOAc/Hex, 15:85 to 55:45) to give the title compound (2.1 g, 77%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 7.58 (d, 1H), 7.37-7.41 (m, 2H), 7.26-7.32 (m, 2H), 7.11 (d, 1H), 6.93 (s, 1H), 2.73 (br s, 1H), 1.61 (s, 6H).

Example 6b

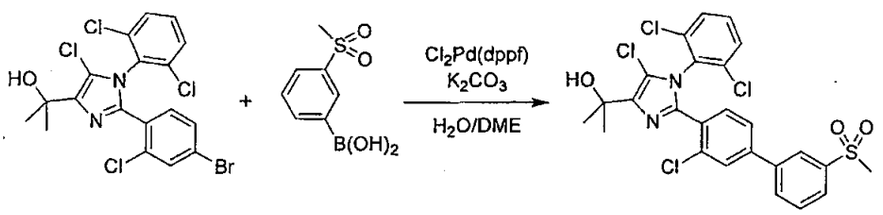
Preparation of 2-[2-(4-bromo-2-chlorophenyl)-5-chloro-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-propan-2-ol



A suspension of 2-[2-(4-bromo-2-chlorophenyl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-propan-2-ol (230 mg, 0.50 mmol) in MeCN (4 mL, anhyd) was charged with N-chlorosuccinimide (70 mg, 0.52 mg) and then heated at 70C. After 22 h the reaction mixture was charged with additional N-chlorosuccinimide (67 mg, 0.50 mmol) and heated at 85C. After 40 h (total reaction time) the reaction mixture was allowed to cool to ambient temperature, concentrated and purified by chromatography (silica, EtOAc/Hex, 0:100 to 30:70) to give the title compound (0.19 g, 77%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 7.61 (d, 1H), 7.42-7.45 (m, 2H), 7.36 (m, 1H), 7.27 (dd, 1H), 7.10 (d, 1H), 3.33 (s, 1H), 1.65 (s, 6H).

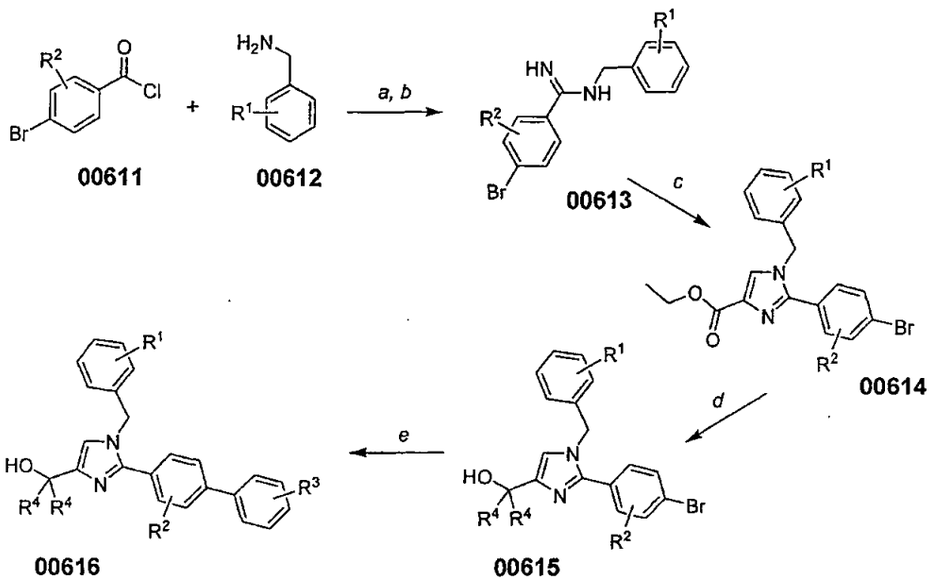
Example 6c

Preparation of 2-[5-chloro-2-(3-chloro-3'-methanesulfonyl-biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-propan-2-ol



A mixture of 2-[2-(4-bromo-2-chlorophenyl)-5-chloro-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-propan-2-ol (184 mg, 0.37 mmol), 3-methanesulfonyl-phenylboronic acid (90 mg, 0.45 mmol), K_2CO_3 (0.15 g, 1.1 mmol), $Cl_2Pd(dppf)\cdot DCM$ (15 mg, 5 mol%) and H_2O (0.2 mL) in DME (2 mL) was sparged with Argon for 5 min and then heated at 60°C as a sealed flask. After 70 min the reaction mixture was allowed to cool to ambient temperature, filtered (Celite™) and the filter agent rinsed with EtOAc. The combined filtrates were concentrated under reduced pressure and purified by chromatography (silica, EtOAc/Hex, 20:80 to 60:40) to give the title compound (165 mg, 78%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 8.08 (m, 1H), 7.93 (m, 1H), 7.84 (m, 1H), 7.73 (d, 1H), 7.67 (m, 1H), 7.33-7.47 (m, 5H), 3.42 (br s, 1H), 3.06 (s, 3H), 1.68 (s, 6H); MS(ES): 591, 593, 595 $[M+Na]^+$.

Scheme 6



(a) Et_3N, THF; (b) $SOCl_2$, 90°C; concentrate and add to NH_3/MeOH; (c) ethyl bromopyruvate, $NaHCO_3$, EtOH, μW 175°C; (d) R^4MgBr, THF, 0°C-rt; (e) $ArB(OH)_2$, $Cl_2Pd(dppf)$, K_2CO_3, H_2O/DME, μW 120°C.

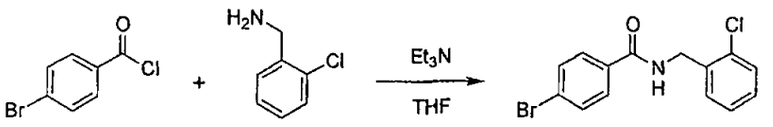
In general, compounds of formula **00616** can be prepared as shown in Scheme 6. First, an amide can be generated from reacting a benzoyl chloride (**00611**) and a benzylamine (**00612**) under basic conditions. The resulting amide can be treated with thionyl chloride at elevated temperature to give an imidoyl chloride, which can be converted directly to its corresponding amidine (**00613**) upon addition to a solution of ammonia. Amidine **00613** and ethyl bromopyruvate can react under basic conditions and at elevated temperature to yield the corresponding imidazole (**00614**). This intermediate ester **00614** can react with a Grignard reagent, such as an alkylmagnesium bromide, to afford the respective carbinol (**00615**). Last intermediate **00615** can undergo cross-couplings reactions, such as a Suzuki-Miyaura reaction with boronic acids (esters), to yield the target imidazole **00616**.

Example 7

2-[1-(2-chlorobenzyl)-2-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol

Example 7a

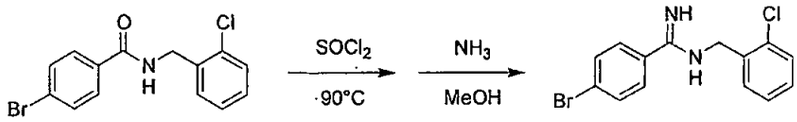
Preparation of 4-bromo-N-(2-chlorobenzyl)-benzamide



To a stirred solution of 2-chlorobenzylamine (2.42 mL, 20 mmol) in THF (80 mL, anhyd) at 0°C added a solution of 4-bromobenzoyl chloride (4.39 g, 20 mmol) in THF (20 mL, anhyd.) and then triethylamine (2.93 mL, 21 mmol). After 12 h the resulting mixture was filtered and the solids rinsed with EtOAc. The combined filtrates were diluted with EtOAc (100 mL), washed with 1N HCl, satd $NaHCO_3$ and brine, then dried (anhyd Na_2SO_4) and concentrated to afford the title compound (6.36 g, 98%) as a white solid, which was used in the next step without purification. GC-MS(EI): 322, 324.

Example 7b

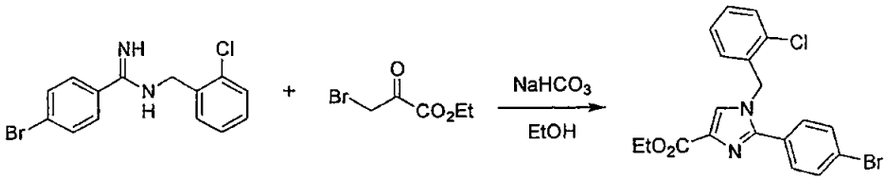
Preparation of 4-bromo-N-(2-chlorobenzyl)-benzamidine



A mixture of 4-bromo-N-(2-chlorobenzyl)-benzamide (1.62 g, 5.0 mmol) and thionyl chloride (0.73 mL, 10 mmol) was heated at 90°C. After 150 min the reaction mixture was cooled and concentrated under reduced pressure. The resulting residue was diluted with toluene (10 mL, anhyd) and concentrated to give the corresponding imidoyl chloride [conversion confirmed by NMR] as a pale yellow solid. To a stirred 2M solution of NH_3 in MeOH (8 mL, 16 mmol) was added this intermediate in small portions. After 12 h the reaction mixture was added to satd $NaHCO_3$ and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound (1.5 g, 93%), which was used in the next step without purification. GC-MS(EI): 321, 323.

Example 7c

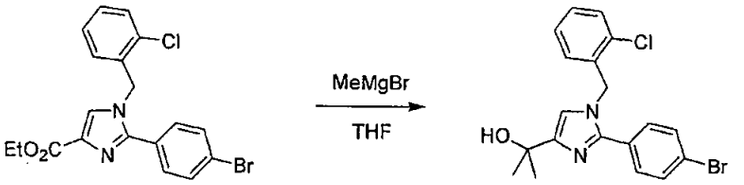
Preparation of 2-(4-bromophenyl)-1-(2-chlorobenzyl)-1H-imidazole-4-carboxylic acid ethyl ester



A mixture of 4-bromo-N-(2-chlorobenzyl)-benzamidine (1.4 g, 4.3 mmol), sodium bicarbonate (0.72 g, 8.6 mmol) and ethyl bromopyruvate (0.98 mL, 7.8 mmol) in EtOH (14 mL) was heated in a microwave unit (Biotage Initiator™) at 175°C for 12 min. The resulting mixture was decanted and the solids rinsed with EtOAc. The combined filtrates were concentrated and purified by chromatography (silica, EtOAc/Hex, 0:100 to 40:60) to give the title compound (0.24 g, 13%) as a pale brown residue. ^{1}H-NMR (DCM-d_2): δ 7.58-7.62 (m, 3H), 7.43-7.49 (m, 3H), 7.34 (m, 1H), 7.28 (m, 1H), 6.96 (d, 1H), 5.30 (s, 2H), 4.32 (q, 2H), 1.35 (t, 3H); MS(ES): 419, 421 $[M+H]^+$.

Example 7d

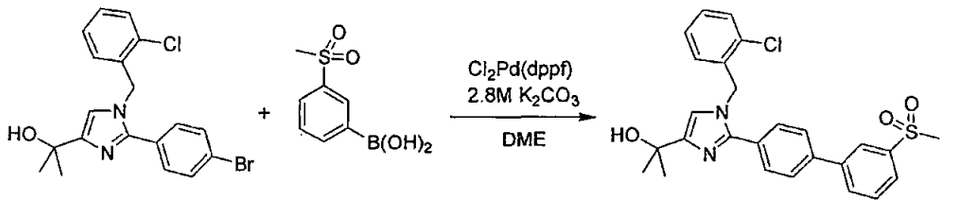
Preparation of 2-[2-(4-bromophenyl)-1-(2-chlorobenzyl)-1H-imidazol-4-yl]-propan-2-ol



To a 3.0 M solution of MeMgBr in Et_2O (1.0 mL, 3.0 mmol) at 0°C added slowly a solution of 2-(4-bromophenyl)-1-(2-chlorobenzyl)-1H-imidazole-4-carboxylic acid ethyl ester (235 mg, 0.56 mmol) in THF (3 mL, anhyd). After addition was completed the flask was removed from the ice-water bath and allowed to warm to ambient temperature. At 40 min the reaction mixture was quenched by addition of satd NH_4Cl, extracted with EtOAc, dried ($MgSO_4$), concentrated and purified by chromatography (silica, EtOAc/Hex, 20:80 to 60:40) to give the title compound (135 mg, 59%) as a pale amber solid. ^{1}H-NMR (DCM-d_2): δ 7.54 (d, 2H), 7.38-7.45 (m, 3H), 7.24-7.33 (m, 2H), 6.89 (d, 1H), 6.82 (s, 1H), 5.25 (s, 2H), 2.86 (br s, 1H), 1.54 (s, 6H); MS(ES): 405, 407 $[M+H]^+$.

Example 7e

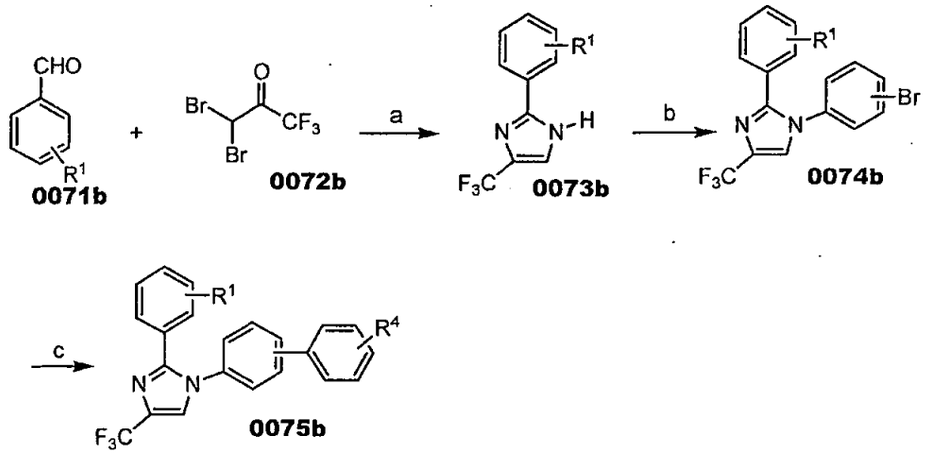
Preparation of 2-[1-(2-chlorobenzyl)-2-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol



A mixture of 2-[2-(4-bromophenyl)-1-(2-chlorobenzyl)-1H-imidazol-4-yl]-propan-2-ol (130 mg, 0.32 mmol), 3-methanesulfonyl-phenylboronic acid (80 mg, 0.40 mmol), $Cl_2Pd(dppf)$·DCM (13 mg, 5 mol%) and a 2.8M aqueous solution of K_2CO_3 (0.35 mL, 0.98 mmol) in DME (2 mL) was heated in a microwave unit (Biotage Initiator™) at 120°C for 4 min. The reaction mixture was concentrated and purified by chromatography (silica, EtOAc/Hex, 45:55 to 90:10) to give the title compound (118 mg, 77%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 8.08 (m, 1H), 7.84 (dd, 2H), 7.55-7.64 (m, 5H), 7.36 (m, 1H), 7.17-7.26 (m, 2H), 6.85 (d, 1H), 6.77 (s, 1H), 5.24 (s, 2H), 3.00 (s, 3H), 2.86 (br s, 1H), 1.49 (s, 6H); MS(ES): 481 $[M+H]^+$.

In a similar manner 2-[1-(2,3-dichlorobenzyl)-2-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol was prepared by replacing 2-chlorobenzylamine with 2,3-dichlorobenzylamine. MS(ES): 515, 517 $[M+H]^+$.

Scheme 7



Reaction and conditions: (a) NaOAc, NH_4OH, MeOH; (b) $ArB(OH)_2$, $[Cu(OH).TMEDA]_2Cl_2$, DCM; (c) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

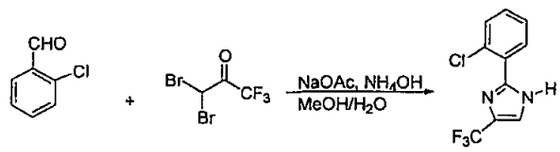
In general, compounds of formula (**0075b**) are prepared by first reacting 3,3-dihaloketone such as 3,3-dibromo-1,1,1-trifluoromethylacetone with aqueous sodium acetate to generate a glyoxal which react *in situ* with aldehyde of formula (**0071b**) and ammonia to yield an imidazole of formula (**0073b**). Conversion of compounds of formula (**0073b**) to compounds of formula (**0074b**) is then accomplished by means of N-arylation such as a Buchwald reaction or Cu(II) catalyzed coupling with boronic acid regents. In a palladium mediated coupling reaction, for example a Suzuki reaction, compounds of formula (**0074b**) are then reacted with a boronate or boronic acid to give compounds of formula (**0075b**) after standard isolation procedures.

Example 8

2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-4-trifluoromethyl-1H-imidazole

Example 8a

Preparation of 2-(2-Chloro-phenyl)-4-trifluoromethyl-1H-imidazole

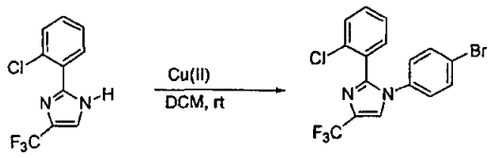


3,3-Dibromo-1,1,1-trifluoroacetone (6.75 g, 25 mmol) was added to a solution of NaOAc (4.11 g, 50 mmol) in 15 mL water, and the mixture was heated at 100°C for 60 min. After cooling to room temperature, 2-chlorobenzaldehyde (2.8 g, 20 mmol) dissolved in MeOH (45 mL) was added, followed by conc. NH_4OH (10 mL). The mixture was stirred at room temperature overnight. After methanol was removed by evaporation, water was added. The precipitate was collected by filtration and washed with

water, and dried under vacuum to give a light yellow solid (4.7 g, 76%). ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.37 (dd, 1H), 7.40 (dd, 1H), 7.46 (dd, 1H), 7.50 (m, 1H), 8.33 (dd, 1H).

Example 8b

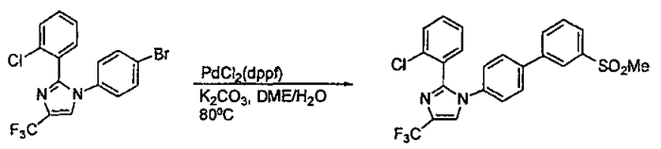
Preparation of 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-4-trifluoromethyl-1H-imidazole



2-(2-Chloro-phenyl)-4-trifluoromethyl-1*H*-imidazole (370 mg, 1.5 mmol), 4-bromo-phenylboronic acid (600 mg, 3 mmol), and $[Cu(OH)\cdot TMEDA]_2Cl_2$ (140 mg, 0.3 mmol) were mixed with 6 mL dry dichloromethane, and stirred at room temperature under atmosphere of dioxygen for 2 days. The reaction mixture was diluted with dichloromethane and filtered through celite. The filtrate was concentrated under vacuum, and the residue was purified by chromatography on silica gel (Hexane/EtOAc 8/2) to give a solid (151 mg, 25% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.02 (d, 2H), 7.34 (m, 3H), 7.47 (d, 2H), 7,53 (dd, 1H), 7.56 (dd, 1H).

Example 8c

Preparation of 2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-4-trifluoromethyl-1H-imidazole



1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-4-trifluoromethyl-1*H*-imidazole (100 mg, 0.25 mmol), (3-methylsulfonyl)phenylboronic acid (100 mg, 0.5 mmol), potassium carbonate (155 mg, 1.13 mmol), and $PdCl_2(dppf).CH_2Cl_2$ (20 mg, 0.025 mmol) were mixed with 3 mL 9:1 DME/H_2O (v/v), then heated at 80^{0}C overnight. All solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (Hexane/EtOAc, 6/4), then by reverse phase HPLC (30% acetonitrile in water) to give a white solid (55 mg, 46% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 3.10 (s, 3H), 7.26 (m, 2H), 7.37 (m, 3H), 7.62 (m, 5H), 7.84 (m, 1H), 7.94 (m, 1H), 8.12 (t, 1H).

In similar manner, all the following compounds were prepared using appropriate aldehydes and boronic acid reagents.

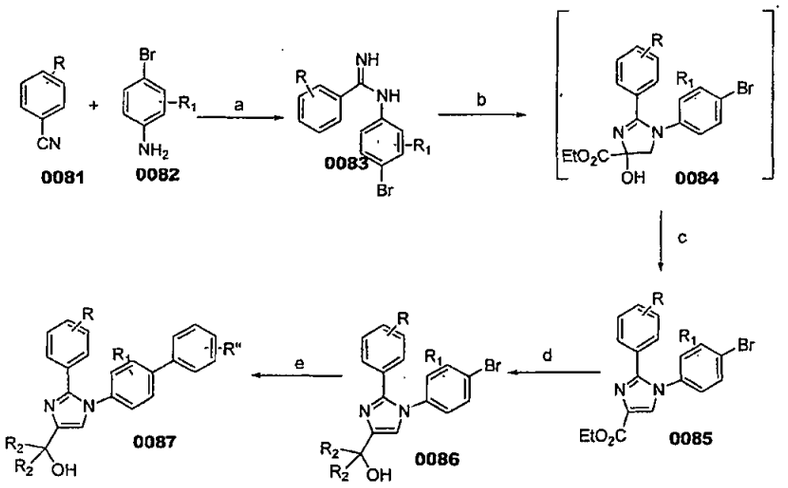
- 2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-4-(trifluoromethyl)-1H-imidazole; MS(ES): 477.0 $[M+H]^+$;

- 4'-[2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]biphenyl-3-sulfonamide; MS(ES): 478.0 $[M+H]^+$;
- 1-(4-bromophenyl)-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole; MS(ES): 435.0 $[M+H]^+$;
- 1-[3'-(methylsulfonyl)biphenyl-4-yl]-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole; MS(ES): 511.3 $[M+H]^+$;
- 4'-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide; MS(ES): 512.3 $[M+H]^+$;

The following compouds were prepared in similar manner as described in Scheme 7, except Cu (II) catalyzed coupling reaction to make compouds of formula (**0074b**) was replaced by base, like sodium hydride, catalyzed replacement reaction with aryl bromids bearing appropriate leaving groups, such as 2,5-dibromopyridine.

- 5-[3-(methylsulfonyl)phenyl]-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine; MS(ES): 512.3 $[M+H]^+$;
- 2-[2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]-5-[3-(methylsulfonyl)phenyl]pyridine; MS(ES): 478.0 $[M+H]^+$;

Scheme 8



(a) Method A: Me_3Al, Toluene, 0°C- 80°C; Method B: NaHMDS, THF; 0°C- rt; (b) Ethyl bromopyruvate, $NaHCO_3$, 2-PrOH, 80°C; (c) $NaHCO_3$ / 2-PrOH or HOAc /2-PrOH, reflux; (d) R_2MgBr, THF, 0°C- rt; (e) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

In general, compounds of formula (**0087**) are prepared by first reacting aniline of formula (**0082**) with aryl nitriles (**0081**), in the presence of either Lewis Acid (Method A) or base (Method B), to

give compounds of formula (**0083**) after standard isolation procedures. In a subsequent step, exposure of amidine (**0083**) to haloester, such as Ethyl α-bromopyruvate, under basic condition at elevated temperature provides intermediate 1*H*-imidazol-4-ol of formula (**0084**), which can be converted to compounds of formula (**0085**) *in situ*, or by means of acid catalyzed dehydration. Compounds of formula (**0085**) are then subjected to functionality transformation, such as from ester to carbinol. In a palladium mediated coupling reaction, for example Suzuki reactions, compounds of formula (**0086**) are then reacted with a diboronate or boronic acid reagent to give compounds of formula (**0087**) after standard isolation procedures.

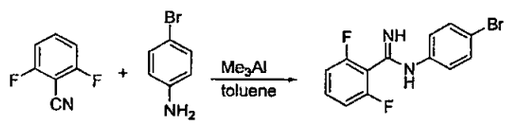
Example 9

2-[2-(2,6-Difluoro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol

Example 9a

(Method A)

Preparation of N-(4-bromophenyl)-2,6-difluorobenzimidamide

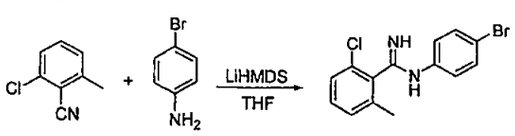


N-(4-Bromo-phenyl)-2,6-difluoro-benzamidine: 4-bromoaniline (1.72 g, 10 mmol) was placed into a three-neck reactor, and the reactor was flushed with argon for 20min. 50 mL anhydrous toluene was added. After cooling to 0^0C, trimethylaluminum (7.5 mL, 2.0M solution in toluene, 15 mmol) was added slowly to keep the inner temperature below 18 ^{0}C. After addition, the reaction mixture was warmed to room temperature and then stirred for additional 2 hrs. A solution of 2, 6-difluorobenzonitirle (2.78 g, 20 mmol) in 50 mL anhydrous toluene was added, and the reaction mixture was heated to 80 ^{0}C. After 18 hrs, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in $CHCl_3$/MeOH (4/1, V/V). After being stirring for 20 min, the mixture was filtered and the residue was washed with a mixture of $CHCl_3$/MeOH (4/1, V/V). The combined filtrates were concentrated *in vacuo*, and the resulting solid was stirred with a solution of Hexane/Ether (3/1, V/V). The intermediate was filtered and washed with additional Hexane/Ether (3/1, V/V) to give a white solid (2.4 g, 79% yield), which was used directly for the next step without further purification.

Example 9aa

(Method B)

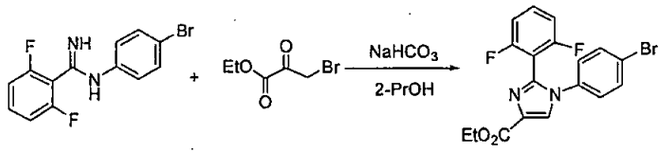
Preparation of N-(4-bromophenyl)-2-chloro-6-methylbenzimidamide



N-(4-Bromo-phenyl)-2-chloro-6-methyl-benzamidine: Under N_2 atmosphere at room temperature to a solution of lithium bis(trimethylsilyl)amide (9.7 mL, 1.0 M solution in THF, 9.7 mmol) was added a solution of 4-bromoaniline (1.67 g, 9.7 mmol) in 10 mL anhydrous THF. After the mixture was stirred at ambient temperature for 40 min, a solution of 2-chloro-6-methylbezonitrile (1.55 mg, 10.2 mmol) in 10 mL anhydrous THF was added. The reaction mixture was stirred at room temperature overnight, and then poured into 300 mL ice water. The orange precipitate was collected by filtration, washed with hexane and air dried to give a light orange solid (2.19 g, 66% yield), which was used directly for the next step without further purification.

Example 9b

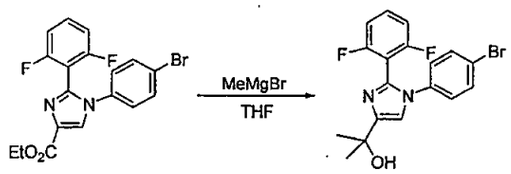
Preparation of ethyl 1-(4-bromophenyl)-2-(2,6-difluorophenyl)-1H-imidazole-4-carboxylate



To a mixture of N-(4-Bromo-phenyl)-2,6-difluorobenzamidine (2.4 g, 7.7 mmol) and sodium bicarbonate (1.3 g, 15.4 mmol) in 40 mL 2-proponal was added ethyl α-bromopyruvate (3.34 g, 15.4 mmol, 90% tech). The mixture was heated at 80 – 85 ^{0}C overnight. After cooling to room temperature, the solvent was removed and the residue was redissolved into dichloromethane. The precipitate was filtered out, and the filtrate was concentrated down. The crude product was purified by column chromatography on silica gel (30 → 50% EtOAc/Hexane) to give a yellow solid (1.82 g, 58% yield).

Example 9c

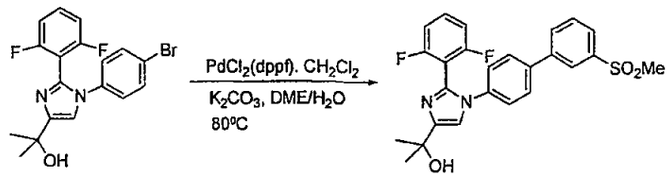
Preparation of 2-(1-(4-bromophenyl)-2-(2,6-difluorophenyl)-1H-imidazol-4-yl)propan-2-ol



Methylmagnesium bromide (11.2 ml, 15.7 mmol, 1.4M in toluene/THF 75:25) was placed into a three-neck flask. Under nitrogen at 0 ^{0}C to it was added a solution of 1-(4-Bromo-phenyl)-2-(2,6-difluoro-phenyl)-1*H*-imidazole-4-carboxylic acid ethyl ester in 15 mL THF. After the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 2.5 hrs. The reaction was quenched with sat. Ammonium chloride. Two layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (30 → 50% EtOAc/Hexane) to give an off-white solid (0.9 g, 51% yield).

Example 9d

Preparation of 2-(2-(2,6-difluorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol



2-[1-(4-Bromo-phenyl)-2-(2,6-difluoro-phenyl)-1H-imidazol-4-yl]-propan-2-ol (250 mg, 0.64 mmol), (3-methylsulfonylphenyl)boronic acid (254 mg, 1.27 mmol), and potassium carbonate (398 mg, 2.88 mmol) were placed into a flask. 6 mL of mixture of DME (1,2-dimethoxyethane) and water (9:1, V/V) was added. The flask was flushed with argon for 15 min, and then Pd catalyst (Dichloro[1,1'-bis (diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, 52 mg, 0.064 mmol) was added. The mixture was heated to 80 ^{0}C overnight. After cooloing to room temperature, all solvent was removed. The crude product was purified by column chromatography on silica gel (45 → 99% EtOAc/Hexane) to give an off-white solid (230 mg, 77% yield). 1H-NMR (400MHz, $CDCl_3$): δ 1.70 (s, 6H), 2.71 (s, 1H), 3.09 (s, 3H), 6.92 – 6.88 (m, 2H), 7.21 (s, 1H), 7.39 – 7.28 (m, 3H), 7.59 – 7.57 (m, 2H), 7.66 (t, 1H, *J*=7.8), 7.86 – 7.83 (M, 1H), 7.95 - 7.92 (m, 1H), 8.12 (t, 1H, *J*=1.7). MS (ES): 491.4 $[M+Na]^+$

In similar manner, all the following compounds were made using either Method A (Example 9a) or Method B (Example 9aa) to prepare amidines. The order of last two steps of Grignard addition and Suzuki coupling were switched in some cases. The boronic acid or boronate reagents for Suzuki coupling, if not commercially available, were made using standard techniques that are readily apparent to one skilled in the art.

- ethyl 1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxylate; MS(ES): 515.3 $[M+H]^+$;
- 2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501.4 $[M+H]^+$, 523.3$[M+Na]^+$;
- 5-{3-[(1-methylethyl)sulfonyl]phenyl}-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine; MS(ES): 540.3 $[M+H]^+$;
- 1-{3'-[(1-methylethyl)sulfonyl]biphenyl-4-yl}-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole; MS(ES): 539.3 $[M+H]^+$;
- N-(4'-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-yl)methanesulfonamide; MS(ES): 526.5 $[M+H]^+$;

- ethyl 1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-phenyl-1H-imidazole-4-carboxylate; MS(ES): 447.3 $[M+H]^+$;
- 2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-phenyl-1H-imidazol-4-yl}propan-2-ol;
- 2-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 467.4 $[M+H]^+$;
- 2-{2-(2-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 451.1 $[M+H]^+$;
- 1-{2-(2-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone; MS(ES): 457.1 $[M+Na]^+$;
- 2-{2-(4-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 451.3 $[M+H]^+$;
- 2-{2-(2-chloro-6-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 481.1 $[M+H]^+$;
- 2-{1-[4'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501.5 $[M+H]^+$;
- 2-{1-[3'-(ethylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 515.5 $[M+H]^+$;
- 2-{1-[3'-(methylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501.4 $[M+H]^+$;
- 2-{1-[4'-(methylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501.4 $[M+H]^+$;
- 2-{2-(2,6-difluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 491.4 $[M+Na]^+$;
- 2-(1-{3'-[(1-methylethyl)sulfonyl]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS(ES): 529.3 $[M+H]^+$;
- 2-(1-{3'-[(1-methylethyl)sulfonyl]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS(ES): 529.3 $[M+H]^+$;
- 2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 481.3 $[M+H]^+$;
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 485.3 $[M+H]^+$;
- 2-{2-(2,6-difluorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 483.4 $[M+H]^+$;

- 2-(1-{5-[3-(methylsulfonyl)phenyl]pyridin-2-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS(ES): 502.5 $[M+H]^+$;
- 2-(1-{6-[3-(methylsulfonyl)phenyl]pyridin-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS(ES): 502.3 $[M+H]^+$;
- 2-{2-(2,6-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 523.3 $[M+Na]^+$;
- 2-{2-[2-fluoro-6-(trifluoromethyl)phenyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 541.3 $[M+Na]^+$;
- 2-{2-(2-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 447.0 $[M+H]^+$;
- 2-(1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-{2-[(trifluoromethyl)oxy]phenyl}-1H-imidazol-4-yl)propan-2-ol; MS(ES): 517.3 $[M+H]^+$, 539.3 $[M+Na]^+$;
- 2-{2-[2-(dimethylamino)-6-fluorophenyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 516.3 $[M+Na]^+$;
- 2-{2-(2,6-dichlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 515.2 $[M+H]^+$;
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 499.5 $[M+H]^+$, 521.3 $[M+Na]^+$;
- 2-{2-(2,6-dichlorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 531.1, 533.3 $[M+H]^+$;
- 2-{2-(2-chloro-6-fluorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 515.7, 517.3 $[M+H]^+$;
- 2-(2-(3-chloro-3'-(methylsulfonyl)biphenyl-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 621.5 $[M+H]^+$
- 2-{2-(2,3-dichlorophenyl)-1-[3'-(hydroxymethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$.
- 2-{2-(2,3-dichlorophenyl)-1-[4'-(hydroxymethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$.
- 2-{1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-2-(3-thienyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 535 $[M+H]^+$.

- 2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 537 $[M+H]^+$.
- 2-{1-[3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl]-2-isoquinolin-5-yl-1H-imidazol-4-yl}propan-2-ol; MS (ES): 512 $[M+H]^+$.
- 2-{2-isoquinolin-5-yl-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 498 $[M+H]^+$.
- 2-{2-(1,5-dimethyl-1H-pyrrol-2-yl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 464 $[M+H]^+$.
- 2-{1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2-thienyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-isoquinolin-1-yl-1H-imidazol-4-yl}propan-2-ol; MS (ES): 529 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-isoquinolin-1-yl-1H-imidazol-4-yl}propan-2-ol; MS (ES): 518 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 513 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 499 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 495 $[M+H]^+$.
- 2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 501 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-naphthalen-1-yl-1H-imidazol-4-yl}propan-2-ol; MS (ES): 531 $[M+H]^+$.
- 2-{1-[3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 529 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-(3-chloro-2-methylphenyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 529 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$.

- 2-{1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-naphthalen-1-yl-1H-imidazol-4-yl}propan-2-ol; MS (ES): 517 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-(2-chlorophenyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 549 $[M+H]^+$.
- 2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 535 $[M+H]^+$.
- 2-{1-[3'-(ethylsulfonyl)-2-fluorobiphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 533 $[M+H]^+$.
- 2-{1-[2-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 519 $[M+H]^+$.
- 2-{1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 533 $[M+H]^+$.
- 2-{1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 519 $[M+H]^+$.
- 2-(2-(2-chloro-6-methylphenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 499.3 $[M+H]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 513.3 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 515.3, 517.3 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 529.3, 531.3 $[M+H]^+$
- 2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 549.3, 551.3, 553.3 $[M+H]^+$
- 2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 565.0, 567.0, 569.2 $[M+H]^+$
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 515.2, 517.3 $[M+H]^+$

- 2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 545.3, 547.3 $[M+H]^+$
- 2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 529.2, 531.2 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 549.3, 551.3 $[M+H]^+$, 571.2, 573.2 $[M+Na]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 509.3, 511.3 $[M+H]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 495.4, 497.4 $[M+H]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 495.4 $[M+H]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 511.3 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 519.3, 521.3 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 529.3, 531.3 $[M+H]^+$, 551.3, 553.3 $[M+Na]^+$
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 535.3, 537.3, 539.3 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 537.0 $[M+Na]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 525.5 $[M+H]^+$, 547.3 $[M+Na]^+$
- 2-(2-(2-chloro-6-methylphenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 529.3, 531.3 $[M+H]^+$
- ethyl 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxylate; MS (ES): 549.0, 551.0, 553.0 $[M+H]^+$
- 2-{1-[2'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-(2',3'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 459 $[M+H]^+$;

- 2-(1-{4'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 481 $[M+H]^+$;
- 2-{1-(4'-fluoro-3'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 455 $[M+H]^+$;
- 2-{1-(3'-fluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 441 $[M+H]^+$;
- 2-{1-(2',4',5'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 477 $[M+H]^+$;
- 2-{1-[5'-fluoro-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 471 $[M+H]^+$;
- 2-{1-(4'-chlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 457 $[M+H]^+$;
- 2-{1-(4-pyrimidin-5-ylphenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 425 $[M+H]^+$;
- 2-{1-[4'-(hydroxymethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$;
- 2-{1-[4'-(dimethylamino)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 466 $[M+H]^+$;
- 2-{1-[4'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[4'-(1-methylethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 465 $[M+H]^+$;
- 2-{1-[4'-chloro-2'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525 $[M+H]^+$;
- 2-{1-(2',3',4'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 477 $[M+H]^+$;
- 2-{1-(3',4'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 459 $[M+H]^+$;
- 2-{1-(2'-chloro-6'-fluoro-3'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 489 $[M+H]^+$;
- 2-{1-[5'-chloro-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 487 $[M+H]^+$;

- 2-{1-[2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509 $[M+H]^+$;
- 2-{1-[2'-(methylthio)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 469 $[M+H]^+$;
- 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid; MS (ES): 467 $[M+H]^+$;
- 2-{1-[4-(1,3-benzodioxol-5-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 467 $[M+H]^+$;
- 2-(1-{4-[6-(methyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 454 $[M+H]^+$;
- 2-(1-{4-[(1E)-3,3-dimethylbut-1-en-1-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 429 $[M+H]^+$;
- 2-{1-(3'-chlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 457 $[M+H]^+$;
- 2-{1-[2'-fluoro-5'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 471 $[M+H]^+$;
- ethyl 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylate; MS (ES): 495 $[M+H]^+$;
- 2-{1-(4-{2-[(1-methylethyl)oxy]pyridin-3-yl}phenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 482 $[M+H]^+$;
- 2-{1-[3'-chloro-4'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 487 $[M+H]^+$;
- 2-{1-[2'-fluoro-3'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 471 $[M+H]^+$;
- 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 466 $[M+H]^+$;
- 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxamide; MS (ES): 466 $[M+H]^+$;
- 2-(1-{4'-[(trifluoromethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 507 $[M+H]^+$;
- 2-{1-[4'-fluoro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509 $[M+H]^+$;

- 2-{1-(4'-propylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 465 $[M+H]^+$;
- 2-{1-[4'-(ethyloxy)-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 535 $[M+H]^+$;
- 2-(1-{2'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 481 $[M+H]^+$;
- 2-(1-{3'-chloro-4'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 515 $[M+H]^+$;
- 2-{1-[4-(1H-indol-4-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 462 $[M+H]^+$;
- 2-{1-[4'-(methylthio)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 469 $[M+H]^+$;
- 2-{1-[3'-(hydroxymethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$;
- 2-{1-[3'-(ethyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 467 $[M+H]^+$;
- 2-{1-(4'-ethylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 451 $[M+H]^+$;
- 2-{1-(2',4'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 459 $[M+H]^+$;
- 2-{1-(3',4'-dichlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[2'-chloro-4'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525 $[M+H]^+$;
- 2-{1-(4-naphthalen-2-ylphenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 473 $[M+H]^+$;
- 2-{1-[3'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$;
- 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-ol; MS (ES): 439 $[M+H]^+$;
- 2-{1-(3',4',5'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 477 $[M+H]^+$;

- 1-[5-(4-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone; MS (ES): 471 $[M+H]^+$;
- 2-{1-(3',5'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 459 $[M+H]^+$;
- 2-{1-(3'-chloro-4'-fluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 475 $[M+H]^+$;
- 2-{1-[5'-methyl-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 467 $[M+H]^+$;
- 2-{1-(2',5'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 459 $[M+H]^+$;
- 2-{1-[3'-(butyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 495 $[M+H]^+$;
- 2-{1-[5'-chloro-2'-(ethyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 501 $[M+H]^+$;
- 2-(1-{3'-[(trifluoromethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 507 $[M+H]^+$;
- 2-{1-(2',3',5'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 477 $[M+H]^+$;
- 2-{1-[3'-(ethylthio)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 483 $[M+H]^+$;
- 2-(1-{3'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 481 $[M+H]^+$;
- 2-{1-[4-(1-benzothien-3-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 479 $[M+H]^+$;
- 2-{1-[4-(4-methylnaphthalen-1-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 487 $[M+H]^+$;
- 2-{1-(2',4'-dichlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[3',4'-bis(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 483 $[M+H]^+$;
- 2-{2-[2-(trifluoromethyl)phenyl]-1-(2',4',5'-trimethylbiphenyl-4-yl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 465 $[M+H]^+$;

- 4-fluoro-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-2-ol; MS (ES): 457 $[M+H]^+$;
- 2-{1-[2'-(hydroxymethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$;
- 2-{1-[3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-(2'-chloro-6'-fluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 475 $[M+H]^+$;
- 2-{1-[3',5'-difluoro-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 489 $[M+H]^+$;
- 2-(1-{4-[2-(methyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 454 $[M+H]^+$;
- 2-{1-[2'-methyl-5'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 467 $[M+H]^+$;
- 2-{1-(2'-ethylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 451 $[M+H]^+$;
- 2-(1-{2'-methyl-4'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 495 $[M+H]^+$;
- 2-{1-[4'-(ethylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$;
- 2-{1-(5'-fluoro-2'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 455 $[M+H]^+$;
- 2-{1-[3'-chloro-4'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525 $[M+H]^+$;
- 2-{1-(2',5'-dimethylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 451 $[M+H]^+$;
- 2-{1-[2'-(ethyloxy)-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 535 $[M+H]^+$;
- 2-{1-(3'-fluoro-4'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 455 $[M+H]^+$;
- methyl (2E)-3-(4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-yl)prop-2-enoate; MS (ES): 507 $[M+H]^+$;

- N-ethyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 494 $[M+H]^+$;
- 2-{1-[4-(2,3-dihydro-1-benzofuran-5-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 465 $[M+H]^+$;
- N-butyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide; MS (ES): 558 $[M+H]^+$;
- N-(1,1-dimethylethyl)-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-6-methylbiphenyl-3-sulfonamide; MS (ES): 572 $[M+H]^+$;
- 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-methylbiphenyl-3-sulfonamide; MS (ES): 516 $[M+H]^+$;
- N-ethyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide; MS (ES): 530 $[M+H]^+$;
- N-(1,1-dimethylethyl)-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide; MS (ES): 558 $[M+H]^+$;
- 2-{1-[2'-amino-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 506 $[M+H]^+$;
- 2-{1-[3'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509 $[M+H]^+$;
- 2-{1-[4'-chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525 $[M+H]^+$;
- 3-chloro-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid; MS (ES): 501 $[M+H]^+$;
- 2-(2-[2-(trifluoromethyl)phenyl]-1-{3'-[(trifluoromethyl)thio]biphenyl-4-yl}-1H-imidazol-4-yl)propan-2-ol; MS (ES): 523 $[M+H]^+$;
- 2-{1-[3'-(morpholin-4-ylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 572 $[M+H]^+$;
- 2-(1-{4-[5-(hydroxymethyl)-1,3-thiazol-2-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 460 $[M+H]^+$;
- 2-{1-[2'-methyl-5'-(piperidin-1-ylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 584 $[M+H]^+$;
- 1-[4-(4-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone; MS (ES): 471 $[M+H]^+$;

- 2-(1-{4-[5-(hydroxymethyl)-3-thienyl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 459 $[M+H]^+$;
- 2-chloro-4'-[2-(2,6-dichlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3'-methylbiphenyl-4-carboxylic acid; MS (ES): 515 $[M+H]^+$;
- 2-(1-{3-[6-(methyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 454 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-3-sulfonamide; MS (ES): 544 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxamide; MS (ES): 466 $[M+H]^+$;
- 2-(1-{3-[2-(cyclopentyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 508 $[M+H]^+$;
- 2-{1-(3'-chlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 457 $[M+H]^+$;
- 2-{1-[2'-fluoro-5'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 471 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 466 $[M+H]^+$;
- 2-{1-[3',4'-bis(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 483 $[M+H]^+$;
- N-(3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-2-yl)methanesulfonamide; MS (ES): 516 $[M+H]^+$;
- 2-{1-[3'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 3-fluoro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid; MS (ES): 485 $[M+H]^+$;
- 4-chloro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 500 $[M+H]^+$;
- 2-{1-(3-{2-[(1-methylethyl)oxy]pyridin-3-yl}phenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 482 $[M+H]^+$;
- N-(3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-yl)acetamide; MS (ES): 480 $[M+H]^+$;

- 2-{1-[2'-methyl-5'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 467 $[M+H]^+$;
- N-(3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-yl)acetamide; MS (ES): 480 $[M+H]^+$;
- 2-{1-(4'-chlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 457 $[M+H]^+$;
- 2-{1-[4'-(phenyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$;
- 2-{1-[5'-fluoro-2'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 471 $[M+H]^+$;
- 2-{1-(2',3'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-(1-{3'-[(trifluoromethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 507 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide; MS (ES): 502 $[M+H]^+$;
- 2-{1-[3',5'-bis(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 559 $[M+H]^+$;
- 2-{1-(3',5'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 3-chloro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-4-carboxamide; MS (ES): 542 $[M+H]^+$;
- N,N-diethyl-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 522 $[M+H]^+$;
- 4-chloro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-3-carboxamide; MS (ES): 542 $[M+H]^+$;
- 2-{1-[3'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxylic acid; MS (ES): 467 $[M+H]^+$;
- N-ethyl-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 494 $[M+H]^+$;

- 4-chloro-N-ethyl-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide; MS (ES): 528 $[M+H]^+$;
- 2-{1-(2',5'-difluorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 459 $[M+H]^+$;
- 2-(1-{3'-[(1-methylethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 481 $[M+H]^+$;
- 2-{1-[2'-fluoro-5'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509 $[M+H]^+$;
- 2-{1-(3',4'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[3'-(ethyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 467 $[M+H]^+$;
- 2-(1-{2'-methyl-4'-[(1-methylethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 495 $[M+H]^+$;
- 2-{1-[3-(1-methyl-1H-indol-5-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 476 $[M+H]^+$;
- 2-{1-[4'-(ethyloxy)-3'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 535 $[M+H]^+$;
- 2-{1-[3'-(ethylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$;
- 2-{1-[2'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[3'-(hydroxymethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 453 $[M+H]^+$;
- 2-{1-[3-(1H-indol-4-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 462 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid; MS (ES): 467 $[M+H]^+$;
- 1-[5-(3-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone; MS (ES): 471 $[M+H]^+$;
- 2-{1-(5'-chloro-2'-methylbiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 471 $[M+H]^+$;

- 2-(1-{4'-[(trifluoromethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol; MS (ES): 507 $[M+H]^+$;
- 2-{1-[2'-chloro-4'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525 $[M+H]^+$;
- 2-{1-(2',5'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[2'-(ethyloxy)-5'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 535 $[M+H]^+$;
- 3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-4-carboxamide; MS (ES): 508 $[M+H]^+$;
- 2-{1-(2',4'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 491 $[M+H]^+$;
- 2-{1-[4'-(ethylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515 $[M+H]^+$;
- 2-{1-[4'-fluoro-3'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509 $[M+H]^+$;
- 2-{1-(3'-fluoro-4'-methylbiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 455 $[M+H]^+$;
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 539(M+Na);
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 533$[M+H]^+$
- 2-{2-(2,6-difluorophenyl)-1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 487 $[M+H]^+$
- 2-{2-(2,6-difluorophenyl)-1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 501 $[M+H]^+$
- 2-{2-(2,6-difluorophenyl)-1-[3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 517$[M+H]^+$
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 503 $[M+H]^+$
- 2-{2-(2,6-difluorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 499$[M+H]^+$

- 2-{2-(2-chloro-6-fluorophenyl)-1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 519[M+H]$^+$
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl}propan-2-ol MS (ES): 533[M+H]$^+$
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl}propan-2-ol MS (ES): 533[M+H]$^+$
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 549[M+H]$^+$
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 499[M+H]$^+$
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 513[M+H]$^+$
- 2-{2-(2-chloro-6-fluorophenyl)-1-[4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 529[M+H]$^+$
- 2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[4-(trifluoromethyl)pyridin-3-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 502[M+H]$^+$
- 2-{1-[3'-(ethylsulfonyl)biphenyl-4-yl]-2-[4-(trifluoromethyl)pyridin-3-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 516[M+H]$^+$
- 2-{1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[4-(trifluoromethyl)pyridin-3-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 532[M+H]$^+$
- 2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-(2-morpholin-4-ylethyl)-1H-imidazol-4-yl}propan-2-ol MS (ES): 470[M+H]$^+$
- 2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2,6-difluorophenyl)-1H-imidazol-4-yl}propan-2-ol MS (ES): 503[M+H]$^+$
- 2-{1-[3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl]-2-(2,6-difluorophenyl)-1H-imidazol-4-yl}propan-2-ol MS (ES): 517[M+H]$^+$
- 2-{1-[3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2,6-difluorophenyl)-1H-imidazol-4-yl}propan-2-ol MS (ES): 533[M+H]$^+$
- 2-{2-(2,6-difluorophenyl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 483[M+H]$^+$
- 2-{2-(2,6-difluorophenyl)-1-[3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 497[M+H]$^+$

- 2-{2-(2,6-difluorophenyl)-1-[4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol MS (ES): 513[M+H]$^+$
- 2-{2-(2,3-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501, 503 [M+H]$^+$
- 2-{2-(2-chloro-3-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 485 [M+H]$^+$
- 2-{2-(2-chlorophenyl)-1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 485 [M+H]$^+$
- 2-{2-(2-chlorophenyl)-1-[2-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;MS(ES): 485 [M+H]$^+$
- 2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[3-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501 [M+H]$^+$
- 2-{2-(3-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 467 [M+H]$^+$
- 2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2-chlorophenyl)-1H-imidazol-4-yl}propan-2-ol; MS(ES): 501, 503 [M+H]$^+$
- 2-{2-(2-chlorophenyl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 481 [M+H]$^+$
- 2-{2-(2,3-dichlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 515, 517 [M+H]$^+$
- 2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 499 [M+H]$^+$
- 2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)-2-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 499 [M+H]$^+$
- 2-{2-(3-chloro-2-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 481 [M+H]$^+$
- 2-{2-(2-chlorophenyl)-1-[2-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 481 [M+H]$^+$
- 2-{2-(3-chloro-2-methylphenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 495 [M+H]$^+$
- 2-(2-(2-chlorophenyl)-1-(3-ethyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 495 [M+H]$^+$

- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 535, 537 $[M+H]^+$
- 2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 549, 551 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 529, 531 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 519, 521 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 533, 535 $[M+H]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 499 $[M+H]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 513 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 531, 533 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 549, 551 $[M+H]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 529 $[M+H]^+$
- 2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 565, 567 $[M+H]^+$
- 2-(2-(2,3-dichlorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 545, 547 $[M+H]^+$
- 2-(1-(3-chloro-5-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 537, 539 $[M+Na]^+$
- 2-(1-(3-chloro-3'-(ethylsulfonyl)-5-methylbiphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 551, 553 $[M+Na]^+$
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-3-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 541, 543 $[M+Na]^+$

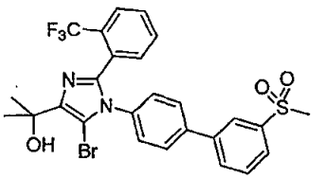
- 2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-chloro-3-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 555, 557 $[M+Na]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 525 $[M+Na]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 517 $[M+H]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; S(ES): 555 $[M+Na]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 571, 573 $[M+Na]^+$
- 2-(2-(2-chloro-3-fluorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 499 $[M+H]^+$

In a similar manner, the following compounds were prepared by replacing methylmagnesium bromide with ethylmagnesium bromide:

- 3-(2-(2,3-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol; MS(ES): 529, 531 $[M+H]^+$;
- 3-(2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;MS(ES): 543, 545 $[M+H]^+$;
- 3-{2-(2,6-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}pentan-3-ol; 529.3,$[M+H]^+$.

In a similar manner, the following compound was prepared by replacing ethyl bromopyruvate with ethyl 3-bromo-2-ketobutyrate: 2-{5-methyl-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;MS(ES): 515 $[M+H]^+$

Example 10



Preparation of 2-[5-bromo-1-(3'-methanesulfonyl-biphenyl-4-yl)-2-(2-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-propan-2-ol

To a solution of 2-[1-(3'-methanesulfonyl-biphenyl-4-yl)-2-(2-trifluoromethyl-phenyl)-1*H*-imidazol-4-yl]-propan-2-ol (100 mg, 0.20 mmol) in MeCN (2 mL, anhyd) was added N-bromosuccinimide (45 mg, 0.25 mmol). After 2h, the reaction mixture was diluted with EtOAc,

washed with saturated $NaHCO_3$, water (3x 10 mL) and brine, then dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (silica), eluting with EtOAc/hexanes (65:40 to 95:5) to yield the title compound (100 g, 86%) as a white solid. ^{1}H-NMR (CD_2Cl_2): δ 8.10 (1H, m), 7.92 (1H, m), 7.86 (1H, m), 7.60-7.74 (4H, m), 7.47 (2H, m), 7.25-7.31 (3H, m), 3.56 (1H, s), 3.06 (3H, s), 1.66 (6H, s); MS (ES): 579, 581 $[M+H]^+$.

In a similar manner, the following compound was prepared by replacing N-bromosuccinimide with N-chlorosuccinimide: 2-{5-chloro-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS(ES): 535 $[M+H]^+$

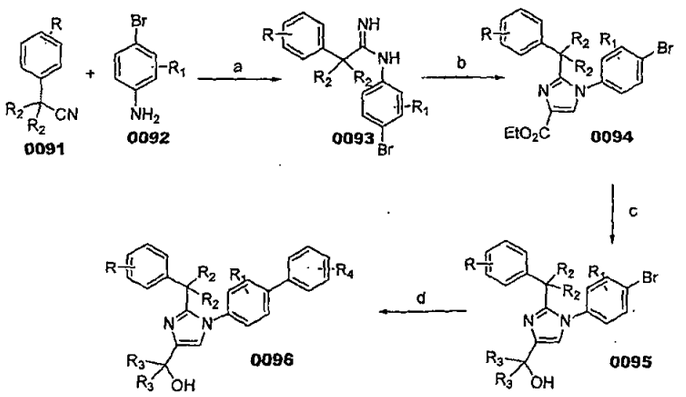
In a similar manner, the following compound was prepared by treating the appropriate imidazole-4-carboxylic acid ethyl ester intermediate with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™) followed by the previously described sequence of Suzuki cross-coupling and reaction with Grignard reagent: 2-{5-fluoro-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;MS(ES): 519 $[M+H]^+$

The following compounds were made in a similar manner, except boronic acid or boronate reagents for Suzuki coupling were prepared as described in Examples 23-29.

- 6-{3-Chloro-4-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methyl-ethyl)-imidazol-1-yl]-phenyl}-1,1-dioxo-2,3-dihydro-1H-1λ*6*-benzo[b]thiophen-3-ol; MS (ES): 547 $[M+H]^+$.
- 2-{2-(2,3-dichlorophenyl)-1-[4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 531, 533 each $[M+H]^+$.
- 2-{2-(2-chloro-6-fluorophenyl)-1-[3-chloro-4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 549, 551 each $[M+H]^+$.
- ethyl 3'-chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-carboxylate; MS (ES): 591, 593 each $[M+H]^+$.
- 2-{2-(2,3-dichlorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 531, 533 each $[M+H]^+$.
- 2-{4'-[2-(2,3-dichlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-yl}propan-2-ol; MS (ES): 559 $[M+H]^+$.
- 2-{3'-chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-yl}propan-2-ol; MS (ES): 577 $[M+H]^+$.
- 2-{1-[3-chloro-4'-(1-hydroxy-1-methylethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 593$[M+H]^+$.

- 2-{3'-chloro-4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-yl}propan-2-ol; MS (ES): 559 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 511 $[M+H]^+$.
- 2-{1-[3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-(3-chloro-2-methylphenyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 545 $[M+H]^+$.
- 2-{1-[3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 549 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 529 $[M+H]^+$.
- 2-{2-(3-chloro-2-methylphenyl)-1-[4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525 $[M+H]^+$.
- 2-{1-[3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-naphthalen-1-yl-1H-imidazol-4-yl}propan-2-ol; MS (ES): 547 $[M+H]^+$.
- 2-{1-[4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 545 $[M+H]^+$.
- 2-{1-[3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 565 $[M+H]^+$.
- 2-{1-[3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2-chlorophenyl)-1H-imidazol-4-yl}propan-2-ol; MS (ES): 531 $[M+H]^+$.
- ethyl 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-5-(methylsulfonyl)biphenyl-3-carboxylate; MS (ES): 573 $[M+H]^+$.
- 2-{1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 531 $[M+H]^+$.
- 2-{1-[4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl[-1H-imidazol-4-yl}propan-2-ol; MS (ES): 531 $[M+H]^+$
- 2-(2-(2,6-dichlorophenyl)-1-(3'-methyl-5'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$
- 2-(1-(2'-chloro-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 535, 537 $[M+H]^+$
- 2-(1-(2',3-dichloro-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 591, 593, 595 $[M+Na]^+$.

Scheme 9



(a) Me_3Al, Toluene, 0°C- 80°C; (b) Ethyl bromopyruvate, $NaHCO_3$, EtOH, 80°C; (c) R_3MgBr, THF, 0°C- rt; (d) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

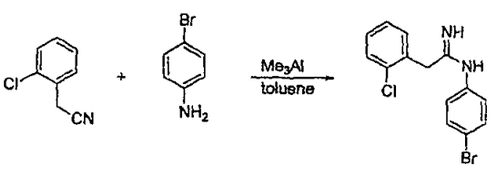
In general, compounds of formula (**0096**) are prepared by first reacting aniline of formula (**0092**) with benzyl cyanide (**0091**), such as 2, 3-dichlorobenzyl cyanide, in the presence of base to give compounds of formula (**0093**) after standard isolation procedures. In a subsequent step, exposure of amidine (**0093**) to haloester, such as ethyl α-bromopyruvate, under basic condition at elevated temperature provides 1*H*-imidazole of formula (**0094**) after standard isolation procedures. Compounds of formula (**0094**) are then subjected to functionality transformation, such as from ester to carbinol. In a palladium mediated coupling reaction, for example Suzuki reactions, compounds of formula (**0095**) are then reacted with a diboronate or boronic acid reagent to give compounds of formula (**0096**) after standard isolation procedures.

Example 11

2-{2-[(2-fluorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol

Example 11a

Preparation of N-(4-bromophenyl)-2-(2-chlorophenyl)acetimidamide

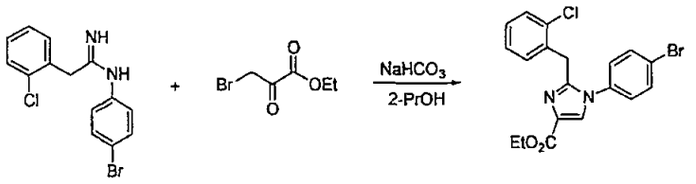


4-Bromoaniline (6.4 g, 37 mmol) was placed into a three-neck reactor, and the reactor was flushed with argon for 20min. 60 mL anhydrous toluene was added. After cooling to 0^0C, trimethylaluminum (28 mL, 2.0M solution in toluene, 56 mmol) was added slowly to keep the inner temperature below 20 ^{0}C. Over 0.5 h, the addition was completed. Ice bath was removed, and the reaction mixture was warmed to room temperature and then stirred for additional 2.5 hrs. A solution of

2-chlorobenzyl cyanide (8.4 g, 55 mmol) in 35 mL anhydrous toluene was added, and the reaction mixture was heated to 80 ^{0}C. After 18 hrs, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in $CHCl_3$/MeOH (4/1, 400 mL). After stirring for 30 min, the mixture was filtered and the residue was washed with a mixture of $CHCl_3$/MeOH (4/1). The combined filtrates were concentrated *in vacuo*, and the resulting solid was washed with hexane to give a light pink solid (5.78 g, 48% yield).

Example 11b

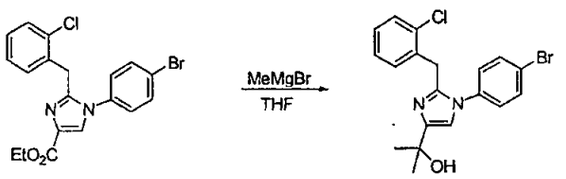
Preparation of ethyl 1-(4-bromophenyl)-2-(2-chlorobenzyl)-1H-imidazole-4-carboxylate



To a mixture of N-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-acetamidine (5.78 g, 17.9 mmol, from above reaction) and sodium bicarbonate (3.0 g, 36 mmol) in 50 mL 2-proponal was added ethyl α-bromopyruvate (7.8 g, 36 mmol, 90% tech.). The mixture was heated to 80 ^{0}C overnight, and then cooled to room temperature. The supernatant was decanted and concentrated *in vacuo*. The residue was redissolved into dichloromethan, and then filtered. The precipitate was washed several times with dichloromethane. The combined filtrates were concentrated down. The crude product was purified by column chromatography on silica gel (30 → 50% EtOAc/Hexane) to give a brown solid (1.75 g, 23% yield).

Example 11c

Preparation of 2-(1-(4-bromophenyl)-2-(2-chlorobenzyl)-1H-imidazol-4-yl)propan-2-ol

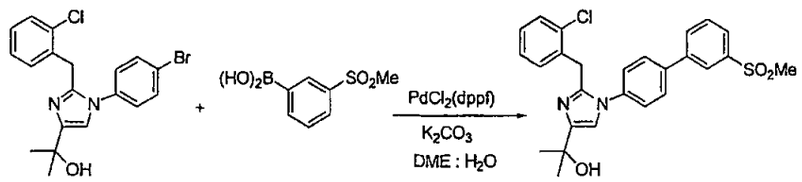


Methylmagnesium bromide (13 ml, 18.6 mmol, 1.4M in toluene/THF 75:25) was placed into a three-neck flask. Under nitrogen at 0 ^{0}C to it was added a solution of 1-(4-Bromo-phenyl)-2-(2-chloro-benzyl)-1*H*-imidazole-4-carboxylic acid ethyl ester (1.74 g, 4.1 mmol) in 15 mL THF. After the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 hrs. The reaction was quenched with sat. Ammonium chloride. Two layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with

brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (30 →50% EtOAc/Hexane) to give a yellow solid (600 mg, 36% yield).

Example 11d

Preparation of 2-(2-(2-chlorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol



2-[1-(4-Bromo-phenyl)-2-(2-chloro-benzyl)-1*H*-imidazol-4-yl]-propan-2-ol (202 mg, 0.5 mmol), (3-methylsulfonyl)phenylboronic acid (200 mg, 1.0 mmol), potassium carbonate (311 mg, 2.3 mmol), and $PdCl_2(dppf).CH_2Cl_2$ (42 mg, 0.05 mmol) were mixed with 5 mL 9:1 DME/H_2O (v/v), then heated at 80^{0}C overnight. All solvent was removed *in vacuo*. The crude product was purified by chromatography on silica gel (50 → 95 % EtOAc/Hexane) to give a white solid (158 mg, 66% yield). 1H-NMR (400MHz, *d*-DMSO): δ 1.43 (s, 6H), 3.30 (s, 3H), 4.13 (s, 2H), 4.73 (s, 1H), 7.11 – 7.09 (m, 1H), 7.13 (m, 1H), 7.24 - 7.20 (m, 2H), 7.37 - 7.34 (m, 1H), 7.47 (m, 2H), 7.75 (t, 1H, *J*=7.8), 7.88 - 7.86 (m, 2H), 7.94 - 7.92 (m, 1H), 8.08 – 8.06 (m, 1H), 8.18 (t, 1H, *J*=1.9). MS (ES): 481.0 $[M+H]^+$.

All the following compounds were made in similar manner using appropriate nitriles and anilines. The boronic acid or boronate reagents for Suzuki coupling, if not commercially available, were made using standard techniques that are readily apparent to one skilled in the art.

- 2-{2-[(2-fluorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 465.0 $[M+H]^+$;
- 2-(1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-{[2-(trifluoromethyl)phenyl]methyl}-1H-imidazol-4-yl)propan-2-ol; MS (ES): 515.3 $[M+H]^+$;
- 2-{2-[(2-chlorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 481.0 $[M+H]^+$;
- 2-{2-[(2-chlorophenyl)methyl]-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 495.4 $[M+H]^+$;
- 2-{2-[(2-chlorophenyl)methyl]-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 511.4 $[M+H]^+$;
- 2-{2-[(2,6-dichlorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 515.3 $[M+H]^+$;

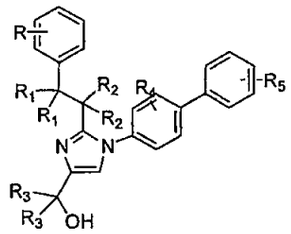
- 2-{2-[(2,6-dichlorophenyl)methyl]-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 529.3 $[M+H]^+$;
- 2-{2-[(2,6-dichlorophenyl)methyl]-1-[3'-(ethylsulfonyl)-4'-(hydroxymethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 545.3 $[M+H]^+$;
- 2-{2-[(2-chloro-6-fluorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 499.5 $[M+H]^+$;
- 2-{2-[(2-chloro-6-fluorophenyl)methyl]-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 513.5 $[M+H]^+$;
- 2-{2-[(2,3-dichlorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 15.3 $[M+H]^+$;
- 2-{2-[(2,3-dichlorophenyl)methyl]-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 529.3 $[M+H]^+$;
- 3-{2-[(2-chlorophenyl)methyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}pentan-3-ol; MS (ES): 509.3 $[M+H]^+$;
- 3-{2-[(2-chlorophenyl)methyl]-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}pentan-3-ol; MS (ES): 523.3 $[M+H]^+$;
- 3-{2-[(2-chlorophenyl)methyl]-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}pentan-3-ol; MS (ES): 539.2 $[M+H]^+$;
- 2-(2-(5-chloro-2-(trifluoromethyl)benzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 549.3 $[M+H]^+$;
- 2-(2-(5-chloro-2-(trifluoromethyl)benzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 563.3 $[M+H]^+$;
- 2-(2-(5-chloro-2-(trifluoromethyl)benzyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 579.2 $[M+H]^+$;
- 2-(2-(2-(2-chlorophenyl)propan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 509.0 $[M+H]^+$;
- 2-(2-(2-(2-chlorophenyl)propan-2-yl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 523.3 $[M+H]^+$;
- 2-(2-(2-(2,3-dichlorophenyl)propan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 543.3 $[M+H]^+$;
- 2-(2-(2-(2,3-dichlorophenyl)propan-2-yl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 557.3 $[M+H]^+$;

- 2-(2-(2,3-dichlorobenzyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 529.3 $[M+H]^+$;
- 2-(2-(2,3-dichlorobenzyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 543.3 $[M+H]^+$;
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 549.3 $[M+H]^+$;
- 2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 565.2 $[M+H]^+$;
- 2-(2-(2,3-dichlorobenzyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 533.0 $[M+H]^+$;
- 2-(2-(2,3-dichlorobenzyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 547.3 $[M+H]^+$;
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(2,3-dichlorophenyl)propan-2-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 579.3 $[M+H]^+$;
- 2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-(2,3-dichlorophenyl)propan-2-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 593.3, 595.3 [M+H];
- 2-(2-(5-chloro-2-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 499.3, $[M+H]^+$; 521.3 $[M+Na]^+$;
- 2-(2-(5-chloro-2-fluorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 535.0 $[M+Na]^+$;
- 2-(1-(2'-chloro-3-methyl-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 563, 565 $[M+H]^+$.

The following compounds were made in a similar manner, except the boronic acid or boronate reagents for the Suzuki coupling were made as described in Examples 23-29.

- 2-{1-[3-chloro-4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[(2,3-dichlorophenyl)methyl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 579, 581, 583 each $[M+H]^+$.
- 2-{2-[(2,3-dichlorophenyl)methyl]-1-[3-methyl-4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 559, 561 [each $[M+H]^+$.
- 2-(1-(2'-chloro-3-methyl-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol; MS(ES): 563, 565 $[M+H]^+$

The following compounds were made in similar manner, except appropriate propionitrile was used as starting material, instead of benzyl cyanide.



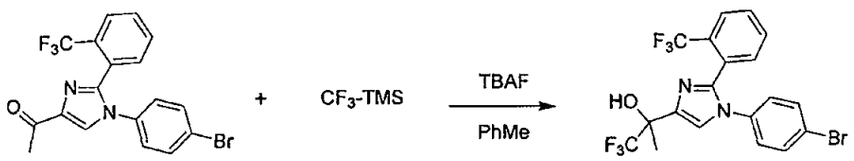
- 2-{2-[2-(2-chlorophenyl)ethyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 495.4 $[M+H]^+$;
- 2-{2-[2-(2-chlorophenyl)ethyl]-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 509.3 $[M+H]^+$;
- 2-{2-[2-(2-chlorophenyl)ethyl]-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 525.3 $[M+H]^+$.

Example 12

1,1,1-trifluoro-2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol

Example 12a

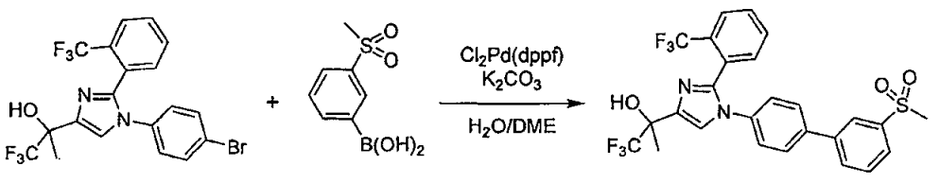
Preparation of 2-[1-(4-bromophenyl)-2-(2-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-1,1,1-trifluoro-propan-2-ol



To a solution of 1-[1-(4-bromophenyl)-2-(2-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-ethanone (0.24 g, 0.59 mmol) and trifluoromethyl-trimethylsilane (0.10 mL, 0.68 mmol) in toluene (3 mL, anhyd) at 0°C was added a 1.0M solution of tetrabutylammonium fluoride (TBAF) in THF (0.12 mL, 20 mol%, dried over 4Å molecular sieves). After 24 h the reaction mixture was charged with additional trifluoromethyl-trimethylsilane (0.10 mL) and 1.0M TBAF (0.12 mL) and then heated at 50°C. After 48 h (total) the reaction mixture was allowed to cool to ambient temperature, quenched with H_2O and extracted with DCM (2 x 30 mL). The combined extracts were dried (Na_2SO_4), concentrated and purified by chromatography (silica, EtOAc/Hex, 20:80 to 60:40) to yield the title compound (0.11 g, 39%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 7.76 (d, 1H), 7.50-7.60 (m, 2H), 7.46 (d, 2H), 7.27 (m, 2H), 7.02 (d, 2H), 4.36 (s, 1H), 1.72 (s, 3H).

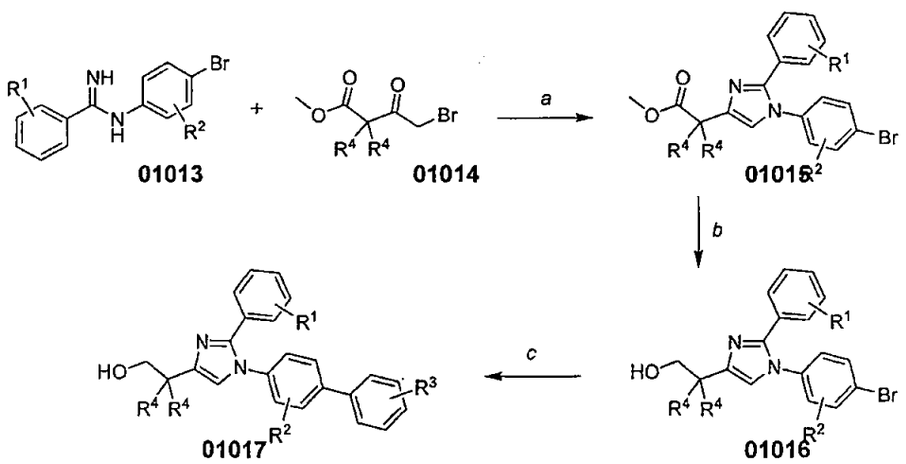
Example 12b

Preparation of 1,1,1-trifluoro-2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol



A mixture of 2-[1-(4-bromophenyl)-2-(2-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-1,1,1-trifluoro-propan-2-ol (0.11 g, 0.23 mmol), 3-methanesulfonyl-phenylboronic acid (54 mg, 0.27 mmol), K_2CO_3 (95 mg, 0.69 mmol), $Cl_2Pd(dppf)\cdot DCM$ (15 mg, 8 mol%) and H_2O (0.25 mL) in DME (2.5 mL) was sparged with Argon for 5 min and then heated at 80°C as a sealed flask. After 90 min the reaction mixture was allowed to cool to ambient temperature, filtered (Celite™) and the filter agent rinsed with EtOAc. The combined filtrates were concentrated under reduced pressure and purified by chromatography (silica, EtOAc/Hex, 35:65 to 80:20) to give the title compound (116 mg, 89%) as a white solid. ^{1}H-NMR (DCM-d_2): δ 8.09 (m, 1H), 7.91 (m, 1H), 7.84 (m, 1H), 7.78 (d, 1H), 7.66 (m, 1H), 7.59 (d, 2H), 7.49-7.57 (m, 2H), 7.33 (m, 2H), 7.25 (d, 2H), 4.40 (s, 1H), 3.06 (s, 3H), 1.75 (s, 3H); MS(ES): 555 $[M+H]^+$.

Scheme 10



(a) $NaHCO_3$, 2-PrOH, μW 180°C; (b) $LiBH_4$, 10-20 mol% $B(OMe)_3$, THF; (c) $ArB(OH)_2$, $Cl_2Pd(dppf)$, K_2CO_3, H_2O/DME, μW 120°C.

In general, compounds of formula **01017** can be prepared as depicted in Scheme 10. First an amidine (**01013**) and a bromoketone (**01014**) can react under basic conditions and at elevated temperature to give the corresponding imidazole (**01015**). This intermediate ester **01015** can be reduced under standard conditions, such as with lithium borohydride and, optionally, catalytic trimethyl borate,

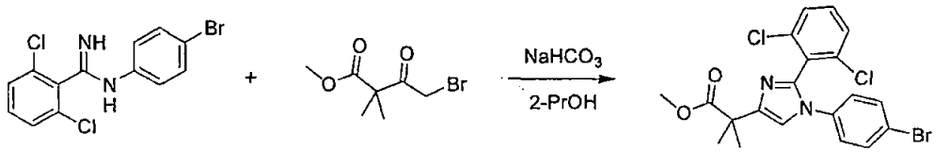
to afford the corresponding carbinol (**01016**). Last intermediate **01016** can undergo cross-couplings reactions, such as a Suzuki-Miyaura reaction with boronic acids (esters), to yield the target imidazole **01017**.

Example 13

2-[2-(2,6-dichlorophenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-2-methyl-propan-1-ol

Example 13a

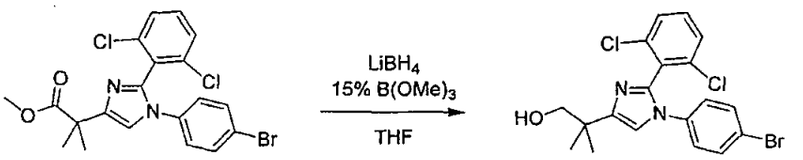
Preparation of 2-[1-(4-bromophenyl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-2-methyl-propionic acid methyl ester



A mixture of N-(4-bromophenyl)-2,6-dichlorobenzamidine (1.03 g, 3.0 mmol), methyl 4-bromo-2,2-dimethylacetoacetate (1.78 g, 8.0 mmol) and $NaHCO_3$ (0.76 g, 9.0 mmol) in isopropanol (12 mL) was heated in a microwave unit (Biotage Initiator™) at 170°C for 25 min. The resulting mixture was decanted and the solids rinsed with EtOAc. The combined filtrates were concentrated and purified by chromatography (silica, EtOAc/Hex, 15:85 to 50:50) to give the title compound (0.80 g, 57%) as a pale yellow solid. ^{1}H-NMR (DCM-d_2): δ 7.44 (d, 2H), 7.27-7.34 (m, 3H), 7.09 (m, 2H), 3.67 (s, 3H), 1.61 (s, 6H); MS(ES): 467, 469, 471 $[M+H]^+$.

Example 13b

Preparation of 2-[1-(4-bromophenyl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-2-methyl-propan-1-ol

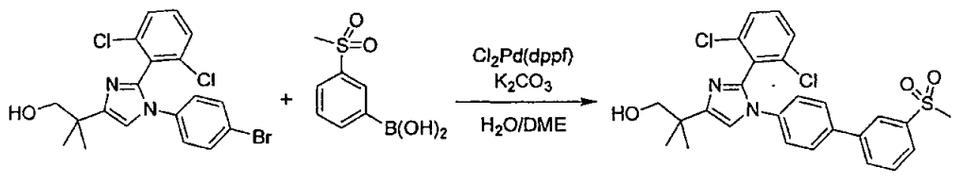


To a stirred suspension of 2-[1-(4-bromophenyl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-2-methyl-propionic acid methyl ester (0.65 g, 1.4 mmol) in Et_2O (3.5 mL, anhyd) added dropwise 2.0M solution of lithium borohydride in THF (1.4 mL, 2.8 mmol) and then added trimethyl borate (22 µL, 15 mol%). After 3 h the reaction mixture was quenched with 1N NaOH (4 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with satd NH_4Cl and brine, dried (Na_2SO_4), concentrated and purified by chromatography (silica, EtOAc/Hex, 15:85 to 50:50) to yield a white solid (0.21 g) consisting of a 2:1 mixture of the title compound, MS(ES): 439, 441, 443 $[M+H]^+$, and 2-[2-(2,6-dichlorophenyl)-1-phenyl-1H-imidazol-4-yl]-2-methyl-propan-1-ol, MS(ES): 361, 363 $[M+H]^+$.

The latter resulted from over-reduction of the title compound under the given conditions. The isolated product was used in the next step without further purification.

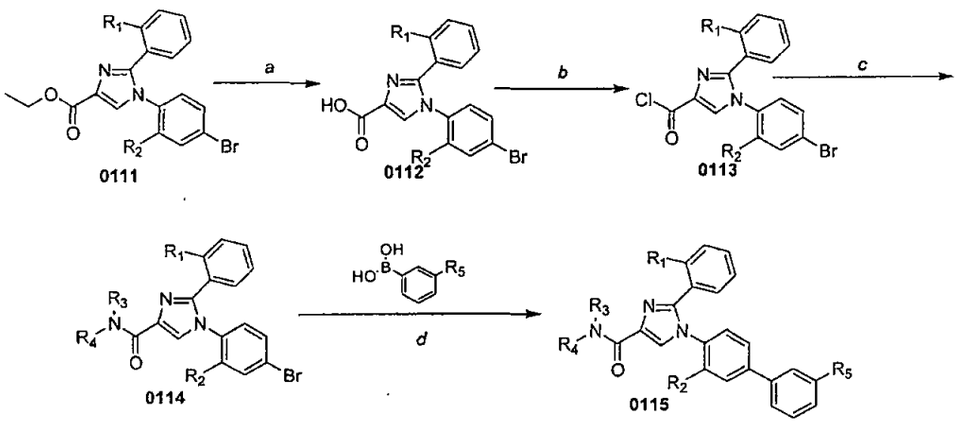
Example 13c

Preparation of 2-[2-(2,6-dichlorophenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-2-methyl-propan-1-ol



A stirred mixture of 2-[1-(4-bromophenyl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl]-2-methyl-propan-1-ol (202 mg, 0.46 mmol), 3-methanesulfonyl-phenylboronic acid (92 mg, 0.46 mmol), potassium carbonate (0.19 g, 1.4 mmol), $Cl_2Pd(dppf)\cdot DCM$ (19 mg, 5 mol%) and H_2O (0.25 mL) in DME (2.5 mL) was sparged with Argon for 5 min and then heated at 60°C as a sealed flask. After 30 min the reaction mixture was concentrated under reduced pressure and purified by chromatography (silica, EtOAc/Hex, 40:60 to 75:25) to give the title compound (35 mg) as a white solid. ^{1}H-NMR (DCM-d_2): δ 8.10 (m, 1H), 7.91 (d, 1H), 7.85 (d, 1H), 7.66 (m, 1H), 7.60 (d, 2H), 7.29-7.37 (m, 5H), 7.10 (s, 1H), 3.79 (br s, 1H), 3.62 (s, 2H), 3.06 (s, 3H), 1.36 (s, 6H); MS(ES): 515, 517 $[M+H]^+$.

Scheme 11.



(a) aq NaOH, MeOH; (b) $(COCl)_2$, DCM, DMF; (c) R_3R_4NH, $CHCl_3$, DIEA; (d) $PdCl_2dppf$, K_2CO_3, DME, H_2O

In general, amide containing compounds of formula (**0115**) can be synthesized following the methodology shown in Scheme 11. The ester group in compound (**0111**) can be hydrolyzed under aqueous basic conditions to give the carboxylic acid (**0112**). Acid (**0112**) can be converted to an acid chloride (**0113**) using known procedures followed by reaction with a primary or secondary amine to

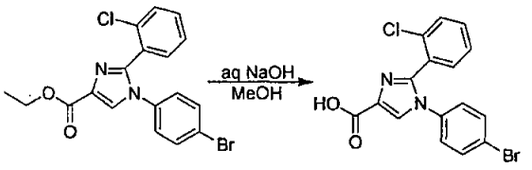
provide amide intermediate (**0114**). The amide intermediate (**0114**) can undergo cross coupling transformations to afford the corresponding 2-biaryl-imidazole (**0115**).

Example 14

2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazole-4-carboxylic acid (2,2,2-trifluoro-ethyl)-amide

Example 14a

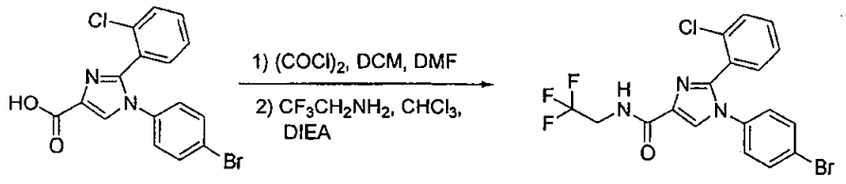
Preparation of 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid



To a 100 mL round bottom flask was added 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester (1.03 g, 2.54 mmol), MeOH (20 mL), and 1N aq NaOH (10 mL). The reaction solution was allowed to stir at 45 °C for 1 hr prior to analysis by LCMS. The reaction solution was diluted with EtOAc (150 mL), poured into a separatory funnel and the organic phase was partitioned. The aqueous phase was neutralized by the addition of aq 1 N HCl and extracted with EtOAc (70 mL x 2). The combined organic phase was dried over Na_2SO_4, filtered into a round bottom flask and concentrated on the Rotavapor. The crude residue was chromatographed thru a 25 g SiO_2 column using a mobile phase gradient of 100 % Hx to 85 % EtOAc to afford 845 mg (88 % yield) carboxylic acid intermediate. MS (ES): 378 $[M+H]^+$.

Example 14b

Preparation of 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid (2,2,2-trifluoro-ethyl)-amide

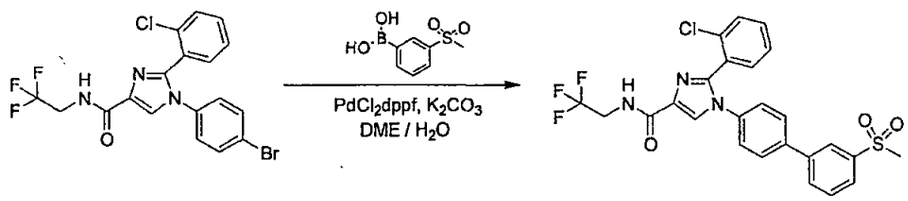


To a dry, N_2 purged 100 mL round bottom flask was added 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid (845 mg, 2.24 mmol), and (10 mL) anhydrous DCM. The solution was cooled to 0 °C prior to addition of oxalyl chloride (590 µL, 6.7 mmol) and several drops anhydrous DMF. The reaction solution was allowed to stir warming to rt over 2 hrs. The solvent and

excess reagent was removed *in vacuo*. To the crude acid chloride residue was added anhydrous $CHCl_3$ (15 mL), 2,2,2-trifluoroethylamine (700 mg, 6.70 mmol) and DIEA (1.3 mL, 7.46 mmol). The reaction solution was allowed to stir at 40 °C for approx 1 hr. The reaction solution was diluted with DCM (70 mL) and transferred to a separatory funnel. The solution was washed with aq NH_4Cl (50 mL x 2) and with aq NaCl (50 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated on the Rotavapor and chromatographed through a 25 g SiO_2 column using a mobile phase gradient of 100 % Hx to 70 % EtOAc to afford 840 mg (82 % yield) of amide product. MS (ES): 461 $[M+H]^+$.

Example 14c

Preparation of 2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazole-4-carboxylic acid (2,2,2-trifluoro-ethyl)-amide



To a 50 mL round bottom flask attached with Vigreux column and magnetic stir bar was added 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid (2,2,2-trifluoro-ethyl)-amide (249 mg, 540 µmol), 3-methylsulfonylphenyl boronic acid (130 mg, 650 µmol), $PdCl_2dppf$ (40 mg, 10 mol %), K_2CO_3 (260 mg, 1.90 mmol), 1,2-dimethoxyethane (14 mL) and H_2O (2 mL). The reaction solution was allowed to stir at 75 °C for 2 hrs. The reaction solution was diluted with EtOAc (150 mL) and filtered through a Celite padded Buchner funnel to remove spent Pd. The filtrate was transferred to a separatory funnel and washed with aq NH_4Cl (100 mL) and aq NaCl (100 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated on the Rotavapor and chromatographed through a 25 g SiO_2 column using a mobile phase gradient of 2% EtOAc to 90 % EtOAc to afford 212 mg (74 % yield) of the title compound. MS (ES): 534 $[M+H]^+$, 557 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.99 (s, 1 H), 7.92 (d, 1H), 7.65 (t, 1H), 7.57 (d, 2H), 7.52 (d, 2H), 7.41-7.34 (m, 3H), 7.24 (d, 2H), 4.11 (q, 2H), 3.08 (s, 3H); ^{19}F NMR (400 MHz, $CDCl_3$) δ -72.4 ppm.

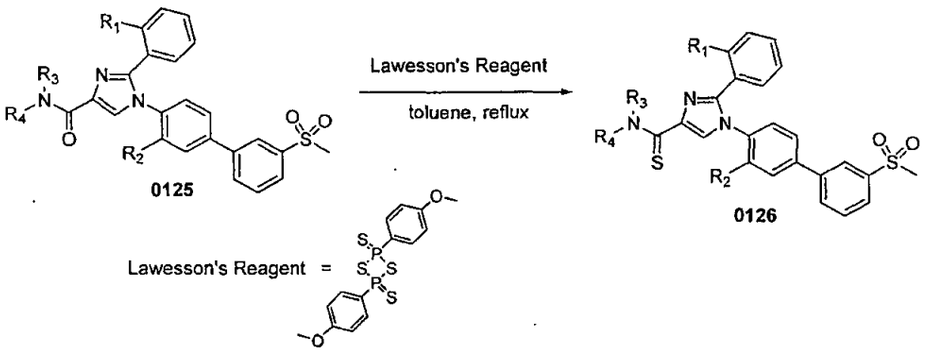
The following compounds were prepared in a manner similar to that described in experimental procedure Example 14:

- 2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 556.3 $[M+H]^+$.
- 2-(2,6-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 582.2, 584.2 $[M+H]^+$.

- 2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 596.3, 598.3 $[M+H]^+$.
- 2-(2,6-dichlorophenyl)-N,N-diethyl-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide; MS (ES): 556.3, 558.3 $[M+H]^+$.
- 2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 568.2, 570.2 $[M+H]^+$.
- 2-(2,6-dichlorophenyl)-N-(2-fluoroethyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide; MS (ES): 532, 534 $[M+H]^+$.
- 2-(2,6-dichlorophenyl)-N-ethyl-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide; MS (ES): 514.3, 516.3 $[M+H]^+$.
- (2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)(4-methylpiperazin-1-yl)methanone; MS (ES): 569.2, 571.3 $[M+H]^+$.
- 2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide; MS (ES): 530.3, 5302.3 $[M+H]^+$.
- 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 602.0, 604.0, 606.3 $[M+H]^+$.
- 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-fluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 566.3, 568.3, 570.2 $[M+H]^+$.
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxamido)acetic acid; MS (ES): 578.3, 580.3, 582.3 $[M+H]^+$.
- 1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide; MS (ES): 616.0, 618.0, 620.0 $[M+H]^+$.
- 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide; MS (ES): 592.0, 594.0, 596.2 $[M+H]^+$
- 1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide; MS (ES): 606.3, 608.3, 610.0 $[M+H]^+$
- N-tert-butyl-1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxamide; MS (ES): 576.3, 578.3, 580.3 $[M+H]^+$
- 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1H-imidazole-4-carboxamide; MS (ES): 564.2, 566.2, 568.3 $[M+H]^+$
- 1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1H-imidazole-4-carboxamide; MS (ES): 578.3, 580.3, 582.2 $[M+H]^+$

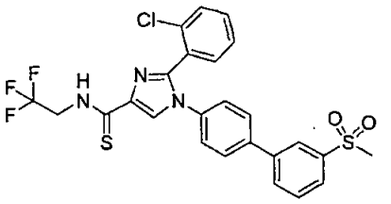
- 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-4-carboxamide; MS (ES): 592.3, 594.3, 596.0 $[M+H]^+$
- 1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-4-carboxamide; MS (ES): 606.2, 608.2, 610.2 $[M+H]^+$
- 2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide; MS (ES): 558.3, 560.3 $[M+H]^+$
- 2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide; MS (ES): 572.3, 574.3 $[M+H]^+$
- N-tert-butyl-2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide; MS (ES): 542.3, 544.3 $[M+H]^+$

Scheme 12



In general, carboxylic acid amides of formula (**0125**) can be converted to the thioamide derivative (**0126**) as shown in Scheme 12. The functional transformation can be carried out using a suitable thiation reagent, such as Lawesson's reagents or related compound.

Example 15



Preparation of 2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazole-4-carbothioic acid (2,2,2-trifluoro-ethyl)-amide

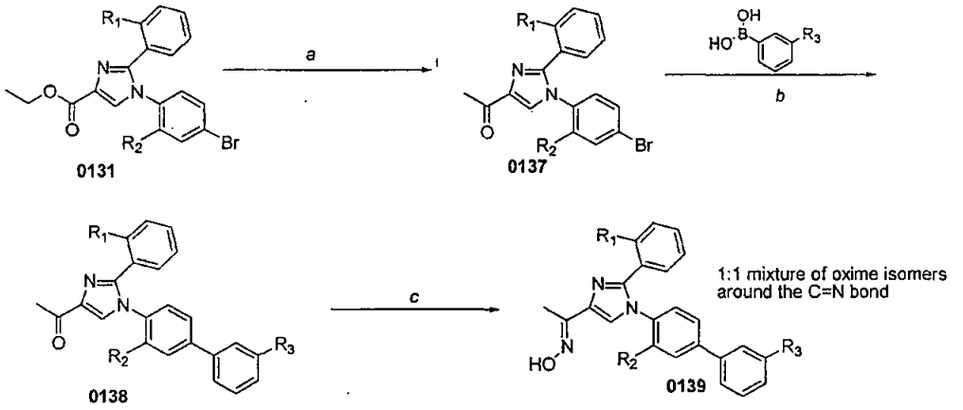
To a 25 mL round bottom flask attached with Vigreux column and magnetic stir bar was added 2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazole-4-carboxylic acid (2,2,2-trifluoro-ethyl)-amide (65 mg, 127 μmol), Lawesson's Reagent (230 mg, 570 μmol), and anhydrous toluene (6 mL). The reaction solution was allowed to stir at reflux 5 hrs prior to TLC analysis showing

full transformation of starting material. The reaction solution was allowed to cool to room temperature prior to addition of a 1:1 mixture of benzene and Et_2O. The resulting precipitate was removed by vacuum filtration through a Buchner funnel. The filtrate was concentrated on the Rotavapor and the crude residue was chromatographed through a 12 g SiO_2 column using a mobile phase gradient of 100 % Hx to 50 % EtOAc to afford 55 mg (79 % yield) of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (t, 1H), 8.11 (s, 1H), 8.04 (t, 1H), 7.85 (d, 1H), 7.75 (d, 1H), 7.59 (t, 1H), 7.53-7.46 (m, 4H), 7.34-7.311 (m, 3H), 7.18 (d, 2H), 4.56 (m, 2H), 3.02 (s, 3H); ^{19}F NMR (400 MHz, $CDCl_3$) δ -70.8 ppm; MS (ES): 550.3, 552.3 $[M+H]^+$.

The following compounds were prepared in a manner similar to that described in experimental procedure Example 15:

- 2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carbothioamide; MS (ES): 572.2 $[M+H]^+$
- 1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carbothioamide; MS (ES): 474.0, 476.0 $[M+H]^+$

Scheme 13



(a) (i)Me_3Al, toluene, $MeNHCH_2CH_2NHMe$, reflux, (ii) aq HCl; (b) $PdCl_2dppf$, K_2CO_3, DME / H_2O; (c) H_2NOH-HCl, 2:1 MeOH/H_2O, NaOAc, reflux

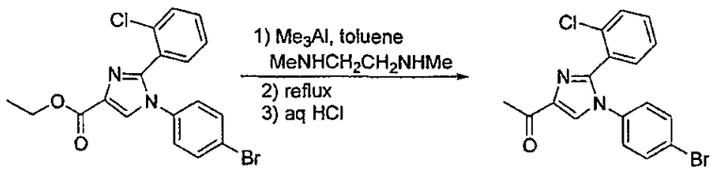
In general, oxime containing compounds of formula (**0139**) can be prepared as shown in Scheme 13. The imidazole-ester intermediate (**0131**) can be converted to the methylketone substituted compound (**0137**) using trimethylaluminium and a diamine chelant, such as N,N,-dimethyl ethylenediamine. Compound (**0137**) can undergo cross-coupling to install the D-ring to yield final compound (**0138**). The oxime substituted product (**0139**) can be prepared by reaction with hydroxylamine under known conditions.

Example 16

1-[2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-ethanone oxime

Example 16a

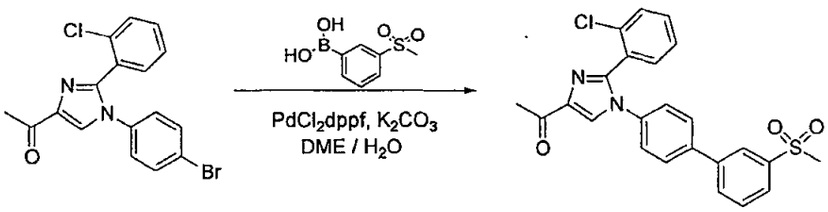
Preparation of 1-[1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazol-4-yl]-ethanone



To a dried, N_2 purged 100 mL RB flask, attached with Vigreux column was added anh. toluene (20 mL) and N,N-dimethylethylenediamine (2.2 mL, 1.1 equiv). The solution was cooled to 0 °C prior to dropwise addition of a 2.0 M solution of Me_3Al in hexanes (28 mL, 3.1 equiv). The reaction solution was stirred at room temperature for 40 min prior to the addition of 1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester (7.41 g, 18.3 mmol) in a solution of toluene (10 mL). The reaction solution was allowed to stir at reflux for 2 hrs. The reaction solution was cooled to room temperature and quenched by the addition of 1N aq HCl (10 mL). The reaction solution was dilute with EtOAc, partitioned, washed with aq NaCl, dried over Na_2SO_4, filtered, concentrated on the Rotavapor and chromatographed through an 80 g SiO_2 column using a mobile phase gradient of 100 % Hx to 75 % EtOAc to afford 3.10 g (45 % yield) of the methyl ketone intermediate. MS (ES): 376 $[M+H]^+$.

Example 16b

Preparation of 1-[2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-ethanone



To a 50 mL round bottom flask attached with Vigreux column and magnetic stir bar was added 1-[1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazol-4-yl]-ethanone (270 mg, 719 μmol), 3-methylsulfonylphenyl boronic acid (220 mg, 1.08 mmol), $PdCl_2dppf$ (55 mg, 10 mol %), K_2CO_3 (300 mg, 2.16 mmol), 1,2-dimethoxyethane (11 mL) and H_2O (1 mL). The reaction solution was allowed to stir at 70 °C for 14 hrs. The reaction solution was diluted with EtOAc (150 mL) and filtered through a Celite padded Buchner funnel to remove spent Pd. The filtrate was transferred to a separatory funnel and washed with aq NH_4Cl (100 mL) and aq NaCl (100 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated on the Rotavapor and chromatographed through a 25 g SiO_2 column

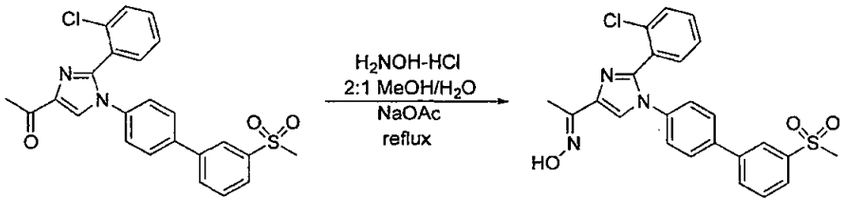
using a mobile phase gradient of 100% Hx to 75 % EtOAc to afford 170 mg (52 % yield) of product. MS (ES): 451 $[M+H]^+$, 473 $[M+Na]^+$.

The following compounds were synthesized in a manner similar to the above procedure:

- 1-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}ethanone; MS (ES): 485.4 $[M+H]^+$
- 1-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone;MS (ES): 485.3, 487.3 $[M+H]^+$

Example 16c

Preparation of 1-[2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-ethanone oxime



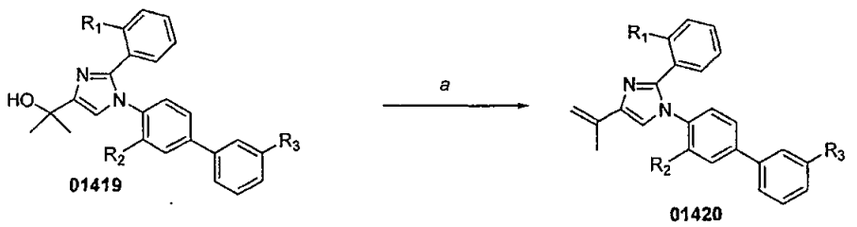
To a 50 mL RB flask attached with Vigreux column was added compound 1-[2-(2-Chloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-ethanone (162 mg, 359 μmol), hydroxylamine-HCl (200 mg, 2.87 mmol), sodium acetate (238 mg, 2.90 mmol), MeOH (12 mL) and H_2O (6 mL). The reaction solution was allowed to stir at reflux for 2 hrs prior to TLC analysis. The reaction solution was diluted with EtOAc (150 mL), washed with aq. NaCl (100 mL), partitioned, dried over Na_2SO_4, filtered, and concentrated on the Rotavapor. The crude product was chromatographed through a 25 g SiO_2 column using a mobile phase gradient of 100 % Hx to 80 % EtOAc to afford 85 mg (51 % yield) of the title compound as a mixture of *E* and *Z* isomers. The isomers were separated by chromatography with a Reverse Phase HPLC using a C_{18} Preparative column. Characterization for one single oxime isomer: ^1H NMR (400 MHz, DMSO-*d6*) δ 9.86 (s, 1H), 8.15 (t, 1H), 8.02 (d, 1H), 7.90 (d, 1H), 7.85 (s, 1H), 7.80 (d, 2H), 7.72 (t, 1H), 7.64 (d, 1H), 7.47-7.44 (m, 3H), 7.35 (d, 2H); MS (ES): 466.1 $[M+H]^+$.

The following compounds were prepared in a manner similar to that described in experimental procedure Example 16:

- 1-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 500.3 $[M+H]^+$
- 1-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 480.0, 482.0 $[M+H]^+$

- 1-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 480.0, 482.0 $[M+H]^+$
- 1-{2-(2-chlorophenyl)-1-[3'-(1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 430.0, 432.0 $[M+H]^+$
- 1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 466.0, 468.0 $[M+H]^+$
- 1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 466.0, 468.0 $[M+H]^+$
- 1-{2-(2-chlorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime; MS (ES): 495.3, 497.3 $[M+H]^+$
- (E)-1-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone oxime; MS (ES): 500.4, 502.3 $[M+H]^+$
- (E)-1-(2-(2-ethylphenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone oxime; MS (ES): 460.3 $[M+H]^+$
- (E)-1-(2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone oxime; MS (ES): 488.3 $[M+H]^+$

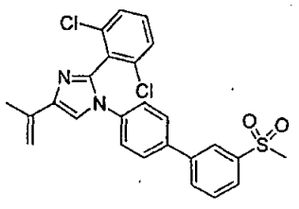
Scheme 14



(a) HCl, dioxane, Δ or HOAc, toluene, Δ

In general, carbinol substituted imidazole compounds of formula (**01419**) can be dehydrated using known methods to provide the corresponding alkene (**01420**) (Scheme 14). The dehydration reaction can be carried out using several different acid catalysts, such as HCl or acetic acid, in a heated and anhydrous solvent system.

Example 17



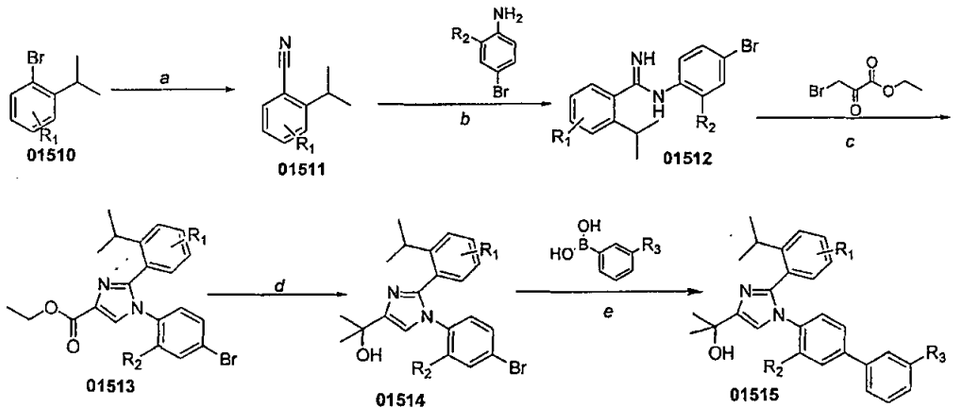
Preparation of 2-(2,6-Dichloro-phenyl)-4-isopropenyl-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazole

To a 25 mL round bottom flask attached with Vigreux column was added 2-[2-(2,6-Dichloro-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol (383 mg, 764 μmol), anhydrous toluene (8 mL) and acetic acid (3.5 mL). The reaction solution was allowed to stir at reflux for 1.5 hr. The cooled reaction solution was concentrated *in vacuo*, and the residue was taken into EtOAc (200 mL) and washed with aq $NaHCO_3$ (100 mL x 2) and aq. NaCl (100 mL). The organic phase was partitioned, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was chromatographed through a 25 g SiO_2 column using a mobile gradient of 100 % Hx to 80 % EtOAc to provide 288 mg (78 % yield) of title compound. ^1H NMR (400 MHz, DMSO-d_6): δ 8.15 (br s, 1H), 8.08-7.97 (m, 2H), 7.92 (d, 1H), 7.89 (d, 2H), 7.75 (t, 1H), 7.64-7.57 (m, 3H), 7.43 (d, 2H), 5.77 (br s, 1H), 5.10 (br s, 1H), 3.29 (s, 3H), 2.11 (s, 3H); MS (ES): 483.1, 485.1 $[M+H]^+$.

The following compound was made according to this scheme:

- 2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-4-(prop-1-en-2-yl)-1H-imidazole; MS(ES): 497, 499 $[M+H]^+$

Scheme 15



(a) CuCN, DMF, reflux; (b) (i) Me_3Al, toluene, (ii) reflux 1 d; (c) (i) EtOH, $NaHCO_3$, (ii) HOAc, reflux; (d) 4 equiv MeMgBr; (e) $PdCl_2dppf$, K_2CO_3, DME / H_2O

In general, compounds of formula (**01515**), with alkyl A-ring substituents larger than Me or Et, can be synthesized following the sequence shown in Scheme 15. By example, the methodology in Scheme 15 can afford imidazole compounds with 2-iso-propyl groups on the phenyl A-ring. In general, the methodology can also afford compounds with either mono- or disubstituted phenyl A-rings. An arylbromide (**01510**) can be converted to an arylnitrile (**01511**) by reaction with copper(I) cyanide. The arylnitrile can be reacted with aniline in the presence of a Lewis acid, such as trimethylaluminium, to

give the corresponding amidine (**01512**). Amidine (**01512**) can be reacted with ethyl bromopyruvate in the presence of sodium bicarbonate, followed by dehydration to afford the cyclized imidazole intermediate (**01513**). Carbinol formation to provide (**01514**) and Suzuki cross coupling can be used to afford compound (**01515**) in a manner similar to that described in Scheme 8.

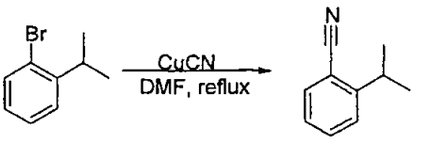
The following compound was made according to this scheme: 2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-4-(prop-1-en-2-yl)-1H-imidazole; MS(ES): 497, 499 $[M+H]^+$

Example 18

2-[2-(2-Isopropyl-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol

Example 18a

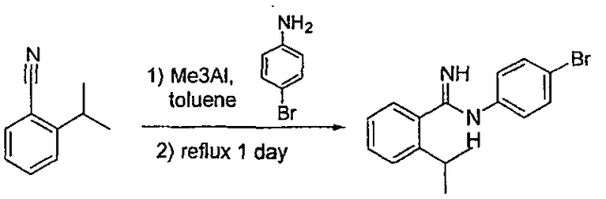
Preparation of 2-isopropylbenzonitrile



To a dry, N_2 purged 100 mL round bottom flask attached with condenser was added 1-bromo-2-isopropylbenzene (10.0 g, 50.2 mmol), anhydrous DMF (26 mL), and CuCN (5.85 g, 65.3 mmol). The reaction slurry was stirred at reflux under N_2 for 4 hrs prior to analysis by GCMS. The reaction mixture was cooled to room temperature and poured into an ice / aq NH_4Cl solution. The resulting precipitates were removed by vacuum filtration through a Buchner funnel. The aqueous filtrate was extracted with EtOAc (150 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated on the Rotavapor to afford 5.97 g (82 % yield) of 2-isopropylbenzonitrile. The product was used in the next step without further purification. GCMS m/z = 145 $[M^+]$.

Example 18b

Preparation of N-(4-Bromo-phenyl)-2-isopropyl-benzamidine

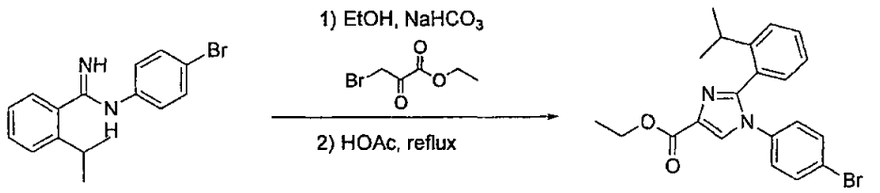


To a dry, N_2 purged 100 mL round bottom flask was added 4-bromo-aniline (2.73g, 15.9 mmol) and anhydrous toluene (40 mL). To the solution at 0 °C was added, dropwise, a 2.0 M solution of Me_3Al in hexanes (9.4 mL). The solution was allowed to stir, warming to room temperature for approximately 1 hr. To the reaction solution was added 2-isopropylbenzonitrile (3.00 g, 20.7 mmol) in a toluene solution (15 mL). The reaction solution was allowed to stir at 80 °C for approximately 24 hrs.

The reaction solution was allowed to cool to room temperature prior to quenching by pouring the reaction solution into an Erlenmeyer containing a 2:1 $CHCl_3$ / MeOH solution and 100 g of silica. The slurry was allowed to stir 30 min prior to filtration into a Buchner funnel under vacuum. The filtrate was concentrated on the Rotavapor and the resulting residue was reprecipitated using a 10:1 Hx / Et_2O mixture. The resulting white precipitates were isolated by vacuum filtration to afford 1.98 g (40 % yield) of amidine product. GCMS m/z = 317 [M^+].

Example 18c

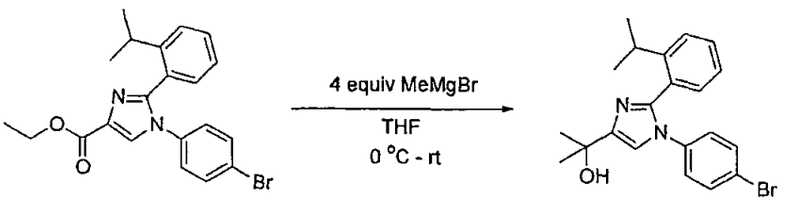
Preparation of 1-(4-Bromo-phenyl)-2-(2-isopropyl-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester



To a 250 mL round bottom flask attached with condenser was added N-(4-Bromo-phenyl)-2-isopropyl-benzamidine (1.94 g, 6.11 mmol), ethyl bromopyruvate (1.54 mL, 12.2 mmol), sodium bicarbonate (1.02 g, 12.2 mmol), and iso-propanol (45 mL). The reaction slurry was allowed to stir at 80 °C for approximately 2 hrs. The reaction solution was decanted into a clean round bottom flask and concentrated *in vacuo*. The resulting residue was dissolved in acetic acid (25 mL), and the solution was allowed to stir at reflux for approximately 2 hrs. The solution was concentrated *in vacuo*, and the product residue was taken into EtOAc (200 mL) and washed with aq NaCl (200 mL x 2) and aq $NaHCO_3$ (100 mL). The organic phase was partitioned, dried over Na_2SO_4, filtered, concentrated, and chromatographed through a 40 g SiO_2 column using a mobile gradient of 100 % Hx to 70 % EtOAc to afford 1.90 g (75 % yield) of title compound. MS (ES): 414.0 $[M+H]^+$.

Example 18d

Preparation of 2-[1-(4-Bromo-phenyl)-2-(2-isopropyl-phenyl)-1H-imidazol-4-yl]-propan-2-ol

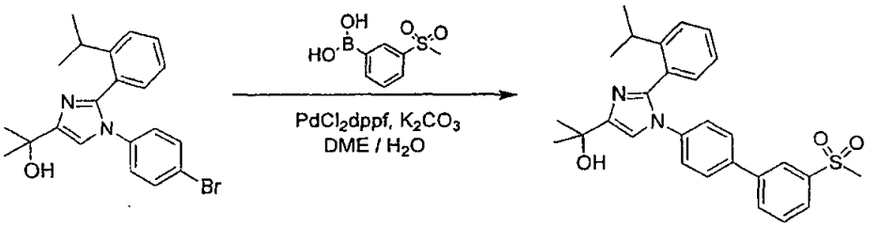


To a dry, N_2 purged round bottom flask containing 1-(4-Bromo-phenyl)-2-(2-isopropyl-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester (1.87 g, 4.52 mmol) was added anhydrous THF (55 mL). The solution was cooled to 0 °C prior to the addition of a 3.0 M solution of methylmagnesium

bromide (5.3 mL). The reaction was stirred 1 hr at room temperature prior to quenching with aq NH_4Cl (30 mL). The organic phase was partitioned, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was chromatographed through a SiO_2 column using a mobile gradient to 100 % Hx to 80 % EtOAc to afford 1.19 g (66 % yield) of 369-45.

Example 18e

Preparation of 2-[2-(2-Isopropyl-phenyl)-1-(3'-methanesulfonyl-biphenyl-4-yl)-1H-imidazol-4-yl]-propan-2-ol



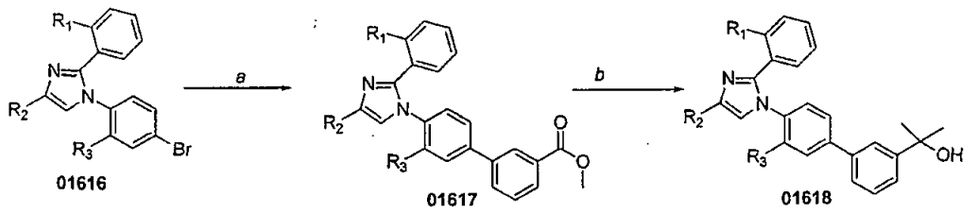
To a 50 mL round bottom flask attached with Vigreux column and magnetic stir bar was added 2-[1-(4-Bromo-phenyl)-2-(2-isopropyl-phenyl)-1H-imidazol-4-yl]-propan-2-ol (297 mg, 743 μmol), 3-methylsulfonylphenyl boronic acid (193 mg, 968 μmol), $PdCl_2dppf$ (60 mg, 10 mol %), K_2CO_3 (310 mg, 2.23 mmol), 1,2-dimethoxyethane (14 mL) and H_2O (4 mL). The reaction solution was allowed to stir at 80 °C for 2 hrs. The reaction solution was diluted with EtOAc (150 mL) and filtered through a Celite padded Buchner funnel to remove spent Pd. The filtrate was transferred to a separatory funnel and washed with aq NH_4Cl (100 mL) and aq NaCl (100 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated on the Rotavapor and chromatographed through a 25 g SiO_2 column using a mobile phase gradient of 100 % Hx to 90 % EtOAc to afford 303 mg (86 % yield) of the title compound. ^1H NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 8.02 (d, 1 H), 7.89 (d, 1H), 7.89 (d, 1H), 7.78 (d, 2H), 7.72 (t, 1H), 7.37-7.34 (m, 3H), 7.26 (d, 2H), 7.18-7.16 (m, 2H), 4.84 (s, 1H), 3.26 (s, 3H), 2.85 (sept, 1H), 1.50 (6H), 0.96 (d, 6H); MS (ES): 475.4 $[M+H]^+$, 497.5 $[M+Na]^+$.

The following compounds were prepared in a manner similar to that described in experimental procedure Example 18:

- 2-(1-(3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 489.4 [M+H], 511.4 $[M+Na]^+$
- 2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 509.3, 511.3 $[M+H]^+$
- 2-(2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 489.3, 511.4 $[M+Na]^+$

- 2-(1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-2-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol; MS (ES): 503.4 $[M+H]^+$

Scheme 16



(a) Suzuki Coupling; (b) 4 equiv MeMgBr, toluene

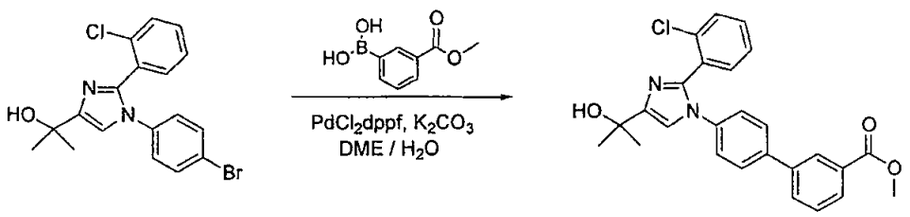
In general, compounds of formula (**01618**) can be synthesized as shown in Scheme 16. The method involves use of a methylester substituted D-ring compound, such as depicted with compound (**01617**). The D-ring ester (**01617**) can be converted to a dimethylcarbinol compound (**01618**) by reaction with a molar excess of methylmagnesium bromide. The transformation can be carried out when R_2 is either and ester group of carbinol. When R_2 is an ester group, four equivalents of methylmagnesium bromide can be used to prepare the *bis*-carbinol version of compound (**01618**).

Example 19

2-{2-(2-Chloro-phenyl)-1-[3'-(1-hydroxy-1-methyl-ethyl)-biphenyl-4-yl]-1H-imidazol-4-yl}-propan-2-ol

Example 19a

Preparation of 4'-[2-(2-Chloro-phenyl)-4-(1-hydroxy-1-methyl-ethyl)-imidazol-1-yl]-biphenyl-3-carboxylic acid methyl ester

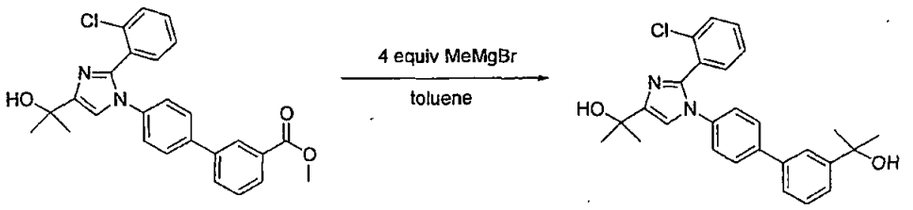


To a 50 mL round bottom flask attached with Vigreux column and magnetic stir bar was added 2-[1-(4-Bromo-phenyl)-2-(2-chloro-phenyl)-1H-imidazol-4-yl]-propan-2-ol (275 mg, 702 μmol), 3-methoxycarbonylphenyl boronic acid (164 mg, 913 μmol), $PdCl_2dppf$ (51 mg, 10 mol %), K_2CO_3 (290 mg, 2.11 mmol), 1,2-dimethoxyethane (13 mL) and H_2O (1.5 mL). The reaction solution was allowed to stir at 70 °C for approximately 2 hrs. The reaction solution was diluted with EtOAc (150 mL) and filtered through a Celite padded Buchner funnel to remove spent Pd. The filtrate was transferred to a separatory funnel and washed with aq NH_4Cl (100 mL) and aq NaCl (100 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated on the Rotavapor and chromatographed through a 25 g SiO_2

column using a mobile phase gradient of 100 % Hx to 90 % EtOAc to afford 122 mg (39 % yield) of product. MS (ES): 446.3, 448.3 $[M+H]^+$.

Example 19b

Preparation of Preparation of 2-{2-(2-Chloro-phenyl)-1-[3'-(1-hydroxy-1-methyl-ethyl)-biphenyl-4-yl]-1H-imidazol-4-yl}-propan-2-ol



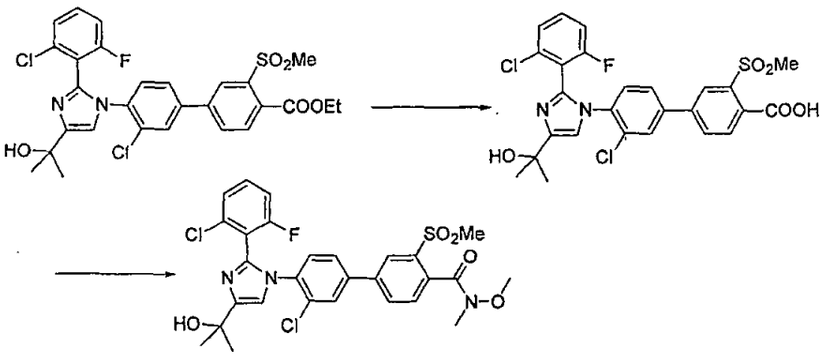
To a dry, N_2 purged 50 mL round bottom flask was added 4'-[2-(2-Chloro-phenyl)-4-(1-hydroxy-1-methyl-ethyl)-imidazol-1-yl]-biphenyl-3-carboxylic acid methyl ester (100 mg, 225 µmol), anhydrous and toluene (7 mL). To the solution at 0 °C was added a 1.4 M solution of methylmagnesium bromide (640 µL). The reaction solution was allowed to stir at room temperature for approximately 1hr. The reaction was quenched by the addition of aq NH_4Cl (20 mL). The organic phase was partitioned, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was chromatographed through a 12 g SiO_2 column using a gradient of 100 % Hx to 100 % EtOAc to afford 45 mg (45 % yield) of title compound. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.55 (d, 2H), 7.48-7.38 (m, 5H), 7.35 (s, 1H), 7.33 (m, 1H), 7.18 (d, 2H), 7.16 (s, 1H), 1.73 (s, 6H), 1.62 (s, 6H); MS (ES): 447.4 $[M+H]^+$, 469.3 $[M+Na]^+$

The following compounds were prepared in a manner similar to that described in experimental procedure Example 19:

- 1-(3-chloro-3'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide; MS (ES): 572.3, 574.3, 576.3 $[M+H]^+$
- 2-{2-(2,3-dichlorophenyl)-1-[3'-(1-hydroxy-1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 481 $[M+H]^+$, 503 $[M+Na]^+$.

Example 20

Preparation of 3'-chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-N-methyl-N-(methyloxy)-3-(methylsulfonyl)biphenyl-4-carboxamide.



Ethyl 3'-chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-carboxylate was prepared as described in Example 9. Into a 500 mL flask was weighed 11.19 g (18.92 mmol) of ester, 100 mL of THF, 100 mL of methanol, and 19.0 mL of 3.0 M LiOH-H_2O. The resulting suspension was stirred at room temperature for 21 h then was concentrated *in vacuo*. The residue was treated with ethyl acetate and 1.0 M HCl and the resulting suspension was filtered of solids. The filtrate was placed into a separatory funnel and the ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and concentrated *in vacuo*. The solids collected by filtration were added and the combined solids were dried under high vacuum to afford 3'-chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-carboxylic acid as a colorless solid, yield: 7.36 g (69%); MS (ES): 563 $[M+H]^+$.

Also recovered as a minor byproduct was 3'-chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-methylethenyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-carboxylic acid; MS (ES): 545 and 547 each $[M+H]^+$.

Into an 8 mL vial was weighed 68 mg (697 μmol) of *N,O*-Dimethyl-hydroxylamine hydrochloride, and 157 mg (279 μmol) of acid. The solids were then treated with 710 μL of a 0.5 M *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate solution in DMF and 200 μL of diisopropylethylamine was added. The reaction was stirred at room temperature for 20 h then was washed into a separatory funnel with ethyl acetate and 1 M HCl. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and was concentrated *in vacuo*. The product was purified by silica gel flash chromatography (Biotage, 12.5 x 150 mm SiO_2, gradient elution from 100% hexanes to 100% ethyl acetate over 0.5 h). Appropriate fractions were combined and concentrate *in vacuo* to afford the product as a colorless solid, yield: 85 mg (47%); ^1H NMR (400MHz, DMSO-d_6): δ 8.26(s, 1H), 8.19(d, J = 8 Hz, 1H), 8.15(s, 1H), 7.87(d, J = 6 Hz, 1H), 7.72(d, J = 8 Hz, 1H), 7.53(q, J = 6 Hz, 1H),

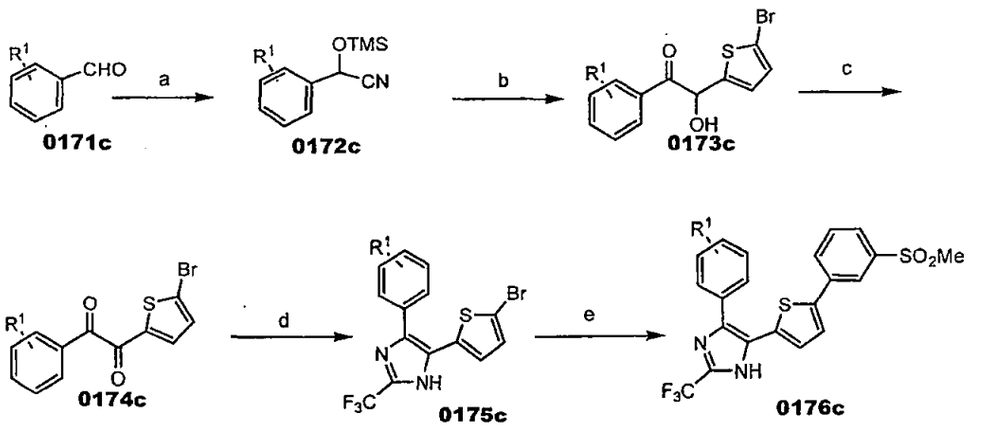
7.4-7.5(m, 3H), 7.31(t, J = 8 Hz, 1H), 3.39(s, 3H), 3.32 and 3.36(each s, 3H), 2.75(s, 3H), 1.58(s, 6H); MS (ES): 606 $[M+H]^+$.

In a manner similar to that described, the following examples of the invention were prepared by substituting an appropriate reagent.

- 3'-Chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)biphenyl-4-carboxamide; MS (ES): 562 $[M+H]^+$.
- 3'-Chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-*N*,*N*-dimethyl-3-(methylsulfonyl)biphenyl-4-carboxamide; MS (ES): 590 $[M+H]^+$.
- 3'-Chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-*N*-ethyl-3-(methylsulfonyl)biphenyl-4-carboxamide; MS (ES): 590 $[M+H]^+$.
- 2-{2-(2-Chloro-6-fluorophenyl)-1-[3-chloro-3'-(methylsulfonyl)-4'-(morpholin-4-ylcarbonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol; MS (ES): 632 $[M+H]^+$.
- 3'-Chloro-4'-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]-3-(methylsulfonyl)-N-(phenylmethyl)biphenyl-4-carboxamide; MS (ES): 652 $[M+H]^+$.

Scheme 17

2,4,5-Trisubstituted imidazole (Isomer IIc and tautomer IId)



Reactions and conditions: (a)TMSCN, ZnI_2, rt; (b) 5-bromothiophen-2-carboxaldehyde, LiHMDS, THF, -78°C; (c) Bi_2O_3, HOAc, 90°C; (d) NH_4OAc, $CF_3CH(OEt)(OH)$, AcOH, reflux; (e) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

The subject imidazole compounds of formula (**0176c**) are synthesized according to the sequence outlined in Scheme **3**. Aldehyde (**0171c**) such as 2-chlorobenzaldehyde is converted to the protected cyanohydrin of formula (**0172c**) by reaction with trialkylsilyl cyanide, such as trimethylsilyl cyanide (TMSCN), in the presence of a catalyst such as zinc iodide. Reaction of cyanohydrin (**0172c**) with aldehyde such as 5-bromothiophene-2-carboxalhedyde, under strong base produces bezoin of

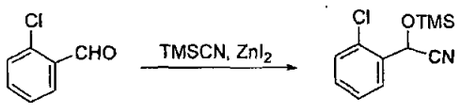
formula (**0173c**). Oxidation of bezoin with a suitable oxidant such as bismuth oxide provides the diketone of formula (**0174c**), which subsequently reacts with ammonium acetate and appropriate aldehyde or its equivalent such as trifluoroacetaldehyde ethyl hemiacetal to give 1*H*-imidazole of formula (**0175c**). In a palladium mediated coupling reaction, for example a Suzuki reaction, compounds of formula (**0175c**) are then reacted with a boronate or boronic acid reagent to give compounds of formula (**0176c**) after standard isolation procedures.

Example 21

4-(2-chlorophenyl)-5-(5-(3-(methylsulfonyl)phenyl)thiophen-2-yl)-2-(trifluoromethyl)-1H-imidazole

Example 21a

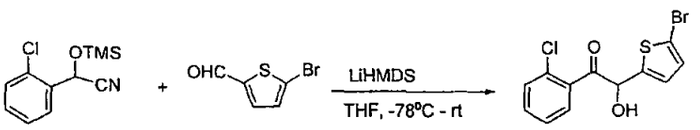
Preparation of (2-Chloro-phenyl)-trimethylsilanyloxy-acetonitrile



Under an atmosphere of nitrogen, anhydrous zinc iodide (30 mg, 0.1 mmol) was placed into a dry flask. At 0°C trimethylsilylcyanide (5.2 g, 52.5 mmol) was added, followed by 2-chlorobenzaldehyde (7.0 g, 50 mmol). The mixture was stirred at 0°C for 3 hrs, then at room temperature overnight. Ethyl ether was added, and the mixture was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil (10.95 g, 91% yield), which wad used directly for the next step without further purification. ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.80 (s, 1H), 7.38 (m, 3H), 7.73 (dd, 1H).

Example 21b

Preparation of 2-(5-Bromo-thiophen-2-yl)-1-(2-chloro-phenyl)-2-hydroxy-ethanone

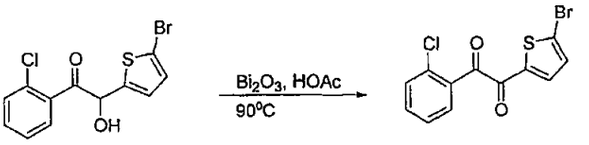


Under an atmosphere of nitrogen, to a clod (-78°C) solution of lithium bis(trimethylsilyl)amide (8.05 mL, 1.0M solution in THF, 8.05 mmol) was added a solution of (2-chloro-phenyl)-trimethylsilanyloxy-acetonitrile (1.69 g, 7 mmol) in tetrahydrofuran (10 mL) dropwise over 10 min. After stirring for another 30min, a solution of 5-bromothiophen-2-carboxaldehyde in tetrahydrofuran (10 mL) was added dropwise. The reaction was stirred overnight from -78°C to reach room temperature, then was quenched by adding 3N HCl (20 mL) and warming at 40°C for 5 hrs. After cooling, the mixture was partitioned between ethyl ether and water. The organic layer was stirred with 1M NaOH (30 mL) for 2 hrs, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel

(Hexane/EtOAc, 8/2) to give a brown oil (320 mg, 14% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 4.35 (d, 1H), 6.12 (d, 1H), 7.02 (d, 1H), 7.26 (m, 2H), 7.41 (d, 1H), 7.44 (dd, 1H).

Example 21c

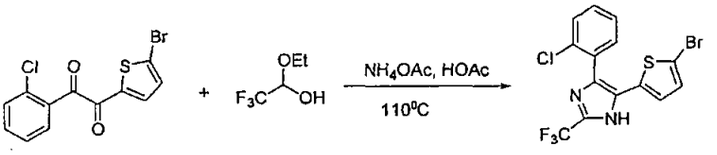
Preparation of 1-(5-Bromo-thiophen-2-yl)-2-(2-chloro-phenyl)-ethane-1,2-dione



A mixture of benzoin prepared from above (316 mg, 0.95 mmol), and bismuth oxide (560 mg, 1.2 mmol) in acetic acid (5 mL) was heated at 90^{0}C for 5 hrs. The hot reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The brown residue was redissolved into hot methanol, and then filtered. The filtrate was evaporated to give a brown oil (311 mg, 99% yield), which is used directly for the next step without further purification. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.21 (d, 1H), 7.43 (m, 1H), 7.45 (m, 1H), 7.54 (m, 1H), 7.70 (d, 1H), 7.77 (dd, 1H).

Example 21d

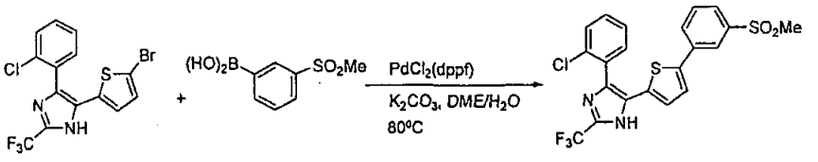
Preparation of 5-(5-Bromo-thiophen-2-yl)-4-(2-chloro-phenyl)-2-trifluoromethyl-1H-imidazole



A mixture of diketone (311 mg, 0.95 mmol), ammonium acetate (366 mg, 4.75 mmol), and trifluoroacetaldehyde ethyl hemiacetal (684 mg, 4.75 mmol) in 5 mL acetic acid was heated at 110^{0}C for 10 hrs under nitrogen atmosphere. All solvent was removed under *vacuo*, and the residue was redissolved into dichloromethane and filtered. The filtrate was concentrated, and then purified by chromatography on silica gel (Hexane/EtOAc, 8/2) to give a light pink solid (141 mg, 36% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 6.81 (d, 1H), 6.87 (d, 1H), 7.38 (t, 1H), 7.49 (m, 2H), 7.56 (d, 1H), 9.55 (s, 1H).

Example 21e

Preparation of 4-(2-Chloro-phenyl)-5-[5-(3-methanesulfonyl-phenyl)-thiophen-2-yl]-2-trifluoromethyl-1H-imidazole



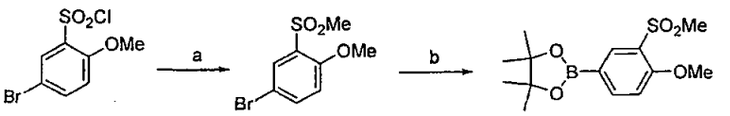
5-(5-Bromo-thiophen-2-yl)-4-(2-chloro-phenyl)-2-trifluoromethyl-1*H*-imidazole (70 mg, 0.17 mmol), (3-methylsulfonyl)phenylboronic acid (69 mg, 0.34 mmol), potassium carbonate (106 mg, 0.77 mmol), and $PdCl_2(dppf).CH_2Cl_2$ (14 mg, 0.017 mmol) were mixed with 2 mL 9:1 (v/v) DME/H_2O, then heated at 80°C overnight. All solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel (Hexane/EtOAc, 6/4) to give a white solid (25 mg, 30% yield). ^{1}H-NMR (400MHz, $CDCl_3$): δ 3.07 (s, 3H), 7.00 (d, 1H), 7.12 (m, 1H), 7.51 (m, 5H), 7.81 (m, 2H), 8.10 (t, 1H), 9.65 (s, 1H).

All the following compounds were prepared in similar manner using appropriate aldehydes as starting materials

- 4-(2-chlorophenyl)-5-[3'-(methylsulfonyl)biphenyl-4-yl]-2-(trifluoromethyl)-1H-imidazole; 477.1, 479.3 $[M+H]^+$;
- 4'-[4-(2-chlorophenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl]biphenyl-3-sulfonamide; 478.0 $[M+H]^+$;
- 3-{5-[4-(2-chlorophenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl]-2-thienyl}benzenesulfonamide; 484.0 $[M+H]^+$.

Example 22

Preparation of 2-(4-methoxy-3-(methylsulfonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



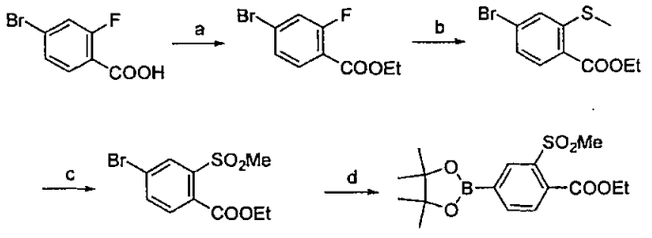
a) $NaHCO_3$, Na_2SO_3, H_2O, 85 °C; b) Bis(pinacolato)diboron, Pd(dppf), KOAc, DMSO, 100 °C.

Into a 1L flask was weighed 41.4 g of sodium sulfite, 29 g of sodium bicarbonate, and 175 mL of water. The suspension was stirred at 80-85 °C and sulfonyl chloride (50 g) was added portionwise over 3 h. Heating was continued for 3 h then the reaction was allowed to stand at room temperature for 3 days. The intermediate sulfinate was collected by filtration with added water then was dried under high vacuum. The dry solids (45 g) were returned to a 1 L flask along with 28.0 g of sodium bicarbonate, 25 mL of dimethylsulfate, and 63.75 mL of water. The resulting suspension was heated at 120-125 °C, where it became a solution, for 20 h then was cooled and washed into a separatory funnel with ethyl acetate and water. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and concentrated *in vacuo*. The product was precipitated from dichloromethane with hexanes and was dried under high vacuum to afford the intermediate 4-Bromo-2-methanesulfonyl-1-methoxy-benzene as a colorless powder, yield: 31.1 g (67%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.08(2, 1H), 7.69(d, J = 8 Hz, 1H), 6.96(d, J = 8 Hz, 1H), 4.00(s, 3H), 3.21(s, 3H).

Into a 500 mL flask was weighed 15.48 g (58.4 mmol) of bromide, 23 g of boronate, 21 g of potassium acetate, 5 g of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dicloromethane adduct, and 150 mL of DMSO. The resulting suspension was heated at ~100 °C for 20 h then was cooled and diluted with 200 mL of ethyl acetate and 200 mL of water. The suspension was filtered through celite to remove solids and the filtrate was transferred to a separatory funnel. The aqueous phase was separated and washed with ethyl acetate. The ethyl acetate washings were combined, washed with brine, were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 100% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo*. The partially purified product was dissolved in ethyl acetate and was precipitated with hexanes. The 2-(3-Methanesulfonyl-4-methoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane was recovered as a faintly yellow powder, yield: 12.56 g (77%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.43(s, 1H), 8.01(d, J = 8 Hz, 1H), 7.03(d, J = 8 Hz, 1H), 4.02(s, 3H), 3.20(s, 3H), 1.33(s, 12H).

Example 23

Preparation of ethyl 2-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate



a) EDCI, DMAP, EtOH, CH_2Cl_2, 45 °C; b) NaSMe, THF, 80 °C; c) MCPBA, CH_2Cl_2, 25 °C; d) Bis(pinacolato)diboron, Pd(dppf), KOAc, DMSO, 85 °C.

Into a 1 L flask was weighed 24.66 g (113 mmol) of acid, 26.5 g (138 mmol) of EDCI, 1.7 g of DMAP, 425 mL of dichloromethane, and 25 mL of ethanol. The resulting solution was heated at 40-45 °C for 24 h then was concentrated *in vacuo* to remove dichloromethane. The residue was washed into a separatory funnel with ethyl acetate and 1 M HCl. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4) and was concentrated *in vacuo*. The intermediate 4-Bromo-2-fluoro-benzoic acid ethyl ester was recovered as a colorless oil, yield: 24.99 g (89.8%).

The ester was treated with 12.2 g of sodium thiomethoxide and 200 mL of THF and the resulting suspension was heated at 80-85 °C for 5 h. The reaction was then concentrated to remove THF and was washed into a separatory funnel with ethyl acetate and 1 M HCl. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and concentrated *in vacuo* affording the intermediate 4-Bromo-2-methylsulfanyl-benzoic acid ethyl ester as a light gray solid, yield: 27.5 g (99%). ^{1}H NMR

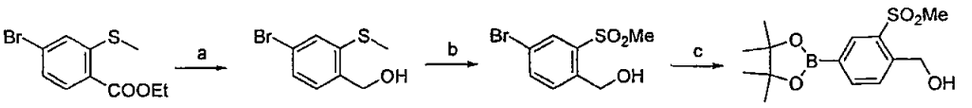
(400MHz, $CDCl_3$): δ 7.86(d, J = 8 Hz, 1H), 7.36(s, 1H), 7.28(d, J = 8 Hz, 1H), 4.38(q, J = 7 Hz, 2H), 2.45(s, 3H), 1.39(t, J = 7 Hz, 3H).

Into a 1 L flask was weighed 15.0 g of 4-Bromo-2-methylsulfanyl-benzoic acid ethyl ester (54.5 mmol), 200 mL of dichloromethane, and 28.0 g of MCPBA (77% max., Aldrich) was added portionwise at room temperature. The resulting suspension was stirred at room temperature for three days then was concentrated *in vacuo* to remove dichloromethane. The residue was washed into a separatory funnel with ethyl acetate and 1.0 M NaOH. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and concentrated *in vacuo*. The intermediate 4-Bromo-2-methanesulfonyl-benzoic acid ethyl ester was recovered as a colorless oil which crystallized on standing, yield: 16.3 g (97%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.27(s, 1H), 7.82(d, J = 8 Hz, 1H), 7.60(d, J = 8 Hz, 1H), 4.44(q, J = 7 Hz, 2H), 3.38(s, 3H), 1.41(t, J = 7 Hz, 3H).

The 4-Bromo-2-methanesulfonyl-benzoic acid ethyl ester (16.3 g, 53 mmol) was weighed into a flask with 21 g of bis(pinacolato)diboron, 19 g of potassium acetate, 5 g of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dicloromethane adduct, and 150 mL of DMSO. The resulting suspension was heated at 80-85 °C for 20 h then was diluted with 200 mL of water, 200 mL of ethyl acetate, and the reaction mixture was filtered through celite to remove solids. The filtrate was transferred to a separatory funnel and the aqueous phase was separated and washed with ethyl acetate. The ethyl acetate washings were combined, washed with brine, were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 40% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo* affording the product as a colorless solid, yield: 12.65 g (67%). ^{1}H-NMR (400MHz, $CDCl_3$): δ 8.52(s, 1H), 8.08(d, J = 8 Hz, 1H), 7.65(d, J = 8 Hz, 1H), 4.45(q, J = 7 Hz, 2H), 3.33(s, 3H), 1.42(t, J = 7 Hz, 3H), 1.35(s, 12H).

Example 24

Preparation of (2-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol



a) $LiBH_4$, THF, 85 °C; b) MCPBA, CH_2C_2, 25 °C; c) Bis(pinacolato)diboron, Pd(dppf), KOAc, DMSO, 100 °C.

The 4-Bromo-2-methanesulfonyl-benzoic acid ethyl ester was prepared as described in Example 23. Into a 1 L flask was weighed 27.5 g of ester (99.9 mmol) and 150 mL of THF. A solution of 2.0 M $LiBH_4$ in THF (50 mL, 100 mmol) was then added and the reaction was heated to 80-85 °C where it remained for 23h. The reaction was then removed from heat and was cooled in an ice bath as it

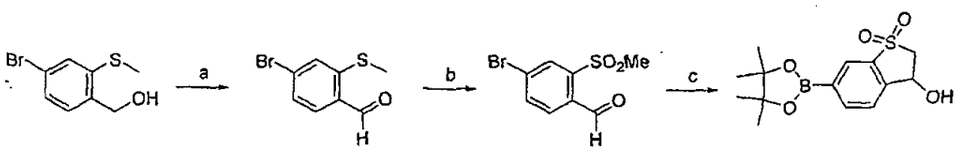
was quenched by addition of acetone. The reaction was then concentrated *in vacuo* and was washed into a separatory funnel with ethyl acetate and 1 M HCl. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and concentrated *in vacuo*. The intermediate (4-Bromo-2-methylsulfanyl-phenyl)-methanol was recovered as a colorless oil that solidified on standing, yield: 25.5 g (100+%). ^1H NMR (400MHz, $CDCl_3$): δ 7.24-7.34(m, 3H), 4.69(s, 2H), 2.50(s, 3H).

The alcohol was then dissolved in 250 mL of dichloromethane, was cooled to 0-3 °C in an ice bath, and 44 g of 3-chloroperbenzoic acid (77% max., Aldrich) was added portionwise. The reaction was then allowed to warm to room temperature where it remained for 22 h. The reaction was then concentrated *in vacuo* to remove dichloromethane and the residue was washed into a separatory funnel with ethyl acetate and 1 M NaOH. The ethyl acetate was separated, washed with 1 M NaOH, was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 100% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo* to afford the intermediate (4-Bromo-2-methanesulfonyl-phenyl)-methanol as a colorless, semi-crystalline solid, yield: 17.13 g (65%). ^1H NMR (400MHz, $CDCl_3$): δ 8.18(s, 1H), 7.77(d, J = 8 Hz, 1H), 7.46(d, J = 8 Hz, 1H), 4.92(s, 2H), 3.19(s, 3H), 2.94(br s, 1H).

Into a 1 L flask was weighed 17.13 g of bromide, 25 g of bis(pinacolato)diboron, 5.0 g of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dicloromethane adduct, 23 g of potassium acetate, and 175 mL of DMSO. The resulting suspension was heated at 98-102 °C for 18 h then was diluted with 200 mL of ethyl acetate and 200 mL of water. The resulting suspension was filtered through celite to remove solids and the filtrate was transferred to a separatory funnel. The aqueous phase was separated and washed with ethyl acetate. The ethyl acetate washings were combined, washed with brine, were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 40% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo*. The partially purified product was dissolved in dichloromethane and was precipitated with hexanes. The [2-Methanesulfonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanol was recovered as an off-white powder, yield: 8.78 g (43%). ^1H NMR (400MHz, $CDCl_3$): δ 8.45(s, 1H), 8.04(d, J = 8 Hz, 1H), 7.57(d, J = 8 Hz, 1H), 4.96(s, 1H), 3.17(s, 3H), 1.35(s, 6H), 1.24(s, 6H).

Example 25

Preparation of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide



a) DMSO, oxalyl chloride, CH_2C_2, -78 °C; b) MCPBA, CH_2C_2, 25 °C; c) Bis(pinacolato)diboron, Pd(dppf), KOAc, DMSO, 100 °C.

The (4-Bromo-2-methylsulfanyl-phenyl)-methanol was prepared as described in Example 24. Into a 500 mL flask was placed 220 mL of dichloromethane and 5.66 mL of oxalyl chloride under nitrogen. The solution was cooled to -70 to -78 °C and 9.80 mL of DMSO was added dropwise. The resulting suspension was stirred at -78 °C for 15 minutes. A solution of alcohol (10.0 g, 42.9 mmol) in 30 mL of dichloromethane was prepared and was added to the suspension via cannula. The reaction was stirred at -78 °C for 0.5 h then 30 mL of triethylamine was added via syringe. The reaction was stirred at -78 °C for 30 minutes then was quenched by addition of saturated ammonium chloride. The mixture was washed into a separatory funnel with added water and dichloromethane. The dichloromethane was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 20% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo* to afford the product as a lemon yellow solid, yield: 6.78 g (88% based on recovered starting material). ^{1}H NMR (400MHz, $CDCl_3$): δ 10.19(s, 1H), 7.65(d, J = 8 Hz, 1H), 7.40-7.45(m, 2H), 2.50(s, 3H).

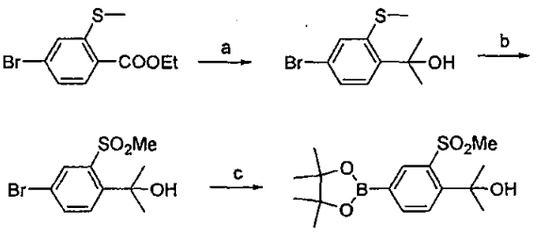
Into a 250 mL flask was weighed 6.78 g (25.8 mmol) of aldehyde and 60 mL of dichloromethane. The reaction was cooled to 0-3 °C in an ice bath and 10 g of MCPBA (77% max., Aldrich) was added portionwise. The reaction was alowed to warm to room temperature where it remained for 21 h. The reaction was then concentrated *in vacuo* to remove dichloromethane and was washed into a separatory funnel with ethyl acetate and 1 M NaOH. The ethyl acetate was separated, washed with 1.0 M NaOH, brine, was dried (Na_2SO_4), and was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography chromatography (Biotage, 45 x 150 mm SiO_2, gradient elution from 100% hexanes to 20% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo* to afford the product as a colorless solid, yield: 5.32 g (89%). ^{1}H NMR (400MHz, $CDCl_3$): δ 10.71(s, 1H), 8.30(s, 1H), 7.95(s, 2H), 3.29(s, 3H).

Into a 250 mL flask was weighed 5.32 g (20.2 mmol) of aldehyde, 7.13 g of potassium acetate, 7.85 g of bis(pinacolato)diboron, 1.88 g of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dicloromethane adduct, and 55 mL of DMSO. The resulting suspension was heated at 98-102 °C for 20 h then was diluted with 100 mL of ethyl acetate and 100 mL of water. The resulting suspension was filtered through celite to remove solids and the filtrate was transferred to a separatory funnel. The

aqueous phase was separated and washed with ethyl acetate. The ethyl acetate washings were combined, washed with brine, were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 40% ethyl acetate over 0.5 h). Appropriate fractions were combined and concentrated *in vacuo*. The partially purified product was dissolved in dichloromethane and was precipitated with hexanes. The 1,1-Dioxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-1H-1λ*6*-benzo[b] thiophen-3-ol was recovered as a tan powder, yield: 1.88 g (30%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.21(s, 1H), 8.08(d, J = 8 Hz, 1H), 7.64(d, J = 8 Hz, 1H), 5.49(m, 1H), 3.80(dd, J = 7, 13 Hz, 1H), 3.45(dd, J = 5, 13 Hz, 1H), 2.79(d, J = 8 Hz, 1H), 1.34(s, 12H).

Example 26

Preparation of 2-(2-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol



a) MeMgBr, THF, -78 °C; b) MCPBA, CH_2C_2, 50 °C; c) Bis(pinacolato)diboron, Pd(dppf), KOAc, DMSO, 100 °C.

The 4-Bromo-2-methanesulfonyl-benzoic acid ethyl ester was prepared as described in Example 25. Into a 500 mL flask was weighed 10.2 g (37.1 mmol) of ester and 100 mL of anhydrous THF. The resulting solution was cooled to -78 °C and 80 mL of 1.4 M MeMgBr in THF (Aldrich) was added portionwise. The reaction was allowed to warm to room temperature where it remained for 3 h. The reaction was then quenched by addition of saturated ammonium chloride and the mixture was washed into a separatory funnel with ethyl acetate and saturated ammonium chloride. The ethyl acetate was separated, washed with brine, was dried (Na_2SO_4), and concentrated *in vacuo*. The intermediate 2-(4-Bromo-2-methylsulfanyl-phenyl)-propan-2-ol was carried into the subsequent step without additional purification.

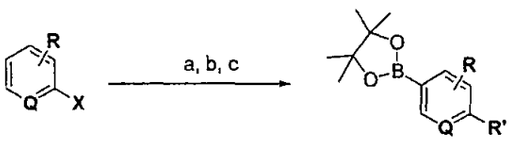
The crude alcohol was dissolved in 100 mL of dichloromethane, was cooled to 0-3 °C in an ice bath, and 20 g of MCPBA (77% max., Aldrich) was added portionwise. The reaction was then removed to an oil bath where it was heated at ~50 °C for 18 h. The reaction was then cooled and concentrated *in vacuo* to remove dichloromethane. The residue was washed into a separatory funnel with ethyl acetate and 1.0 M NaOH. The ethyl acetate was separated, washed with 1.0 M NaOH, brine,

was dried (Na2SO4), and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage 45 x 150 mm SiO_2, gradient elution from 100% hexanes to 40% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo* affording the intermediate 2-(4-Bromo-2-methanesulfonyl-phenyl)-propan-2-ol as a colorless solid, yield: 10.02 g (92% for both steps). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.33(s, 1H), 7.68(d, J = 8 Hz, 1H), 7.33(d, J = 8 Hz, 1H), 3.41(s, 3H), 1.76(s, 1H), 1.69(s, 6H).

Into a 500 mL flask was weighed 9.88 g (33.7 mmol) of bromide, 12 g of potassium acetate, 13.1 g of bis)pinacolato)diboron, 3.0 g of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dicloromethane adduct, and 90 mL of DMSO. The resulting suspension was heated at 98-102 °C for 20 h then was diluted with 200 mL of ethyl acetate and 200 mL of water. The resulting suspension was filtered through celite to remove solids and the filtrate was transferred to a separatory funnel. The aqueous phase was separated and washed with ethyl acetate. The ethyl acetate washings were combined, washed with brine, were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Biotage, 65 x 200 mm SiO_2, gradient elution from 100% hexanes to 100% ethyl acetate over 1 h). Appropriate fractions were combined and concentrated *in vacuo* affording the 2-[2-Methanesulfonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propan-2-ol as a gray solid, yield: 10.0 g (87%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.61(s, 1H), 7.96(d, J = 8 Hz, 1H), 7.45(d, J = 8 Hz, 1H), 3.39(s, 3H), 1.70(s, 6H), 1.34(s, 12H).

Several different boronates can by synthesized by the general methods outlined in Scheme 18 and exemplified in Example 27. A suitable aromatic substrate, such as a 2-halopyridine, can react to produce an intermediate with an '*directing*' group attached. Such a system can then be halogenated to afford a *para*-disposed halogen. Such a system can then be converted to a boronate using methods such as those described below. Alternatively, several commercially available intermediates could be used such as 2,4-Dibromo-3-methylpyridine, 4-Bromo-2-chlorpyrimidine, and several substituted benzene rings.

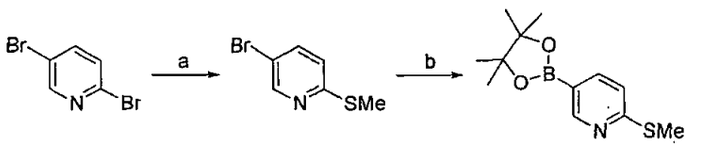
Scheme 18



Q = Used to identify any aromatic ring system that can be suitably functionalized as would be readily apparent to one skilled in the art.
X = halogen or prexisting 'directing' group
R' = 'directing group'
R = any suitable functionality that will not interfere with the directing effect of the R' group

Example 27

Preparation of 2-(methylthio)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



Reaction condition a) NaSMe, DMF, 160 °C; b) Bis(pinacolato)diboron, Pd(dppf), KOAc, DMSO, 80 °C.

2,5-Dibromo-pyridine (3.0g, 12.7mmol) and sodium thiomethoxide (0.84g, 12mmol) were dissolved in 18ml anhydrous *N, N*-dimethylformamide. The mixture was heated at 160^{0}C under nitrogen for 6 hrs. After cooling to room temperature, water and ethyl acetate were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate several times. The combined extract was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (0→6% EtOAC/Hexane) to give 5-Bromo-2-methylsulfanyl-pyridine as a white solid (2.18g, 84% yield). 1H-NMR (400MHz, $CDCl_3$): δ 2.55 (s, 3H), 7.09 (dd, 1H, *J*=0.7, *J*=8.6), 7.59 (dd, 1H, J=2.4, *J*=8.6), 8.50 (m, 1H).

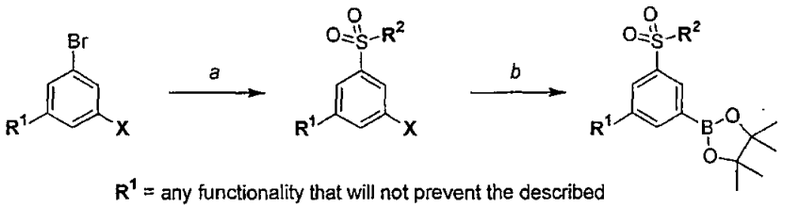
Palladium catalyst ([1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1), 167mg, 0.21mmol), potassium acetate (1.81g, 18.5mmol, Aldrich), and bis(pinacolato)diboron (1.56g, 6.1mmol) were placed into a vial and degassed with stream of nitrogen for 20min. In a separate vial, 5-bromo-2-methylsulfanylpyridine (no. (2)) (836mg, 4.1mmol) was dissolved in 8ml anhydrous DMSO and degassed with stream of nitrogen for 20min. This DMSO solution was added to the "catalyst" vial, and then heated at 80^{0}C overnight. After cooling to room temperature, water and ethyl acetate were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10→30% EtOAC/Hexane, 025% Et_3N in hexane) to give the 2-Methylsulfanyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine as a colorless oil (1.00g, 97% yield). 1H NMR (400MHz, $CDCl_3$): δ 1.35 (s, 12H), 2.58 (s, 3H), 7.16 (dd, 1H, *J*=1.0, *J*=8.0), 7.83 (dd, 1H, *J*=1.8, *J*=8.0), 8.50 (dd, 1H, *J*=1.7, *J*=1.0)

In a manner similar to that stated the following examples of the invention were prepared by substituting an appropriate reagent.

- 2-Methylsulfanyl-3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine. 1H-NMR (400MHz, $CDCl_3$): δ 1.35 (s, 12H), 2.24 (s, 3H), 2.59 (s, 3H), 7.64 (d, *J*=0.8, 1H,), 8.63 (d, *J*=1.0, 1H).

- 2-Ethylsulfanyl-3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine. 1H-NMR (400MHz, $CDCl_3$): δ 1.35 (s, 12H), 1.38 (t, *J*=7.4, 3H), 2.22 (s, 3H), 3.23 (q, *J*=7.4, 2H), 7.64 (d, *J*=0.8, 1H,), 8.61 (d, *J*=1.0, 1H). MS (ES): 280.2, 282.1 $[M+H]^+$.

Scheme 19



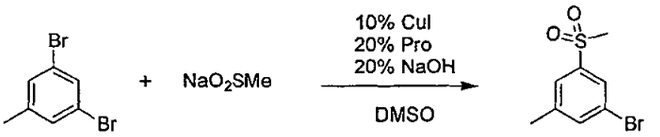
R^1 = any functionality that will not prevent the described chemistry from occuring
R^2 = alkyl, aryl, or other appropriate attachments
X = halogen

a) NaO_2SR^2, 10 mol% CuI, 20 mol% proline, 20 mol% NaOH, DMSO, μW 210°C; b) bis(pinacolato)-diboron, KOAc, $Cl_2Pd(dppf)$, DMSO, μW 130°C.

In general, compounds of formula 1,3- (or 3,5-) disubstitued aryl systems can be prepared as depicted in Scheme 19. A dibromoarene can react with a sulfinic acid sodium salt (NaO_2SR^2) in the presence of catalytic copper iodide and the sodium salt of proline at elevated temperature to give the corresponding sulfone. This intermediate then can be converted into the corresponding arylboronate or boronic acid under standard conditions apparent to one skilled in the art.

Example 28

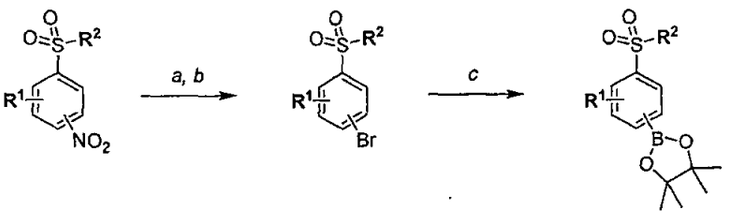
Preparation of 1-bromo-3-methanesulfonyl-5-methyl-benzene



A mixture of 3,5-dibromotoluene (2.0 g, 8.0 mmol), sodium methanesulfinate (0.92 g, 9.0 mmol), copper(I) iodide (152 mg, 0.8 mmol), proline (0.18 g, 1.6 mmol) and sodium hydroxide (64 mg, 1.6 mmol) in DSMO (15 mL, anhyd) was heated in a microwave unit (Biotage Initiator™) at 210°C for 20 min. The reaction was repeated two more times and the reaction mixtures were combined, diluted with H_2O and extracted with EtOAc. The combined extracts were washed with H_2O and brine, then dried (Na_2SO_4), concentrated and purified by chromatography (silica, EtOAc/Hex, 0:100 to 40:60) to give the title compound (1.2 g, 20% combined yield) as a white solid. GC-MS(EI): 248, 250.

2-(3-Methanesulfonyl-5-methyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane was prepared from 1-bromo-3-methanesulfonyl-5-methyl-benzene in a similar manner as other boronate syntheses previously described.

Scheme 20.

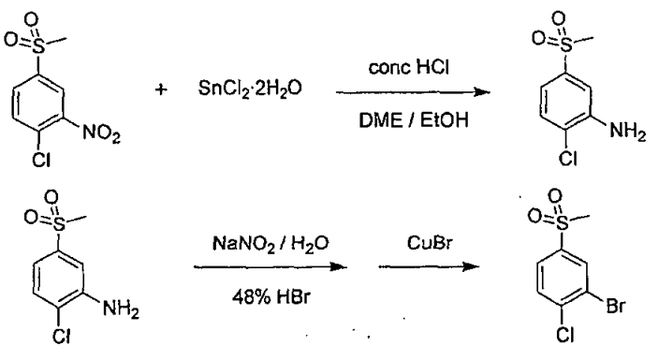


a) $SnCl_2 \cdot 2H_2O$, conc HCl, DME/EtOH; b) $NaNO_2$, 48% HBr, H_2O; then CuBr; c) bis(pinacolato)-diboron, KOAc, $Cl_2Pd(dppf)$, DMSO, μW 130°C.

In general, several different boronates can be prepared as depicted in Scheme 20 A nitroarene can be reduced under standard conditions, such as with tin chloride, to yield the corresponding arylamine, which can be converted to the corresponding bromearene via the Sandmeyer reaction. Aryl bromides can easily be converted to boronates using conditions apparent to one skilled in the art.

Example 29

Preparation of 2-bromo-1-chloro-4-methanesulfonyl-benzene



To a stirred mixture of 1-chloro-4-methanesulfonyl-2-nitrobenzene (5.2 g, 22 mmol) and 3:4 DME/EtOH (77 mL) was added dropwise a solution of tin(II) chloride dihydrate (15.3 g, 68 mmol) in 9N HCl (36 mL). After 3 h the reaction mixture was poured onto ice and treated with 10% NaOH until pH 11 had been achieved. The resulting mixture was extracted with EtOAc (4 x 75 mL) and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated to afford the title compound (4.5 q, quant) as a white solid, which was used without purification in the next step. GC-MS(EI): 205.

To a slurry of 2-chloro-5-methanesulfonyl-aniline (4.50 g, 21.9 mmol) in 48% HBr (12 mL) at 0°C was added dropwise a solution of sodium nitrite (2.28 g, 33 mmol) in H_2O (8 mL) at such a rate that the temperature never exceeds 5°C. The resulting yellow mixture was allowed to stir 20 min at 0°C and then charged with copper(I) bromide (3.3 g, 23 mmol). After 30 min the resulting mixture was extracted with EtOAc (2 x 100 mL) and the combined extracts were washed successively with satd NH_4Cl, 3N

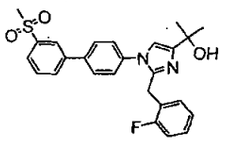
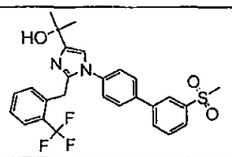
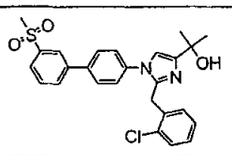
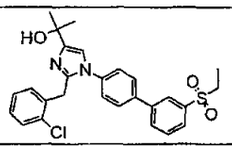
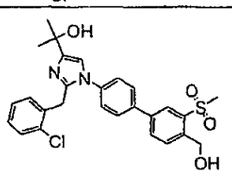
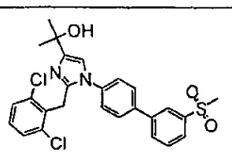
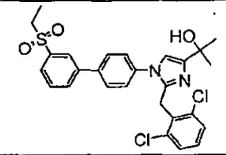
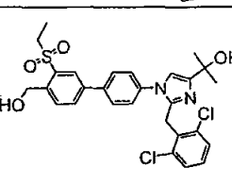
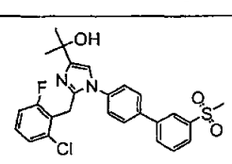
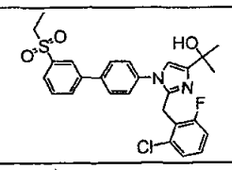
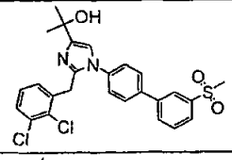
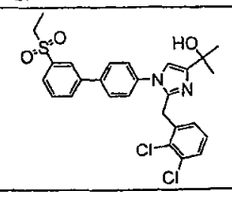
HCl and brine, then dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by chromatography (silica, EtOAc/Hex, 0:100 to 50:50) to give the title compound (4.92 g, 83%) as a white solid. GC-MS(EI): 268, 270.

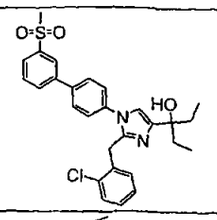
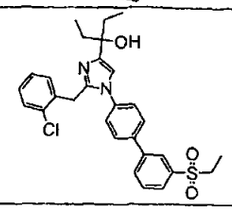
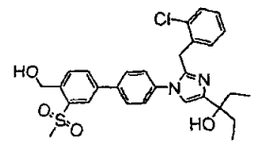
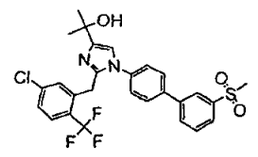
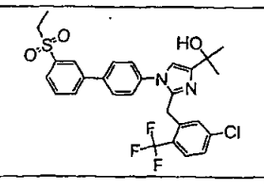
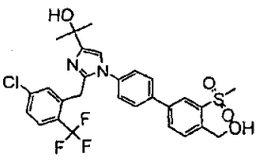
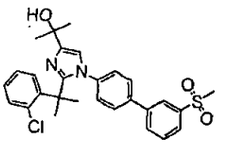
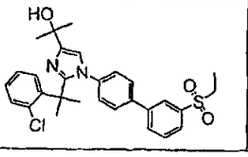
2-(2-Chloro-5-methanesulfonyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane was prepared from 2-bromo-1-chloro-4-methanesulfonyl-benzene in a similar manner as other boronate syntheses previously described.

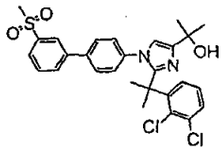
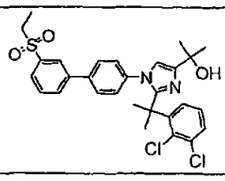
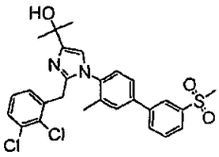
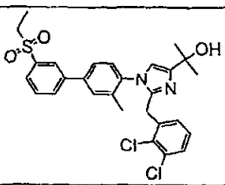
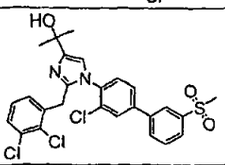
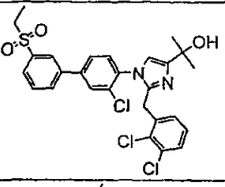
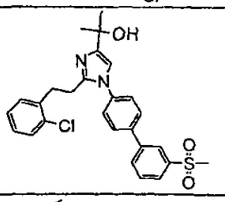
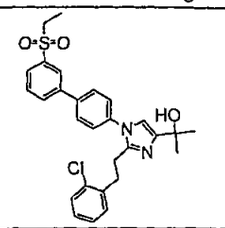
Example 30

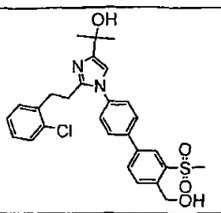
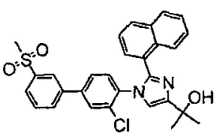
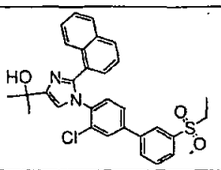
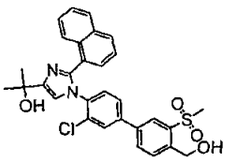
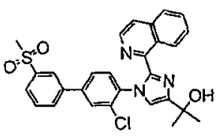
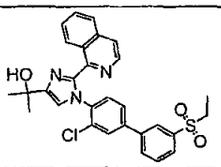
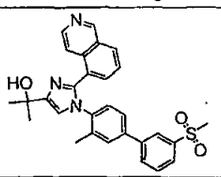
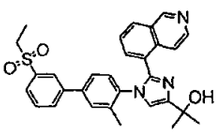
The following compounds of the invention, in Tables 1 and 2, were prepared according to one of the previous Example 1-29.

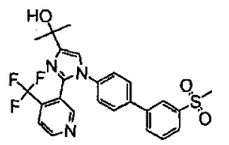
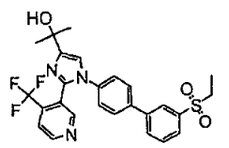
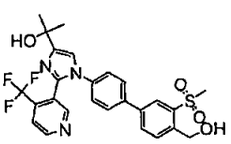
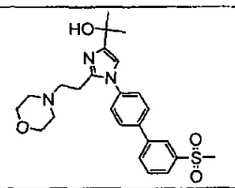
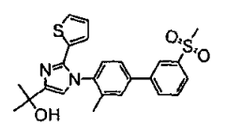
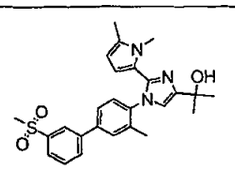
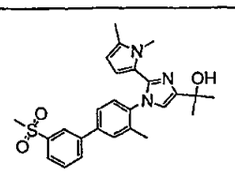
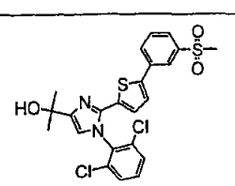
Table 1

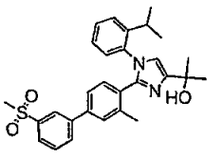
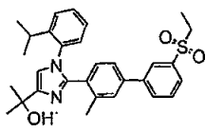
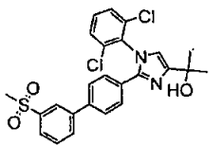
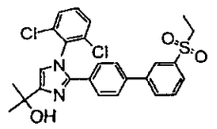
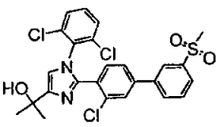
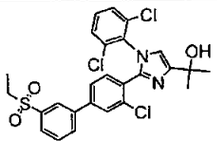
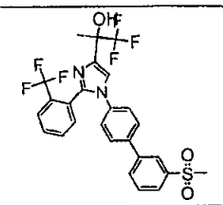
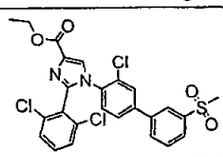
Cpd #	Structure	Name
1		2-(2-(2-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
2		2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)benzyl)-1H-imidazol-4-yl)propan-2-ol;
3		2-(2-(2-chlorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
4		2-(2-(2-chlorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
5		2-(2-(2-chlorobenzyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
6		2-(2-(2,6-dichlorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
7		2-(2-(2,6-dichlorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
8		2-(2-(2,6-dichlorobenzyl)-1-(3'-(ethylsulfonyl)-4'-(hydroxymethyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
9		2-(2-(2-chloro-6-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
10		2-(2-(2-chloro-6-fluorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
11		2-(2-(2,3-dichlorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
12		2-(2-(2,3-dichlorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

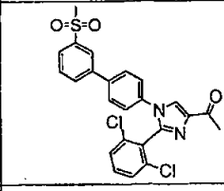
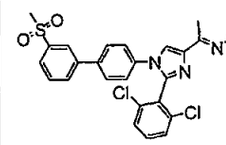
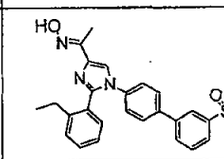
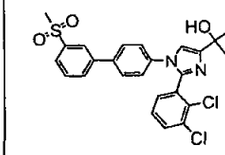
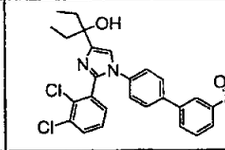
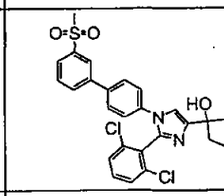
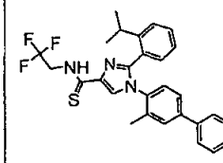
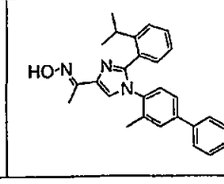
Cpd #	Structure	Name
13		3-(2-(2-chlorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;
14		3-(2-(2-chlorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;
15		3-(2-(2-chlorobenzyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;
16		2-(2-(5-chloro-2-(trifluoromethyl)benzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
17		2-(2-(5-chloro-2-(trifluoromethyl)benzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
18		2-(2-(5-chloro-2-(trifluoromethyl)benzyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
19		2-(2-(2-(2-chlorophenyl)propan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
20		2-(2-(2-(2-chlorophenyl)propan-2-yl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

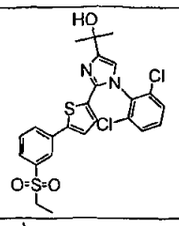
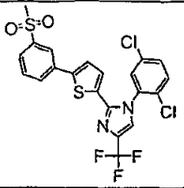
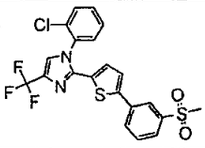
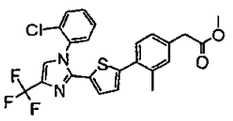
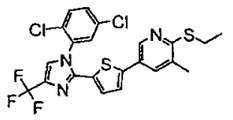
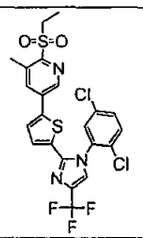
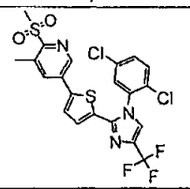
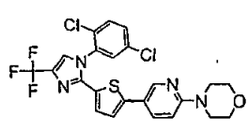
Cpd #	Structure	Name
21		2-(2-(2-(2,3-dichlorophenyl)propan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
22		2-(2-(2-(2,3-dichlorophenyl)propan-2-yl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
23		2-(2-(2,3-dichlorobenzyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
24		2-(2-(2,3-dichlorobenzyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
25		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol;
26		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol;
27		2-(2-(2-chlorophenethyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
28		2-(2-(2-chlorophenethyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

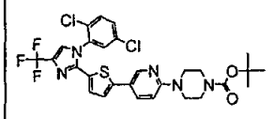
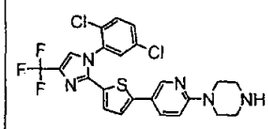
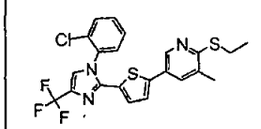
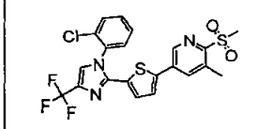
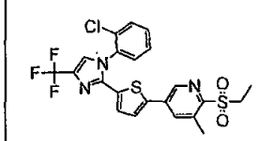
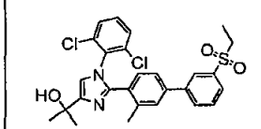
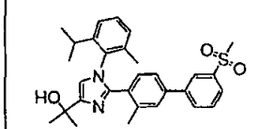
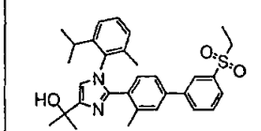
Cpd #	Structure	Name
29		2-(2-(2-chlorophenethyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
30		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(naphthalen-1-yl)-1H-imidazol-4-yl)propan-2-ol;
31		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(naphthalen-1-yl)-1H-imidazol-4-yl)propan-2-ol;
32		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(naphthalen-1-yl)-1H-imidazol-4-yl)propan-2-ol;
33		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(isoquinolin-1-yl)-1H-imidazol-4-yl)propan-2-ol;
34		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(isoquinolin-1-yl)-1H-imidazol-4-yl)propan-2-ol;
35		2-(2-(isoquinolin-5-yl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
36		2-(1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-2-(isoquinolin-5-yl)-1H-imidazol-4-yl)propan-2-ol;

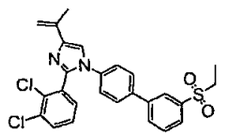
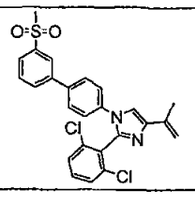
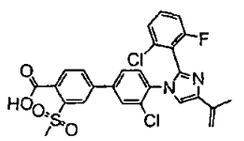
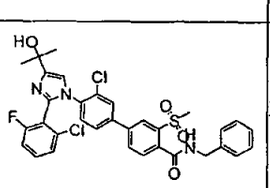
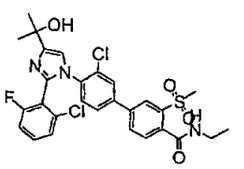
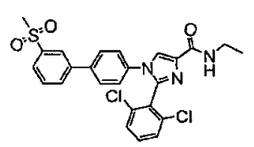
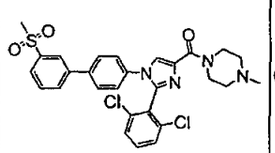
Cpd #	Structure	Name
37		2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(4-(trifluoromethyl)pyridin-3-yl)-1H-imidazol-4-yl)propan-2-ol;
38		2-(1-(3'-(ethylsulfonyl)biphenyl-4-yl)-2-(4-(trifluoromethyl)pyridin-3-yl)-1H-imidazol-4-yl)propan-2-ol;
39		2-(1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(4-(trifluoromethyl)pyridin-3-yl)-1H-imidazol-4-yl)propan-2-ol;
40		2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-morpholinoethyl)-1H-imidazol-4-yl)propan-2-ol;
41		2-(1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-2-(thiophen-2-yl)-1H-imidazol-4-yl)propan-2-ol;
42		2-(2-(1,5-dimethyl-1H-pyrrol-2-yl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
43		2-(2-(1,5-dimethyl-1H-pyrrol-2-yl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
44		2-(1-(2,6-dichlorophenyl)-2-(5-(3-(methylsulfonyl)phenyl)thiophen-2-yl)-1H-imidazol-4-yl)propan-2-ol;

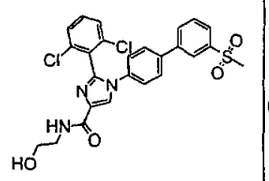
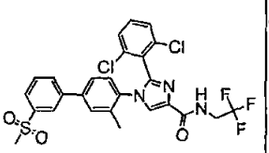
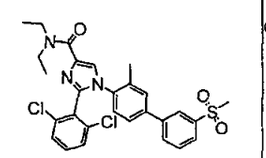
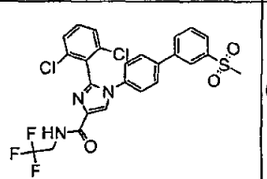
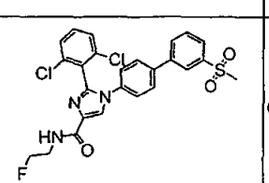
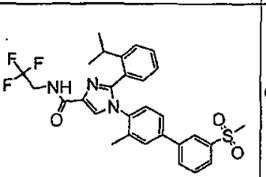
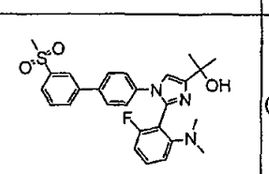
Cpd #	Structure	Name
61		2-(1-(2-isopropylphenyl)-2-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
62		2-(2-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol;
63		2-(1-(2,6-dichlorophenyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
64		2-(1-(2,6-dichlorophenyl)-2-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
65		2-(2-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
66		2-(2-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
67		1,1,1-trifluoro-2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
68		ethyl 1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxylate;

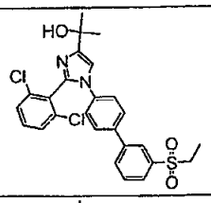
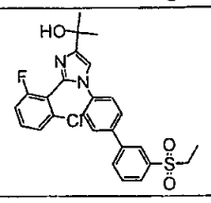
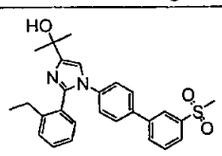
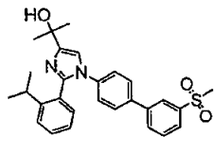
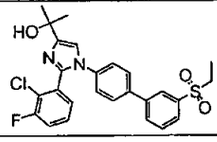
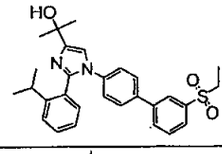
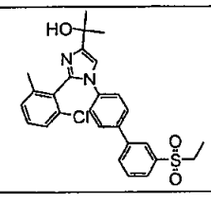
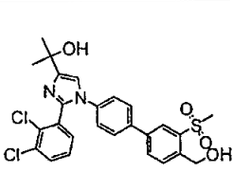
Cpd #	Structure	Name
69		1-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone;
70		(E)-1-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone oxime;
71		(E)-1-(2-(2-ethylphenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone oxime;
72		3-(2-(2,3-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;
73		3-(2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;
74		3-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)pentan-3-ol;
75		2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carbothioamide;
76		(E)-1-(2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)ethanone oxime;

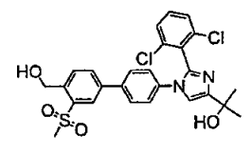
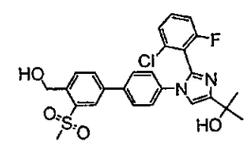
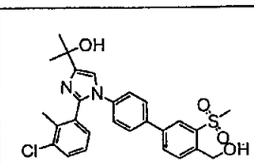
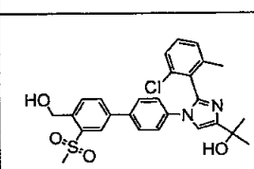
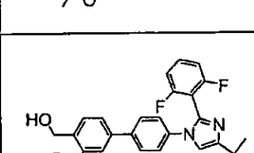
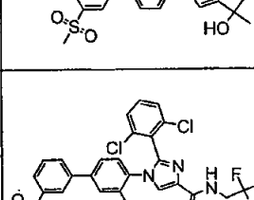
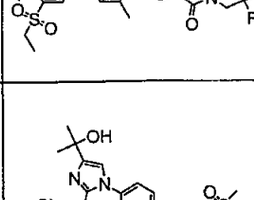
Cpd #	Structure	Name
45		2-(1-(2,6-dichlorophenyl)-2-(5-(3-(ethylsulfonyl)phenyl)thiophen-2-yl)-1H-imidazol-4-yl)propan-2-ol;
46		1-(2,5-dichlorophenyl)-2-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1H-imidazole;
47		1-(2-chlorophenyl)-2-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-4-(trifluoromethyl)-1H-imidazole;
48		methyl (4-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methylphenyl)acetate;
49		5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylthio)-3-methylpyridine;
50		5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylsulfonyl)-3-methylpyridine;
51		5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methyl-2-(methylsulfonyl)pyridine;
52		4-(5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}pyridin-2-yl)morpholine;

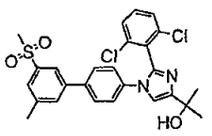
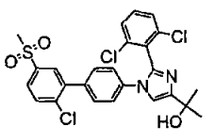
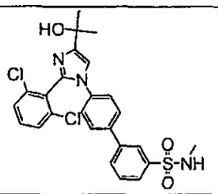
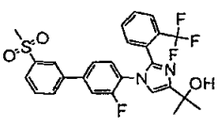
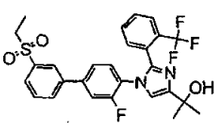
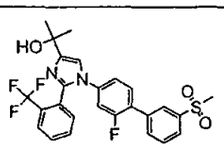
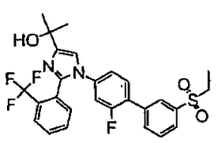
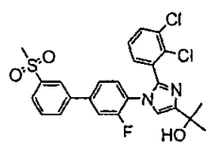
Cpd #	Structure	Name
53		1,1-dimethylethyl 4-(5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}pyridin-2-yl)piperazine-1-carboxylate;
54		1-(5-{5-[1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}pyridin-2-yl)piperazine;
55		5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylthio)-3-methylpyridine;
56		5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-3-methyl-2-(methylsulfonyl)pyridine;
57		5-{5-[1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl]-2-thienyl}-2-(ethylsulfonyl)-3-methylpyridine;
58		2-(1-(2,6-dichlorophenyl)-2-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
59		2-(1-(2-isopropyl-6-methylphenyl)-2-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
60		2-(2-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1-(2-isopropyl-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol;

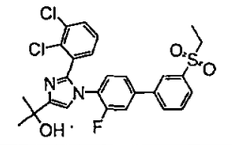
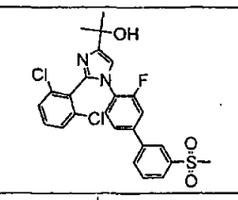
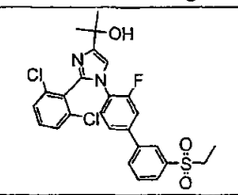
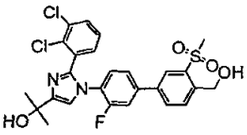
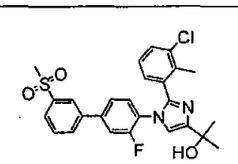
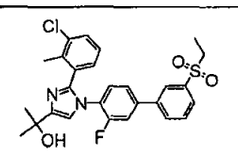
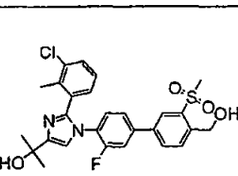
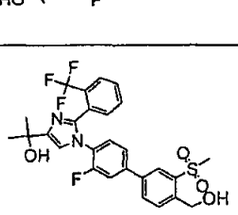
Cpd #	Structure	Name
77		2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-4-(prop-1-en-2-yl)-1H-imidazole;
78		2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-4-(prop-1-en-2-yl)-1H-imidazole;
79		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(prop-1-en-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxylic acid;
80		N-benzyl-3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxamide;
81		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-N-ethyl-3-(methylsulfonyl)biphenyl-4-carboxamide;
82		2-(2,6-dichlorophenyl)-N-ethyl-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide;
83		(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)(4-methylpiperazin-1-yl)methanone;

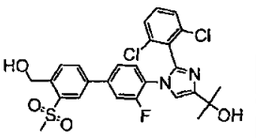
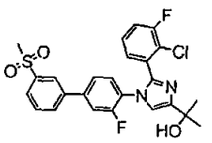
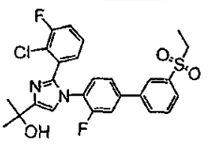
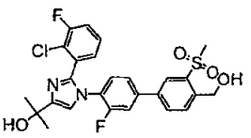
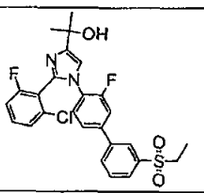
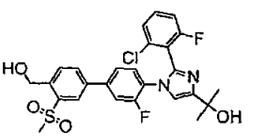
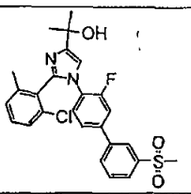
Cpd #	Structure	Name
84		2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide;
85		2-(2,6-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide;
86		2-(2,6-dichlorophenyl)-N,N-diethyl-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide
87		2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide;
88		2-(2,6-dichlorophenyl)-N-(2-fluoroethyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide;
89		2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide;
90		2-(2-(2-(dimethylamino)-6-fluorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

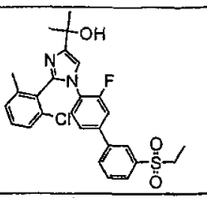
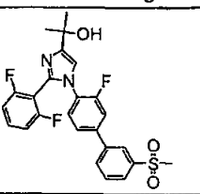
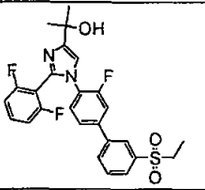
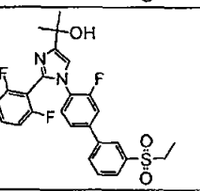
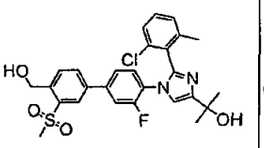
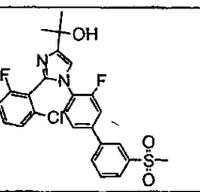
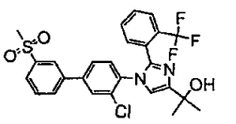
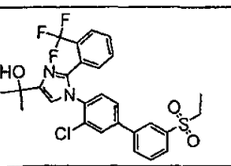
Cpd #	Structure	Name
91		2-(2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
92		2-(2-(2-chloro-6-fluorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
93		2-(2-(2-ethylphenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
94		2-(2-(2-isopropylphenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
95		2-(2-(2-chloro-3-fluorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
96		2-(1-(3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol;
97		2-(2-(2-chloro-6-methylphenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
98		2-(2-(2,3-dichlorophenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

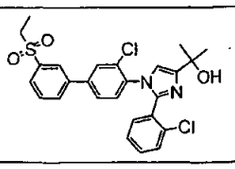
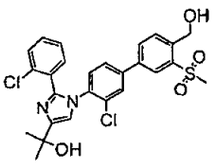
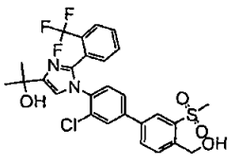
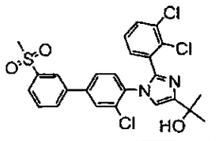
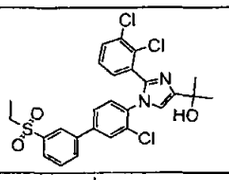
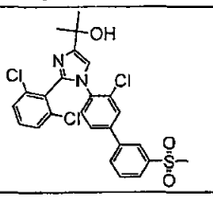
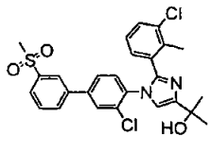
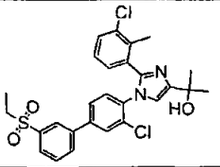
Cpd #	Structure	Name
99		2-(2-(2,6-dichlorophenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
100		2-(2-(2-chloro-6-fluorophenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
101		2-(2-(3-chloro-2-methylphenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
102		2-(2-(2-chloro-6-methylphenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
103		2-(2-(2,6-difluorophenyl)-1-(4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
104		2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide;
105		2-(2-(2,3-dichlorophenyl)-1-(4'-(2-hydroxypropan-2-yl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

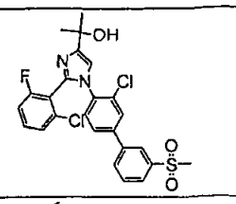
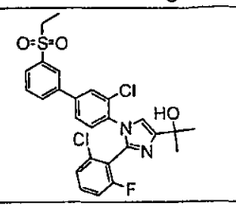
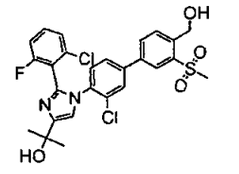
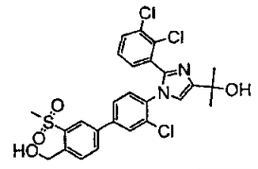
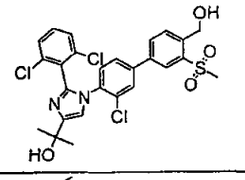
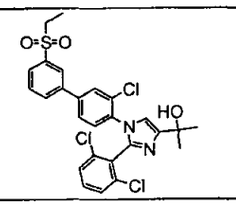
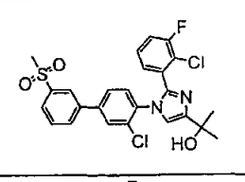
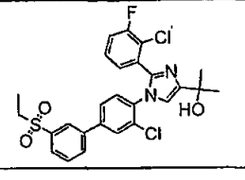
Cpd #	Structure	Name
106		2-(2-(2,6-dichlorophenyl)-1-(3'-methyl-5'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
107		2-(1-(2'-chloro-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
108		4'-(2-(2,6-dichlorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-N-methylbiphenyl-3-sulfonamide;
109		2-(1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
110		2-(1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
111		2-(1-(2-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
112		2-(1-(3'-(ethylsulfonyl)-2-fluorobiphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
113		2-(2-(2,3-dichlorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

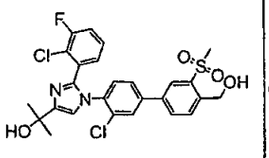
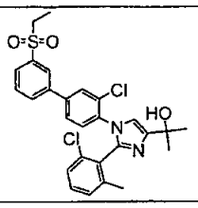
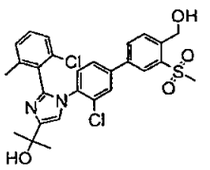
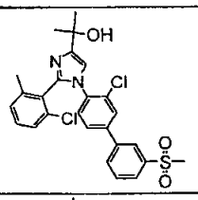
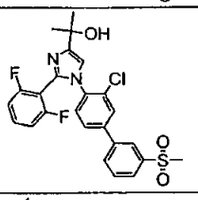
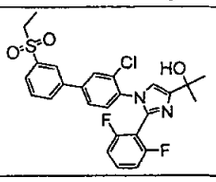
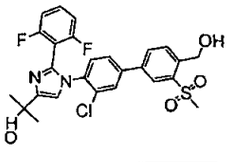
Cpd #	Structure	Name
114		2-(2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
115		2-(2-(2,6-dichlorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
116		2-(2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
117		2-(2-(2,3-dichlorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
118		2-(2-(3-chloro-2-methylphenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
119		2-(2-(3-chloro-2-methylphenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
120		2-(2-(3-chloro-2-methylphenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
121		2-(1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;

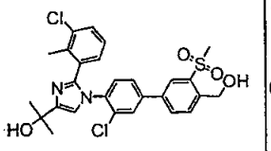
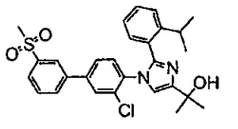
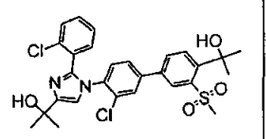
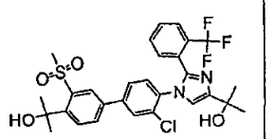
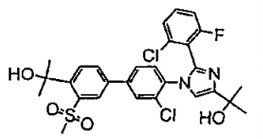
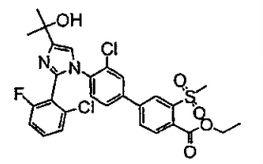
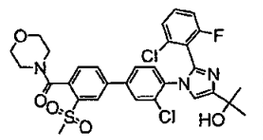
Cpd #	Structure	Name
122		2-(2-(2,6-dichlorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
123		2-(2-(2-chloro-3-fluorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
124		2-(2-(2-chloro-3-fluorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
125		2-(2-(2-chloro-3-fluorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
126		2-(2-(2-chloro-6-fluorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
127		2-(2-(2-chloro-6-fluorophenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
128		2-(2-(2-chloro-6-methylphenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

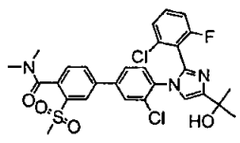
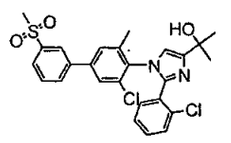
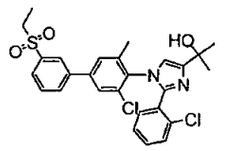
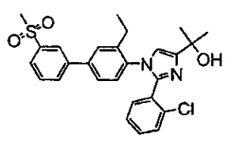
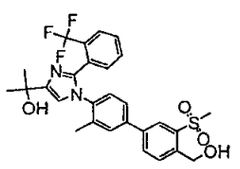
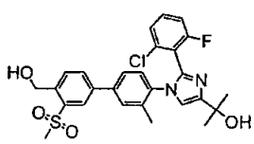
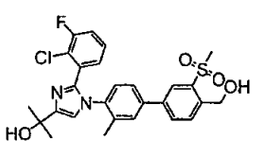
Cpd #	Structure	Name
129		2-(2-(2-chloro-6-methylphenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
130		2-(2-(2,6-difluorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
131		2-(2-(2,6-difluorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
132		2-(2-(2,6-difluorophenyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
133		2-(2-(2-chloro-6-methylphenyl)-1-(3-fluoro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
134		2-(2-(2-chloro-6-fluorophenyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
135		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
136		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;

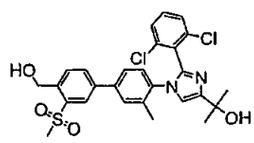
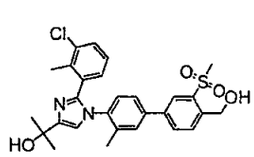
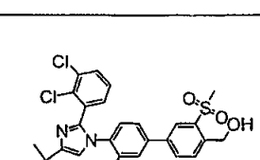
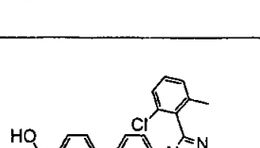
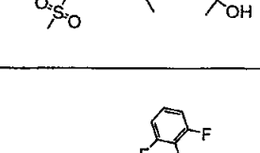
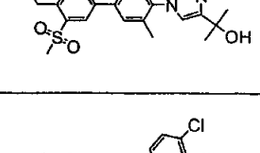
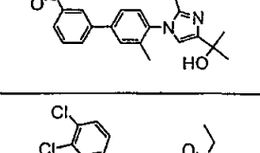
Cpd #	Structure	Name
137		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
138		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
139		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
140		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
141		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
142		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
143		2-(2-(3-chloro-2-methylphenyl)-1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
144		2-(2-(3-chloro-2-methylphenyl)-1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

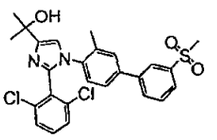
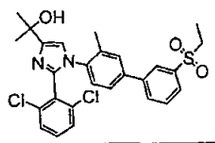
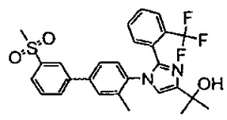
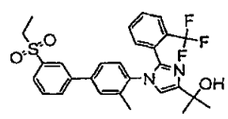
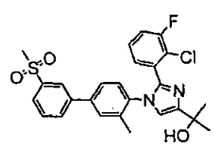
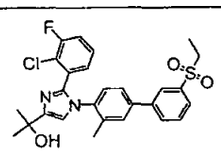
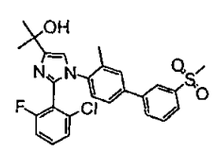
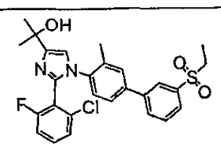
Cpd #	Structure	Name
145		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol;
146		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol;
147		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol;
148		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
149		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
150		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
151		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-3-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol;
152		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-chloro-3-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol;

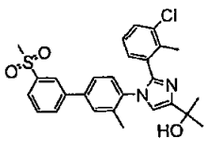
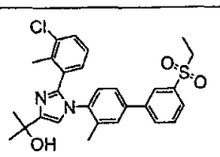
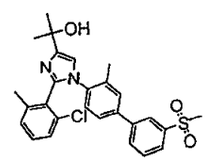
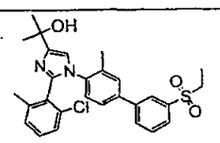
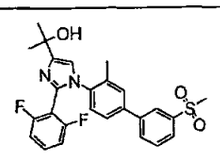
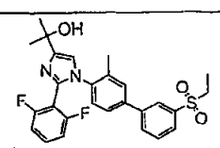
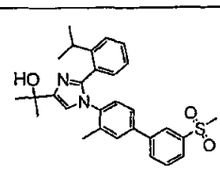
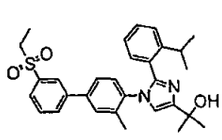
Cpd #	Structure	Name
153		2-(2-(2-chloro-3-fluorophenyl)-1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
154		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol;
155		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol;
156		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-methylphenyl)-1H-imidazol-4-yl)propan-2-ol;
157		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-difluorophenyl)-1H-imidazol-4-yl)propan-2-ol;
158		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-difluorophenyl)-1H-imidazol-4-yl)propan-2-ol;
159		2-(1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-difluorophenyl)-1H-imidazol-4-yl)propan-2-ol;

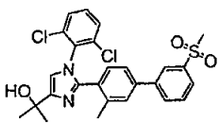
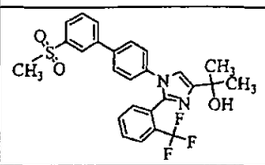
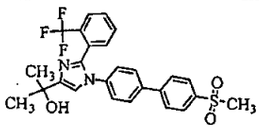
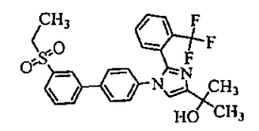
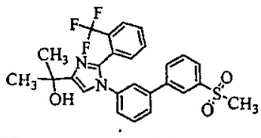
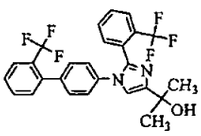
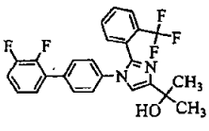
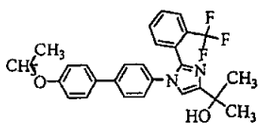
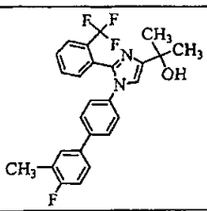
Cpd #	Structure	Name
160		2-(2-(3-chloro-2-methylphenyl)-1-(3-chloro-4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
161		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol;
162		2-(3'-chloro-4'-(2-(2-chlorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-yl)propan-2-ol;
163		2-(1-(3-chloro-4'-(2-hydroxypropan-2-yl)-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
164		2-(3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-yl)propan-2-ol;
165		ethyl 3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxylate;
166		(3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-yl)(morpholino)methanone;

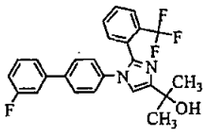
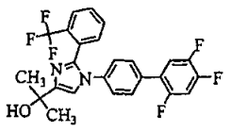
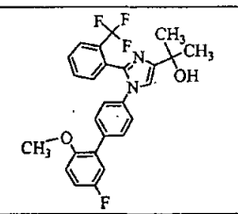
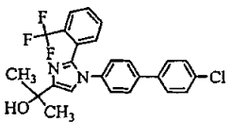
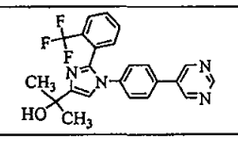
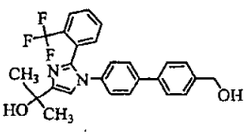
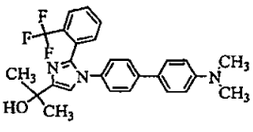
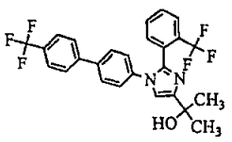
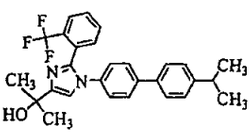
Cpd #	Structure	Name
167		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-N,N-dimethyl-3-(methylsulfonyl)biphenyl-4-carboxamide;
168		2-(1-(3-chloro-5-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
169		2-(1-(3-chloro-3'-(ethylsulfonyl)-5-methylbiphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl)propan-2-ol;
170		2-(2-(2-chlorophenyl)-1-(3-ethyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
171		2-(1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
172		2-(2-(2-chloro-6-fluorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
173		2-(2-(2-chloro-3-fluorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

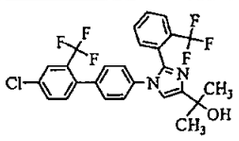
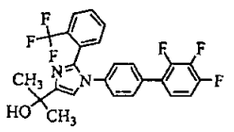
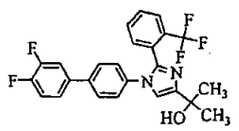
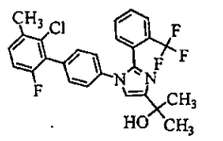
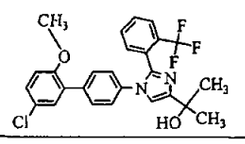
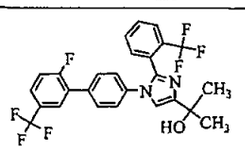
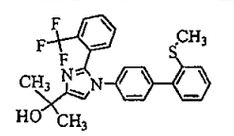
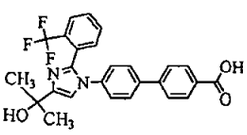
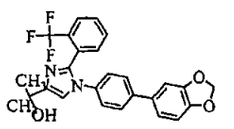
Cpd #	Structure	Name
174		2-(2-(2,6-dichlorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
175		2-(2-(3-chloro-2-methylphenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
176		2-(2-(2,3-dichlorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
177		2-(2-(2-chloro-6-methylphenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
178		2-(2-(2,6-difluorophenyl)-1-(4'-(hydroxymethyl)-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
179		2-(2-(2,3-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
180		2-(2-(2,3-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

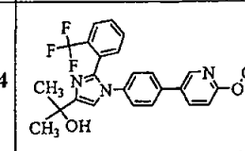
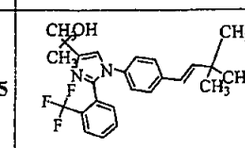
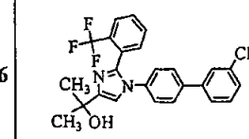
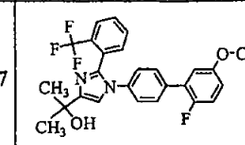
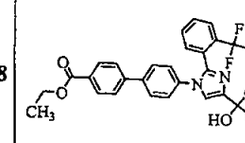
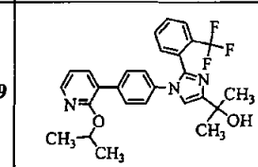
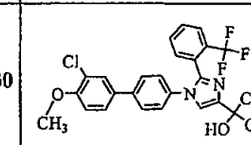
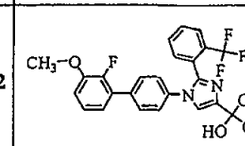
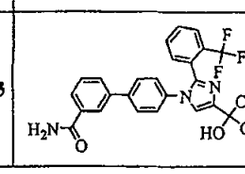
Cpd #	Structure	Name
181		2-(2-(2,6-dichlorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
182		2-(2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
183		2-(1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
184		2-(1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-2-(2-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)propan-2-ol;
185		2-(2-(2-chloro-3-fluorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
186		2-(2-(2-chloro-3-fluorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
187		2-(2-(2-chloro-6-fluorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
188		2-(2-(2-chloro-6-fluorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;

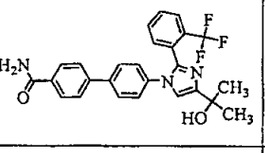
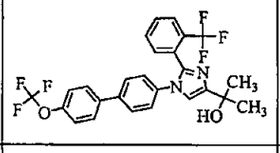
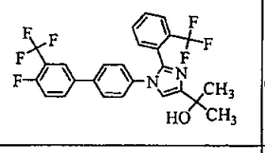
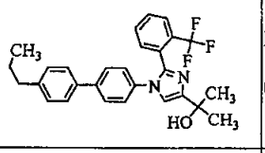
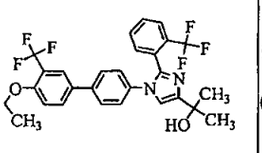
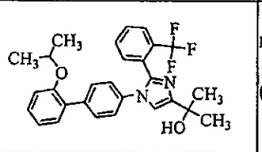
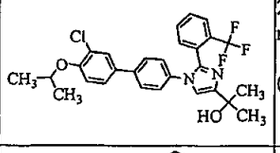
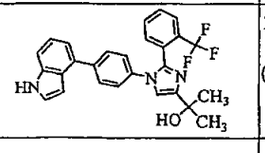
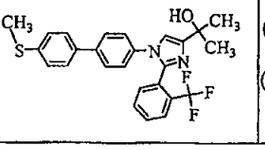
Cpd #	Structure	Name
189		2-(2-(3-chloro-2-methylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
190		2-(2-(3-chloro-2-methylphenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
191		2-(2-(2-chloro-6-methylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
192		2-(2-(2-chloro-6-methylphenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
193		2-(2-(2,6-difluorophenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
194		2-(2-(2,6-difluorophenyl)-1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
195		2-(2-(2-isopropylphenyl)-1-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
196		2-(1-(3'-(ethylsulfonyl)-3-methylbiphenyl-4-yl)-2-(2-isopropylphenyl)-1H-imidazol-4-yl)propan-2-ol;

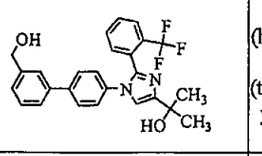
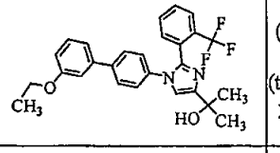
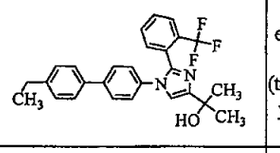
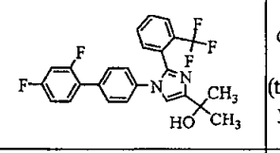
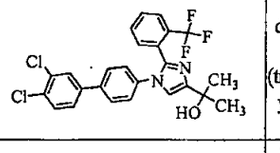
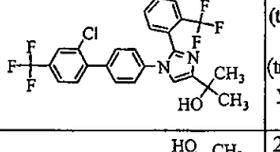
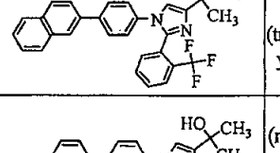
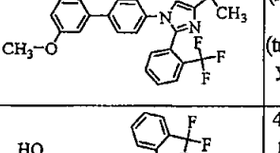
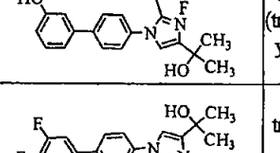
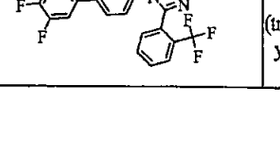
Cpd #	Structure	Name
197		2-(1-(2,6-dichlorophenyl)-2-(3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol;
198		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
199		2-{1-[4'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
200		2-{1-[3'-(ethylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
201		2-{1-[3'-(methylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
202		2-{1-[2'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
203		2-{1-(2',3'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
204		2-(1-{4'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
205		2-{1-(4'-fluoro-3'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

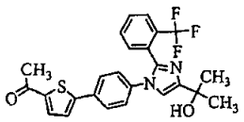
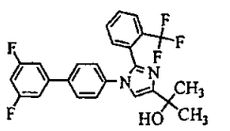
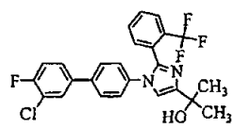
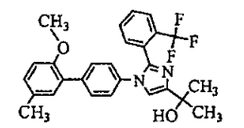
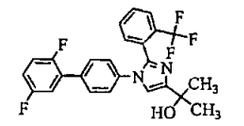
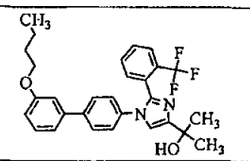
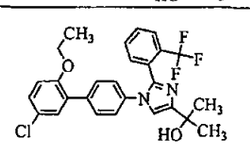
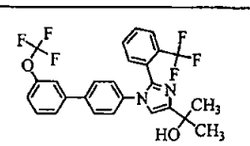
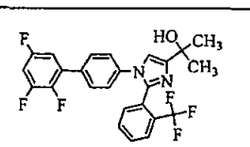
Cpd #	Structure	Name
206		2-{1-(3'-fluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
207		2-{1-(2',4',5'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
208		2-{1-[5'-fluoro-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
209		2-{1-(4'-chlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
210		2-{1-(4-pyrimidin-5-ylphenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
211		2-{1-[4'-(hydroxymethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
212		2-{1-[4'-(dimethylamino)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
213		2-{1-[4'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
214		2-{1-[4'-(1-methylethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

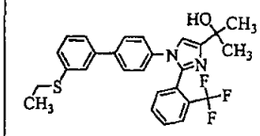
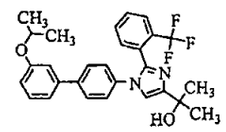
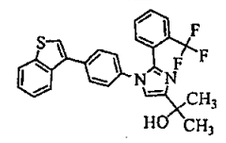
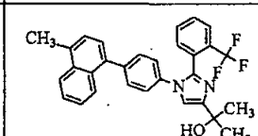
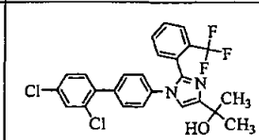
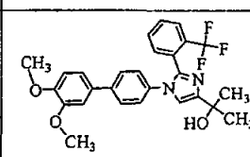
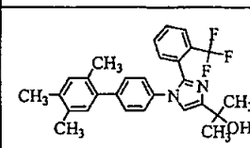
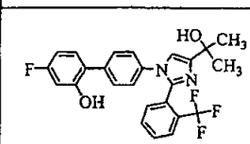
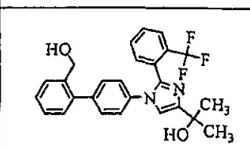
Cpd #	Structure	Name
215		2-{1-[4'-chloro-2'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
216		2-{1-(2',3',4'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
217		2-{1-(3',4'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
218		2-{1-(2'-chloro-6'-fluoro-3'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
219		2-{1-[5'-chloro-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
220		2-{1-[2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
221		2-{1-[2'-(methylthio)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
222		4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid;
223		2-{1-[4-(1,3-benzodioxol-5-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

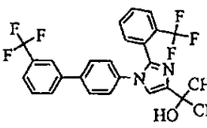
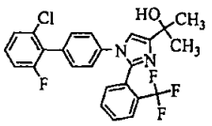
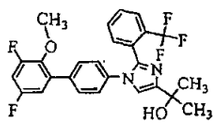
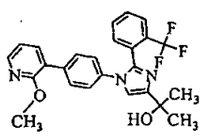
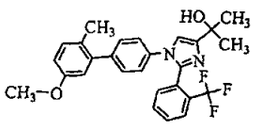
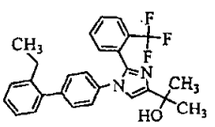
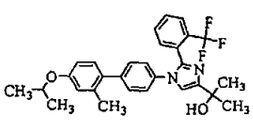
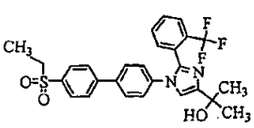
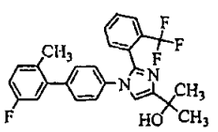
Cpd #	Structure	Name
224		2-(1-{4-[6-(methyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
225		2-(1-{4-[(1E)-3,3-dimethylbut-1-en-1-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
226		2-{1-(3'-chlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
227		2-{1-[2'-fluoro-5'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
228		ethyl 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylate;
229		2-{1-(4-{2-[(1-methylethyl)oxy]pyridin-3-yl}phenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
230		2-{1-[3'-chloro-4'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
232		2-{1-[2'-fluoro-3'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
233		4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;

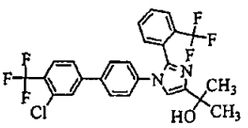
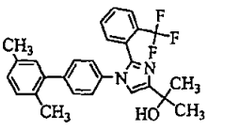
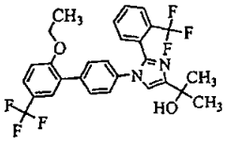
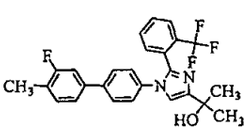
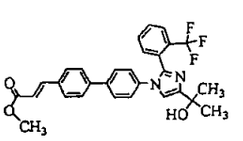
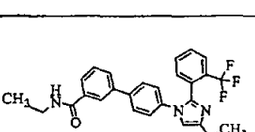
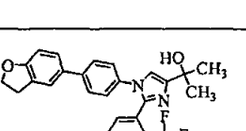
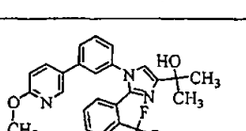
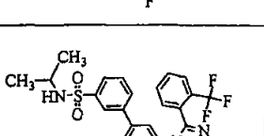
Cpd #	Structure	Name
234		4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxamide;
235		2-(1-{4'-[(trifluoromethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
236		2-{1-[4'-fluoro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
237		2-{1-(4'-propylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
238		2-{1-[4'-(ethyloxy)-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
239		2-(1-{2'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
240		2-(1-{3'-chloro-4'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
241		2-{1-[4-(1H-indol-4-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
242		2-{1-[4'-(methylthio)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

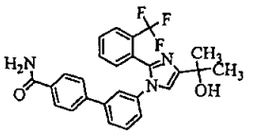
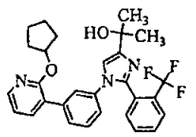
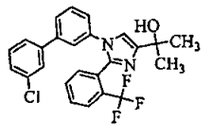
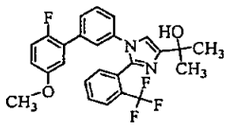
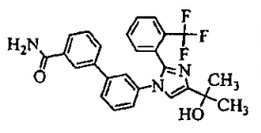
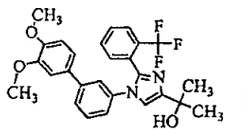
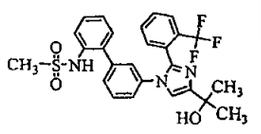
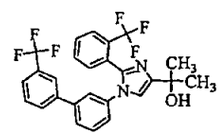
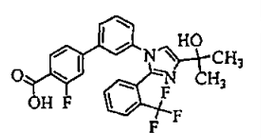
Cpd #	Structure	Name
243		2-{1-[3'-(hydroxymethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
244		2-{1-[3'-(ethyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
245		2-{1-(4'-ethylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
246		2-{1-(2',4'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
247		2-{1-(3',4'-dichlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
248		2-{1-[2'-chloro-4'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
249		2-{1-(4-naphthalen-2-ylphenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
250		2-{1-[3'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol
251		4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-ol;
252		2-{1-(3',4',5'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

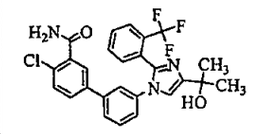
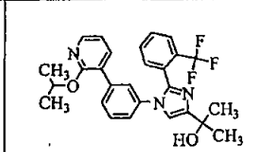
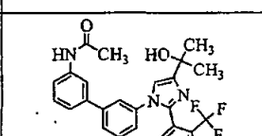
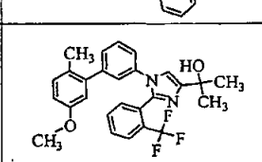
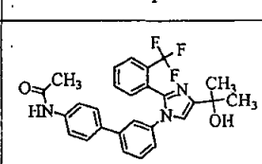
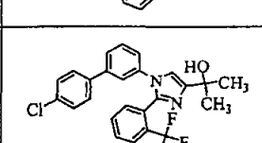
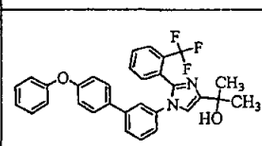
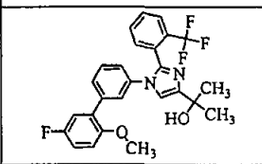
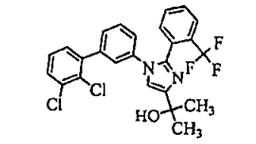
Cpd #	Structure	Name
253		1-[5-(4-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone;
254		2-{1-(3',5'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
255		2-{1-(3'-chloro-4'-fluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
256		2-{1-[5'-methyl-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
257		2-{1-(2',5'-difluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
258		2-{1-[3'-(butyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
259		2-{1-[5'-chloro-2'-(ethyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
260		2-(1-{3'-[(trifluoromethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
261		2-{1-(2',3',5'-trifluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

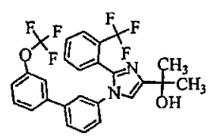
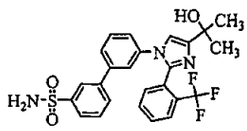
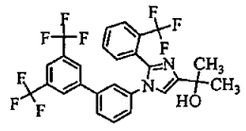
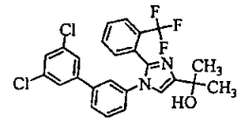
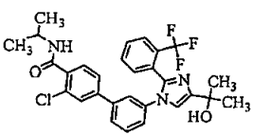
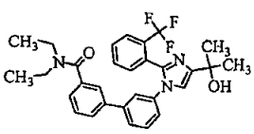
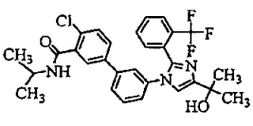
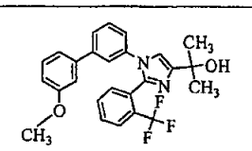
Cpd #	Structure	Name
262		2-{1-[3'-(ethylthio)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
263		2-(1-{3'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
264		2-{1-[4-(1-benzothien-3-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
265		2-{1-[4-(4-methylnaphthalen-1-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
266		2-{1-(2',4'-dichlorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
267		2-{1-[3',4'-bis(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
268		2-{2-[2-(trifluoromethyl)phenyl]-1-(2',4',5'-trimethylbiphenyl-4-yl)-1H-imidazol-4-yl}propan-2-ol;
269		4-fluoro-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-2-ol;
270		2-{1-[2'-(hydroxymethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

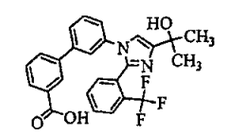
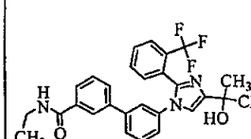
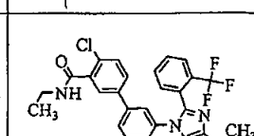
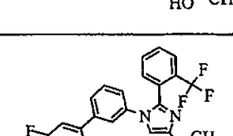
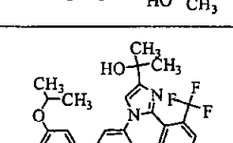
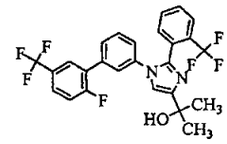
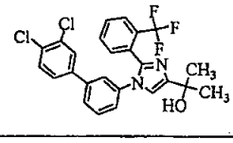
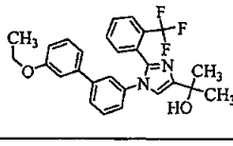
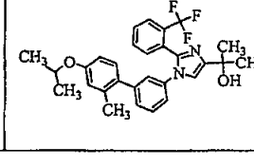
Cpd #	Structure	Name
271		2-{1-[3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
272		2-{1-(2'-chloro-6'-fluorobiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
273		2-{1-[3',5'-difluoro-2'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
274		2-(1-{4-[2-(methyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
275		2-{1-[2'-methyl-5'-(methyloxy)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
276		2-{1-(2'-ethylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
277		2-(1-{2'-methyl-4'-[(1-methylethyl)oxy]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
278		2-{1-[4'-(ethylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
279		2-{1-(5'-fluoro-2'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

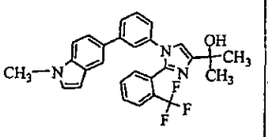
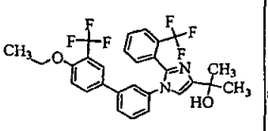
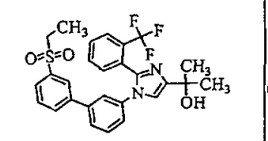
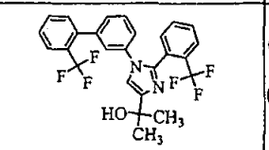
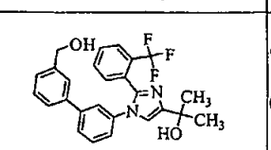
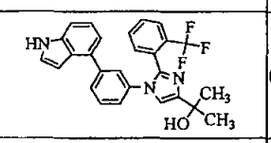
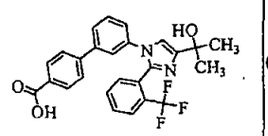
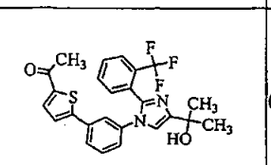
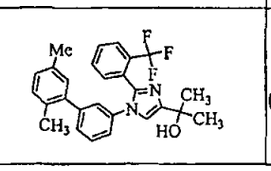
Cpd #	Structure	Name
280		2-{1-[3'-chloro-4'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
281		2-{1-(5'-chloro-2'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
282		2-{1-[2'-(ethyloxy)-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
283		2-{1-(3'-fluoro-4'-methylbiphenyl-4-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
284		methyl (2E)-3-(4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-yl)prop-2-enoate;
285		N-ethyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;
286		2-{1-[4-(2,3-dihydro-1-benzofuran-5-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
287		2-(1-{3-[6-(methyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
288		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-3-sulfonamide;

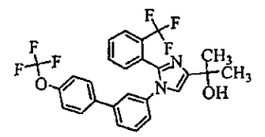
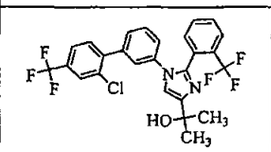
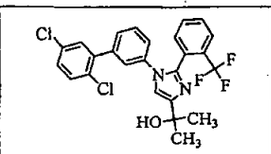
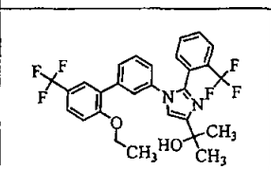
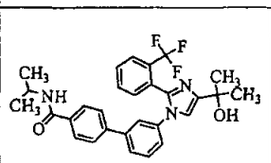
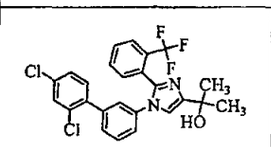
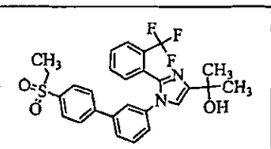
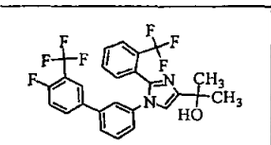
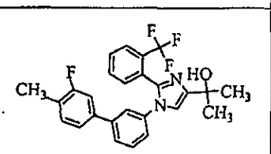
Cpd #	Structure	Name
289		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxamide;
290		2-(1-{3-[2-(cyclopentyloxy)pyridin-3-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
291		2-{1-(3'-chlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
292		2-{1-[2'-fluoro-5'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
293		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;
294		2-{1-[3',4'-bis(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
295		N-(3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-2-yl)methanesulfonamide;
296		2-{1-[3'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
297		3-fluoro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid;

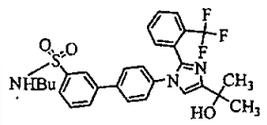
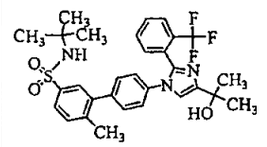
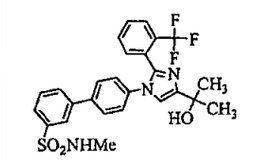
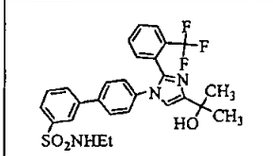
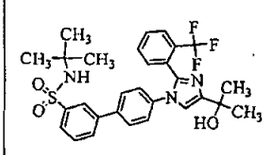
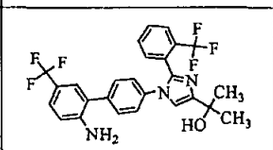
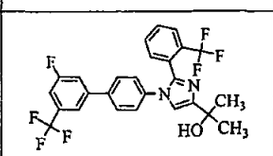
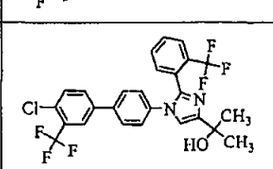
Cpd #	Structure	Name
298		4-chloro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;
299		2-{1-(3-{2-[(1-methylethyl)oxy]pyridin-3-yl}phenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
300		N-(3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-yl)acetamide;
301		2-{1-[2'-methyl-5'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
302		N-(3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-yl)acetamide;
303		2-{1-(4'-chlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
304		2-{1-[4'-(phenyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
305		2-{1-[5'-fluoro-2'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
306		2-{1-(2',3'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

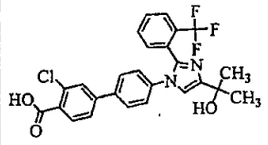
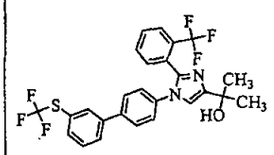
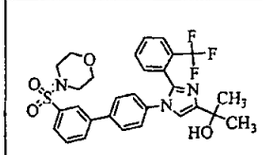
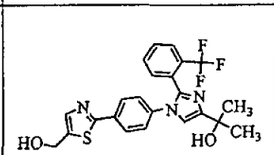
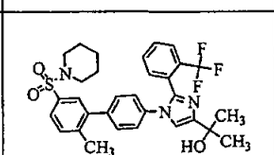
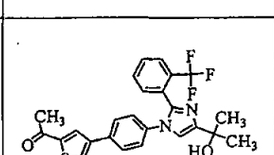
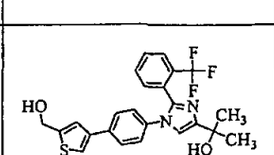
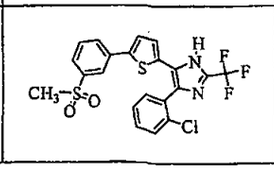
Cpd #	Structure	Name
307		2-(1-{3'-[(trifluoromethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
308		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
309		2-{1-[3',5'-bis(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
310		2-{1-(3',5'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
311		3-chloro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-4-carboxamide;
312		N,N-diethyl-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;
313		4-chloro-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-3-carboxamide;
314		2-{1-[3'-(methyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

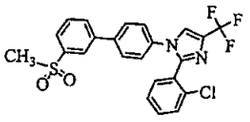
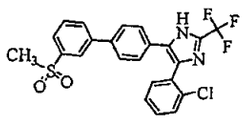
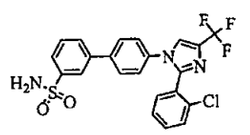
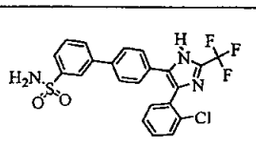
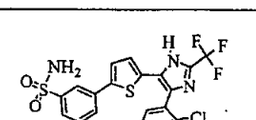
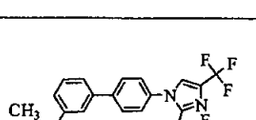
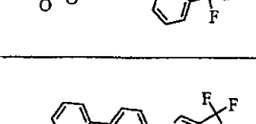
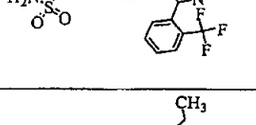
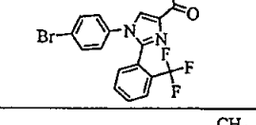
Cpd #	Structure	Name
315		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxylic acid;
316		N-ethyl-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;
317		4-chloro-N-ethyl-3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-carboxamide;
318		2-{1-(2',5'-difluorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
319		2-(1-{3'-[(1-methylethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
320		2-{1-[2'-fluoro-5'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
321		2-{1-(3',4'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
322		2-{1-[3'-(ethyloxy)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
323		2-(1-{2'-methyl-4'-[(1-methylethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;

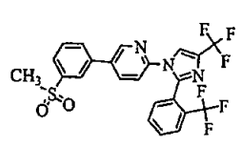
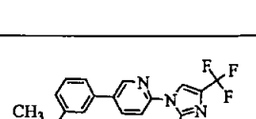
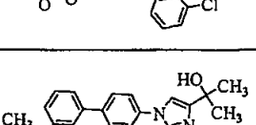
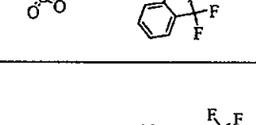
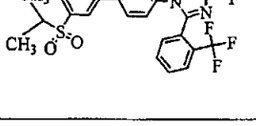
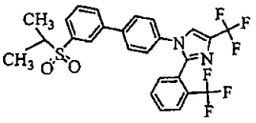
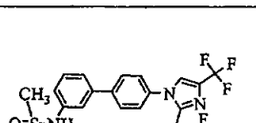
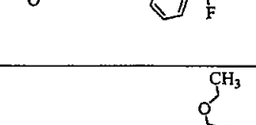
Cpd #	Structure	Name
324		2-{1-[3-(1-methyl-1H-indol-5-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
325		2-{1-[4'-(ethyloxy)-3'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
326		2-{1-[3'-(ethylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
327		2-{1-[2'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
328		2-{1-[3'-(hydroxymethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
329		2-{1-[3-(1H-indol-4-yl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
330		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid;
331		1-[5-(3-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone;
332		2-{1-(5'-chloro-2'-methylbiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

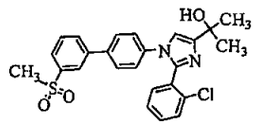
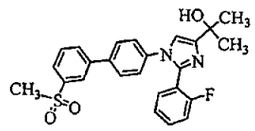
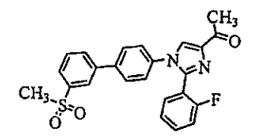
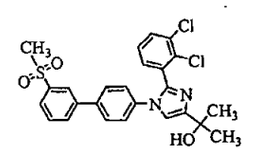
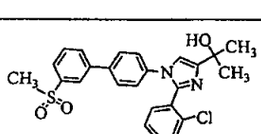
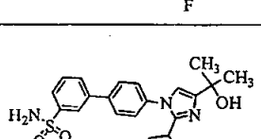
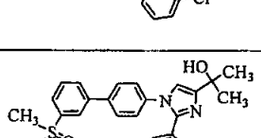
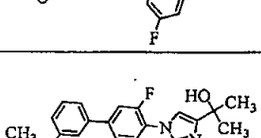
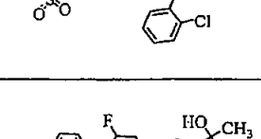
Cpd #	Structure	Name
333		2-(1-{4'-[(trifluoromethyl)oxy]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
334		2-{1-[2'-chloro-4'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
335		2-{1-(2',5'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
336		2-{1-[2'-(ethyloxy)-5'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
337		3'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-(1-methylethyl)biphenyl-4-carboxamide;
338		2-{1-(2',4'-dichlorobiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
339		2-{1-[4'-(ethylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
340		2-{1-[4'-fluoro-3'-(trifluoromethyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
341		2-{1-(3'-fluoro-4'-methylbiphenyl-3-yl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

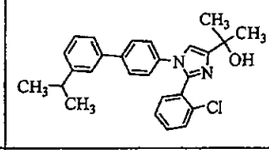
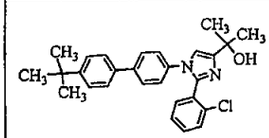
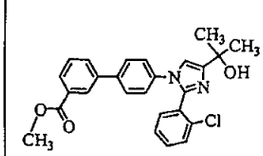
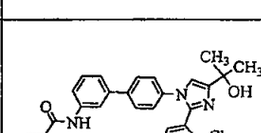
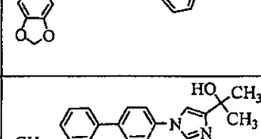
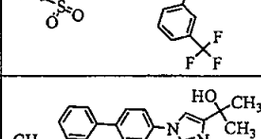
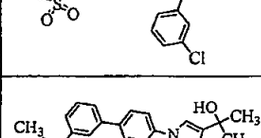
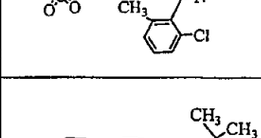
Cpd #	Structure	Name
342		N-butyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
343		N-(1,1-dimethylethyl)-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-6-methylbiphenyl-3-sulfonamide;
344		4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-methylbiphenyl-3-sulfonamide;
345		N-ethyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
346		N-(1,1-dimethylethyl)-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
347		2-{1-[2'-amino-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
348		2-{1-[3'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
349		2-{1-[4'-chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

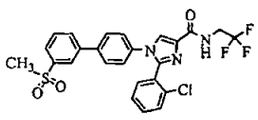
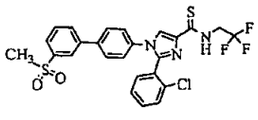
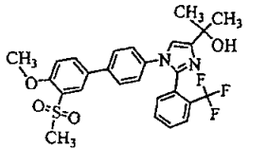
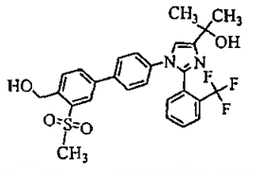
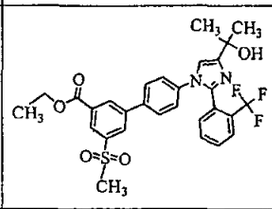
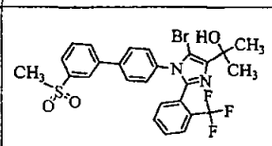
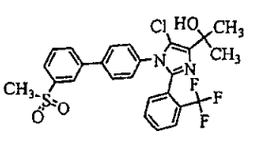
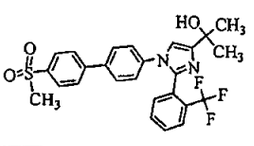
Cpd #	Structure	Name
350		3-chloro-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid;
351		2-(2-[2-(trifluoromethyl)phenyl]-1-{3'-[(trifluoromethyl)thio]biphenyl-4-yl}-1H-imidazol-4-yl)propan-2-ol;
352		2-{1-[3'-(morpholin-4-ylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
353		2-(1-{4-[5-(hydroxymethyl)-1,3-thiazol-2-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
354		2-{1-[2'-methyl-5'-(piperidin-1-ylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
355		1-[4-(4-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone;
356		2-(1-{4-[5-(hydroxymethyl)-3-thienyl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
357		4-(2-chlorophenyl)-5-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-(trifluoromethyl)-1H-imidazole;

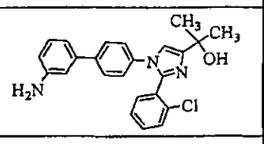
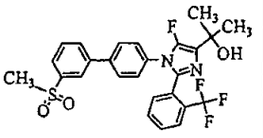
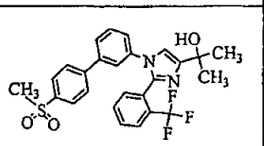
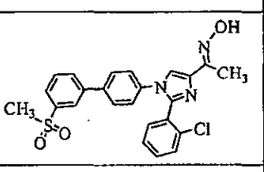
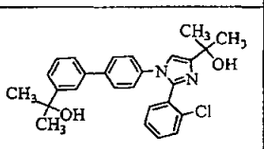
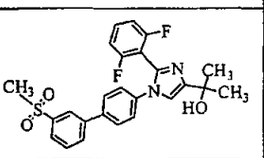
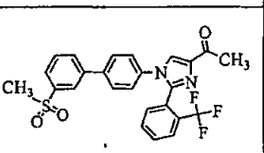
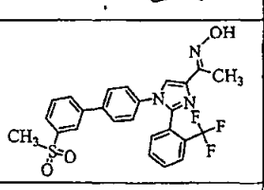
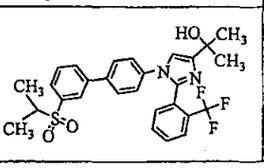
Cpd #	Structure	Name
358		2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-4-(trifluoromethyl)-1H-imidazole;
359		4-(2-chlorophenyl)-5-[3'-(methylsulfonyl)biphenyl-4-yl]-2-(trifluoromethyl)-1H-imidazole;
360		4'-[2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]biphenyl-3-sulfonamide;
361		4'-[4-(2-chlorophenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl]biphenyl-3-sulfonamide;
362		3-{5-[4-(2-chlorophenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl]-2-thienyl}benzenesulfonamide;
364		1-[3'-(methylsulfonyl)biphenyl-4-yl]-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole;
365		4'-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
366		ethyl 1-(4-bromophenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxylate;
367		ethyl 1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxylate;

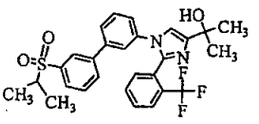
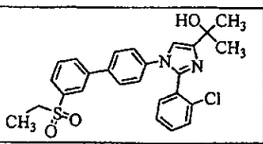
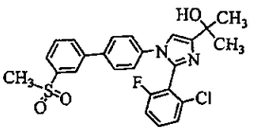
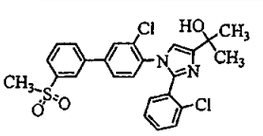
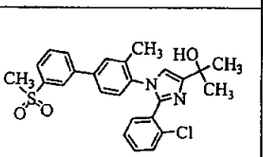
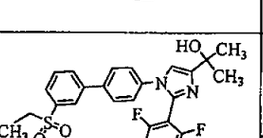
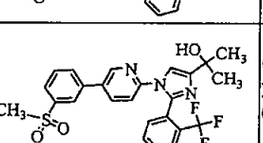
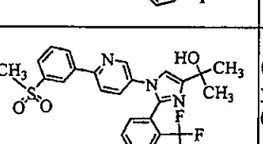
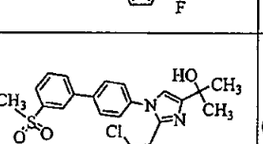
Cpd #	Structure	Name
369		5-[3-(methylsulfonyl)phenyl]-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine;
370		2-[2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]-5-[3-(methylsulfonyl)phenyl]pyridine;
371		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
372		5-{3-[(1-methylethyl)sulfonyl]phenyl}-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine;
373		1-{3'-[(1-methylethyl)sulfonyl]biphenyl-4-yl}-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole;
375		N-(4'-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-yl)methanesulfonamide;
376		ethyl 1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-phenyl-1H-imidazole-4-carboxylate;
378		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-phenyl-1H-imidazol-4-yl}propan-2-ol;

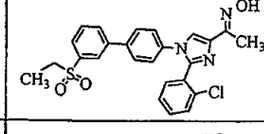
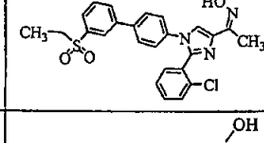
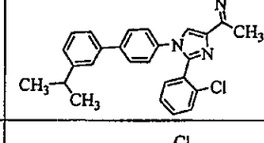
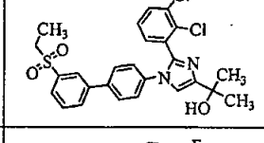
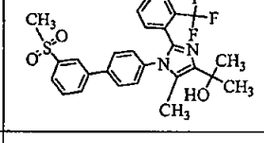
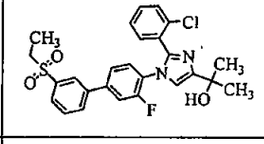
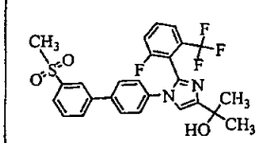
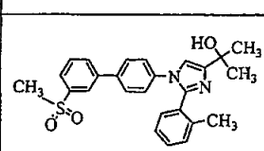
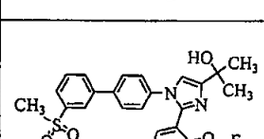
Cpd #	Structure	Name
379		2-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
380		2-{2-(2-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
381		1-{2-(2-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone;
382		2-{2-(2,3-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
383		2-{2-(2-chloro-3-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
384		4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-sulfonamide;
385		2-{2-(4-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
386		2-{2-(2-chlorophenyl)-1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
387		2-{2-(2-chlorophenyl)-1-[2-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;

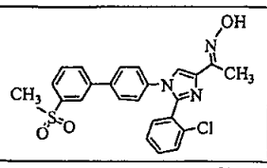
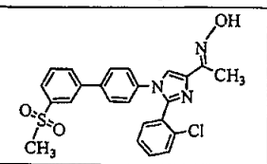
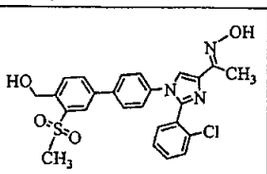
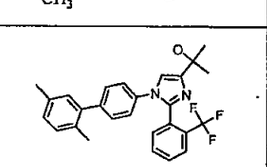
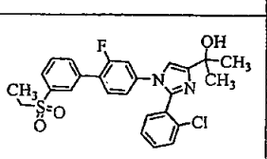
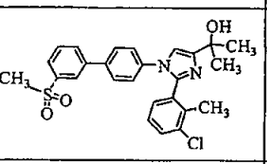
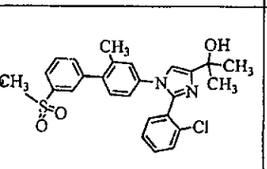
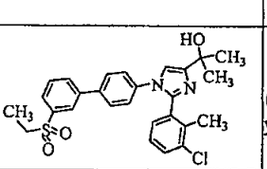
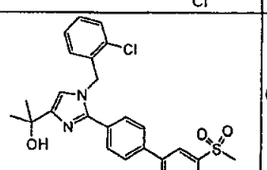
Cpd #	Structure	Name
388		2-{2-(2-chlorophenyl)-1-[3'-(1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
389		2-{2-(2-chlorophenyl)-1-[4'-(1,1-dimethylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
390		methyl 4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-carboxylate;
391		N-{4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-yl}-1,3-benzodioxole-5-carboxamide;
392		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[3-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
393		2-{2-(3-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
394		2-{2-(2-chloro-6-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
395		4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-carboxylic acid;

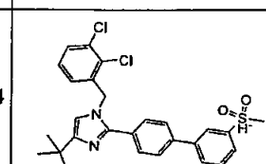
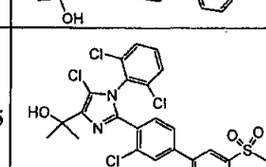
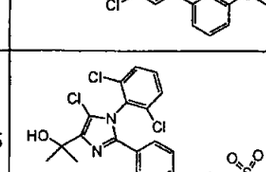
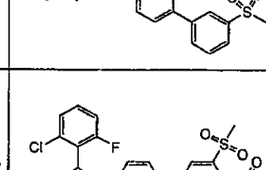
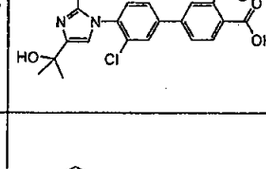
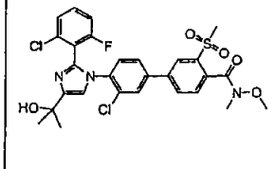
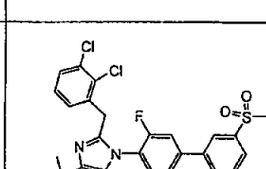
Cpd #	Structure	Name
397		2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide;
398		2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carbothioamide;
399		2-{1-[4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
400		2-{1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
401		ethyl 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-5-(methylsulfonyl)biphenyl-3-carboxylate;
402		2-{5-bromo-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
403		2-{5-chloro-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
404		2-{1-[4'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

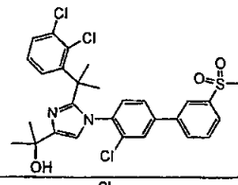
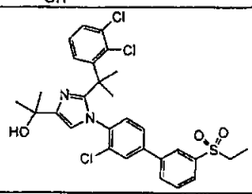
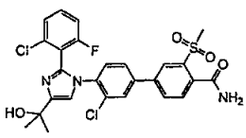
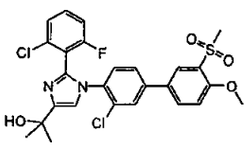
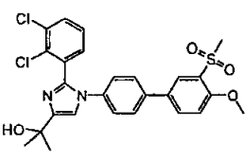
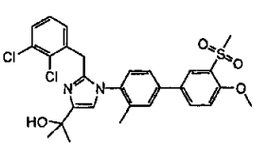
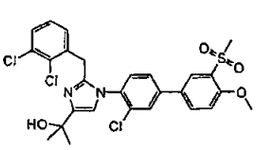
Cpd #	Structure	Name
405		2-[1-(3'-aminobiphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl]propan-2-ol;
406		2-{5-fluoro-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
407		2-{1-[4'-(methylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
408		1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
409		2-{2-(2-chlorophenyl)-1-[3'-(1-hydroxy-1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
410		2-{2-(2,6-difluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
411		1-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}ethanone;
412		1-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}ethanone oxime;
413		2-(1-{3'-[(1-methylethyl)sulfonyl]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;

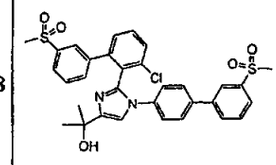
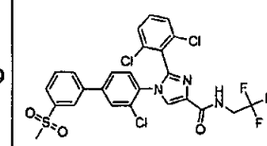
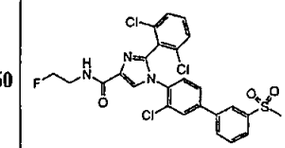
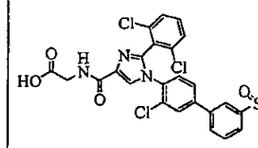
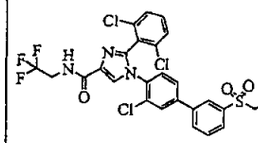
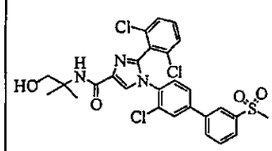
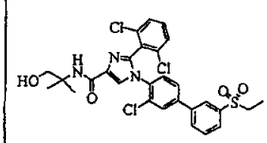
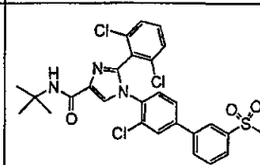
Cpd #	Structure	Name
414		2-(1-{3'-[(1-methylethyl)sulfonyl]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
415		2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
416		2-{2-(2-chloro-6-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
417		2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2-chlorophenyl)-1H-imidazol-4-yl}propan-2-ol;
418		2-{2-(2-chlorophenyl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
419		2-{2-(2,6-difluorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
420		2-(1-{5-[3-(methylsulfonyl)phenyl]pyridin-2-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
421		2-(1-{6-[3-(methylsulfonyl)phenyl]pyridin-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
422		2-{2-(2,6-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;

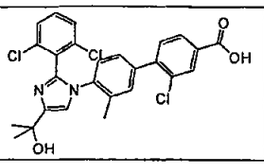
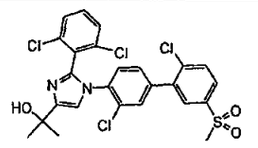
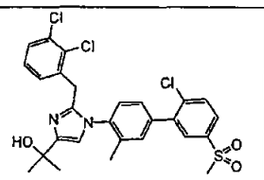
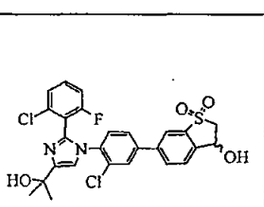
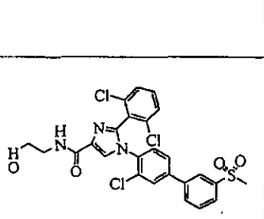
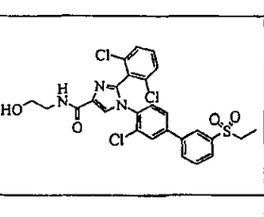
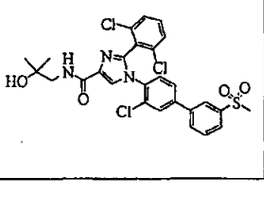
Cpd #	Structure	Name
424		1-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
425		1-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
426		1-{2-(2-chlorophenyl)-1-[3'-(1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
427		2-{2-(2,3-dichlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
428		2-{5-methyl-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
429		2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
430		2-{2-[2-fluoro-6-(trifluoromethyl)phenyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
431		2-{2-(2-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
432		2-(1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-{2-[(trifluoromethyl)oxy]phenyl}-1H-imidazol-4-yl)propan-2-ol;

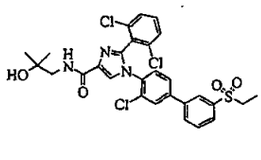
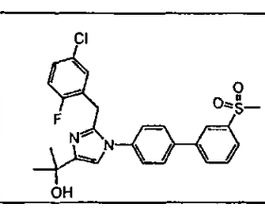
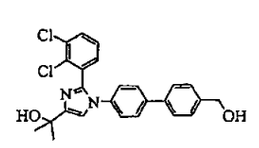
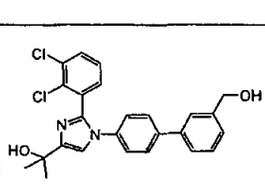
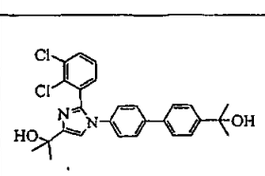
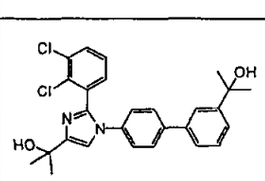
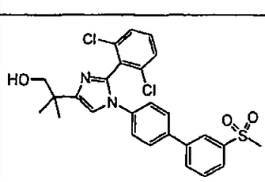
Cpd #	Structure	Name
433		1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
434		1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
435		1-{2-(2-chlorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
436		2-(1-(2',5'-dimethylbiphenyl-4-yl-2-(2-trifluoromethyl) phenyl)1H-imidazol-4-yl)propan-2-ol;
437		2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)-2-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
438		2-{2-(3-chloro-2-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
439		2-{2-(2-chlorophenyl)-1-[2-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
440		2-{2-(3-chloro-2-methylphenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
443		2-(1-(2-chlorobenzyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol

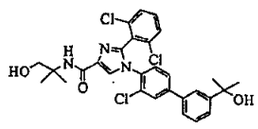
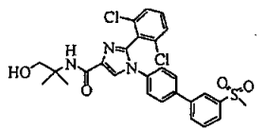
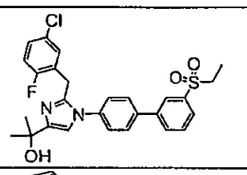
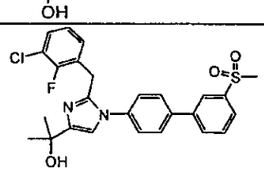
Cpd #	Structure	Name
444		2-(1-(2,3-dichlorobenzyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
445		2-(5-chloro-2-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol
446		2-(5-chloro-1-(2,6-dichlorophenyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
447		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxylic acid
448		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-N-methoxy-N-methyl-3-(methylsulfonyl)biphenyl-4-carboxamide
449		2-(2-(2,3-dichlorobenzyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
450		2-(2-(2,3-dichlorobenzyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol

Cpd #	Structure	Name
451		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(2,3-dichlorophenyl)propan-2-yl)-1H-imidazol-4-yl)propan-2-ol
452		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-(2,3-dichlorophenyl)propan-2-yl)-1H-imidazol-4-yl)propan-2-ol
453		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxamide
454		2-(1-(3-chloro-4'-methoxy-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol
455		2-(2-(2,3-dichlorophenyl)-1-(4'-methoxy-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
456		2-(2-(2,3-dichlorobenzyl)-1-(4'-methoxy-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
457		2-(1-(3-chloro-4'-methoxy-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol

Cpd #	Structure	Name
458		2-(2-(3-chloro-3'-(methylsulfonyl)biphenyl-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
459		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide
460		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-fluoroethyl)-1H-imidazole-4-carboxamide
461		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxamido)acetic acid
462		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide
463		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
464		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
465		N-tert-butyl-1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxamide

Cpd #	Structure	Name
466		2-chloro-4'-(2-(2,6-dichlorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3'-methylbiphenyl-4-carboxylic acid
467		2-(1-(2',3-dichloro-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol
468		2-(1-(2'-chloro-3-methyl-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol
469		6-{3-chloro-4-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]phenyl}-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide
470		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1H-imidazole-4-carboxamide
471		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1H-imidazole-4-carboxamide
472		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-4-carboxamide

Cpd #	Structure	Name
473		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-4-carboxamide
474		2-(2-(5-chloro-2-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
475		2-(2-(2,3-dichlorophenyl)-1-(4'-(hydroxymethyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
476		2-(2-(2,3-dichlorophenyl)-1-(3'-(hydroxymethyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
477		2-(2-(2,3-dichlorophenyl)-1-(4'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
478		2-(2-(2,3-dichlorophenyl)-1-(3'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
479		2-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)-2-methylpropan-1-ol

Cpd #	Structure	Name
480		1-(3-chloro-3'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
481		2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide
482		2-(2-(5-chloro-2-fluorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
483		2-(2-(3-chloro-2-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol

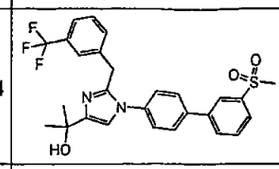
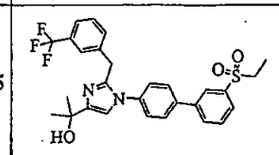
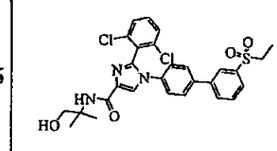
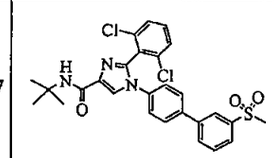
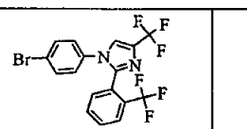
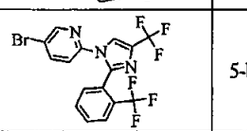
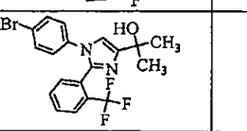
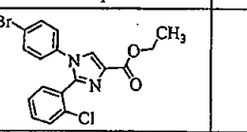
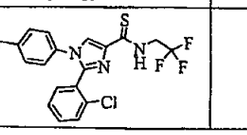
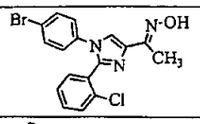
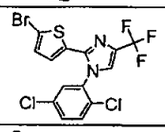
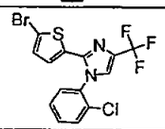
Cpd #	Structure	Name
484		2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(3-(trifluoromethyl)benzyl)-1H-imidazol-4-yl)propan-2-ol
485		2-(1-(3'-(ethylsulfonyl)biphenyl-4-yl)-2-(3-(trifluoromethyl)benzyl)-1H-imidazol-4-yl)propan-2-ol
486		2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
487		N-tert-butyl-2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide

Table 2

363		1-(4-bromophenyl)-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole;
368		5-bromo-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine;
374		2-{1-(4-bromophenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
377		ethyl 1-(4-bromophenyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxylate;
396		1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carbothioamide;

423		1-[1-(4-bromophenyl)-2-(2-chlorophenyl)-1H-imidazol-4-yl]ethanone oxime;
441		2-(5-bromo-2-thienyl)-1-(2,5-dichlorophenyl)-4-(trifluoromethyl)-1H-imidazole;
442		2-(5-bromo-2-thienyl)-1-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazole;

Example 31

FRET Coactivator assay

The FRET coactivator assay measures the ability of LXR ligands to promote protein-protein interactions between the ligand binding domain (LBD) of LXR and transcriptional coactivator proteins. The assay involves the use a recombinant Glutathione-*S*-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequence derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought into close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction.

Required Materials:

Partially purified recombinant protein comprising glutathione-S-transferase fused in frame to the LXR-ligand binding domain (comprising amino acids 188-447 of human LXRα, or amino acids 198-461 of human LXRβ). Biotinylated peptide containing a SRC-1 LXXLL receptor interaction motif (B-SRC-1). Anti-GST antibody conjugated to a Europium chelate (αGST-K) (From Wallac/PE Life Sciences Cat# AD0064). Streptavidin linked allophycocyanin (SA-APC) (From Wallac/PE Life Sciences CAT# AD0059A). 1x FRET Buffer: (20 mM KH_2PO_4/K_2HPO_4 pH 7.3, 150 mM NaCl, 2.5

mM CHAPS, 2 mM EDTA, 1 mM DTT (add fresh)). 96 well or 384 well black multiwell plates (from LJL)

Stock Solutions:

0.5 M KH_2PO_4/K_2HPO_4: pH 7.3; 5 M NaCl; 80 mM (5%) CHAPS; 0.5 M EDTA pH 8.0; 1 M DTT (keep at –20°C)

Preparation of Screening Reagents:

Prepare reaction mixture for the appropriate number of wells by combining the following reagents 5 nM/well GST-hLXRαLBD, 5 nM/well GST-hLXRβLBD, 5 nM/well Anti-GST antibody (Eu), 12 nM/well biotin-SRC-1 peptide, 12 nM/well APC-SA adjust the volume to 10 µL/well with 1x-FRET buffer.

Procedure:

Add 0.5 µL of a 1 mM stock compound (for approx. 10 µM final concentration) or solvent to each well in a 96 well or 384 well black plate (LJL). Add 10 µl reaction mixture (prepared above) to each well of the multiwell plate. Incubate covered or in the dark (the APC is light sensitive) at ambient temperature for 1-4 hours. After this time if reactions are not read they can be stored at 4°C for several more hours without too much loss of signal.

Read the plate using an LJL Analyst, or similar instrument, using the following conditions: Channel 1: Excitation is 330 nm and emission is 615. This is for Eu chelate; Channel 2: Excitation is 330 nm and emission is 665. This is for APC; For channel 1: Flashes per well = 100; Integration time = 1000 µs; interval between flashes = 1x10 ms; Delay after flash = 200 µs; For channel 2: Flashes per well = 100; Integration time = 100 µs; interval between flashes = 1x10 ms; Delay after flashes = 65 µs.

Example 32

Scintillation proximity assay (SPA)

The SPA assay measures the radioactive signal generated by the binding of ^{3}H-24,25-epoxycholesterol to LXRα or LXRβ. The basis of the assay is the use of SPA beads containing a scintillant, such that when binding to the receptor brings the labeled ligand into proximity with the bead, the energy from the label stimulates the scintillant to emit light. The light is measured using a standard microplate scintillation reader. The ability of a ligand to bind to a receptor can be measured by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor.

Required Materials:

Label: ^{3}H-24,25-epoxy-cholesterol (Amersham)

LXRα lysate: Baculovirus expressed LXRα/RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate

LXRβ lysate: Baculovirus expressed LXRβ/RXR heterodimer with RXR having a 6-HIS tag produced as a crude lysate

SPA beads: Ysi copper His-tag SPA beads (Amersham)

Plates: Non-binding surface 96-well plate (Corning)

Protein lysate dilution buffer: (20 mM Tris-HCl pH 7.9, 500 mM NaCl, 5 mM Imidazole). 2x SPA Buffer: (40 mM K_2HPO_4/KH_2PO_4 pH7.3, 100 mM NaCl, 0.05% Tween 20, 20% Glycerol, 4 mM EDTA) 2x SPA Buffer w/o EDTA: (40 mM K_2HPO_4/KH_2PO_4 pH7.3, 100mM NaCl, 0.05% Tween 20, 20% Glycerol)

Stock Solutions

0.5 M K_2HPO_4/KH_2PO_4 pH 7.3; 0.5 M EDTA pH 8.0; 5 M NaCl; 10% Tween-20; Glycerol

Preparation of protein lysates

Baculovirus expression plasmids for human RXR α, accession No NM_002957)LXRα accession No U22662), LXRβ accession No U07132) were made by cloning the appropriate full-length cDNAs into the pBacPakhis1 vector (Clontech, CA) following standard procedures. Insertion of the cDNAs into the pBAcPakhis1 vector polylinker created an in frame fusion to the cDNA to an N-terminal poly-His tag present in pBacPakhis1. Correct cloning was confirmed by restriction mapping, and /or sequencing.

Cell lysates were prepared by infecting healthy, Sf9 insect cells at a density of approximately $1.25x10^6$ /ml at 27°C, in a total volume of 500 mL per 1L sized spinner flasks, cultured under standard conditions. To prepare LXRα lysate, insect cells were co-transfected with theLXRα expression cassette at an M.O.I of 0.5 to 0.8 and with the RXR expression cassette at a M.O.I. of approximately 1.6. To prepare LXRβ lysate, insect cells were co-transfected with the LXRβ expression cassette at an M.O.I of approximately 1.6 and with the RXR expression cassette at a M.O.I. of approximately 1.6. In both cases cells were incubated for 48 hours at 27°C with constant shaking prior to harvesting.

After incubation, cells were harvested by centrifugation and pelleted. Cell pellets were resuspended in two volumes of ice-cold freshly prepared extraction buffer (20mM Tris pH 8.0, 10mM Imidazole, 400mM NaCl, containing one EDTA free protease inhibitor tablet (Roche Catalog No: 1836170) per 10 ml of extraction buffer). Cells were homogenized slowly on ice using a Douncer to achieve 80-90% cell lysis. The homogenate was centrifuged in a pre-chilled rotor (Ti50 or Ti70, or equivalent) at 45,000 rpm for 30 minutes at 4°C. Aliquots of the supernatant were frozen on dry ice and stored frozen at –80°C until quantification and quality control. Aliquots of the lysates were tested in the

SPA assay to ensure lot to lot consistency, and via SDS-PAGE analysis after purification using Ni-NTA Resin (Qiagen) and adjusted for protein concentration and expression level prior to use in screening assays.

Preparation of Screening Reagents

[^{3}H] 24,25 Epoxycholesterol (EC) solution: For a single 384-well plate (or 400 wells), 21 µL of [^{3}H] EC (specific activity 76.5 Ci/mmol, concentration 3.2 mCi/mL) was added to 4.4 mL of 2x SPA buffer to provide for a final concentration of 200 nM. For each additional 384-well plate, an additional 19.1 µL of [^{3}H] EC was added to 4.0 mL of additional 2x SPA buffer. The final concentration of [^{3}H] EC in the well was 50 nM. LXRα lysate (prepared as above) was diluted with protein lysate dilution buffer. 1400 µL of diluted LXRα lysate was prepared per 384-well plate, (or 200 wells) and 1120 µL of diluted LXRα lysate was prepared for each additional 384-well plate. LXRβ lysate (prepared as above) was diluted with protein lysate dilution buffer. 1400 µL of diluted LXRβ lysate was prepared per 384-well plate, (or 200 wells) and 1120 µL of diluted LXRβ lysate was prepared for each additional 384-well plate. SPA bead solution: For a 384-well plate (or 400 wells), 3.75 mL of 2x SPA buffer w/o EDTA, 2.25 mL of H_2O, and 1.5 mL of Ysi His-tag SPA beads (vortex well before taking) were mixed together. For each additional 384-well plate, an additional 3.5 mL of 2x SPA buffer w/o EDTA, 2.1 mL of H_2O, and 1.4 mL of Ysi His-tag SPA beads were mixed together.

Procedure:

Appropriate dilutions of each compound were prepared and pipetted into the appropriate wells of a multiwell plate. 9.1 µL of [^{3}H] EC was added to each well of column 2-23 of the multiwell plate. 5 µl of diluted LXRα lysate was added to each well of column 2-23 on odd rows of the multiwell plate. 5 µL of diluted LXRβ lysate was added to each well of column 2-23 on even rows of the multiwell plate. 17.5 µL of SPA bead solution was added to each well of column 2-23 of the multiwell plate.

The plates were covered with clear sealer and placed in an incubator at ambient temperature for 1 hour. After incubation plates were analyzed using a luminescent plate reader (MicroBeta, Wallac) using the program n ABASE 3H_384DPM. The setting for n ABASE 3H_384DPM was: Counting Mode: DPM; Sample Type: SPA; ParaLux Mode: low background; Count time: 30 sec.

Assays for LXRα and LXRβ were performed in the identical manner. The determined Ki represents the average of at least two independent dose response experiments. The binding affinity for each compound may be determined by non-linear regression analysis using the one site competition formula to determine the IC_{50} where:

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{(1+10^{X-\log IC50})}$$

The Ki is than calculated using the Cheng and Prusoff equation where:

$Ki = IC_{50}/(1 + [Concentration\ of\ Ligand]/Kd\ of\ Ligand)$

For this assay, typically the Concentration of Ligand = 50 nM and the Kd of EC for the receptor is 200 nM as determined by saturation binding.

The compounds of the invention demonstrated the ability to bind to LXRα and/or LXRβ when tested in this assay.

Example 33

Co-Transfection Assay

To measure the ability of compounds to activate or inhibit the transcriptional activity of LXR in a cell based assay, the co-transfection assay was used. It has been shown that LXR functions as a heterodimer with RXR. For the co-transfection assay, expression plasmids for LXR and RXR are introduced via transient transfection into mammalian cells along with a luciferase reporter plasmid that contains one copy of a DNA sequence that is bound by LXR-RXR heterodimers (*LXRE*; Willy, P. *et.al.* 1995). Treatment of transfected cells with an LXR agonist increases the transcriptional activity of LXR, which is measured by an increase in luciferase activity. Similarly, LXR antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of a LXR agonist.

Required Materials

CV-1 African Green Monkey Kidney Cells Co-transfection expression plasmids, comprising full- length LXRα (pCMX-h LXRα,, LXRβ (pCMX-hLXRβ), or RXRα (pCMX-RXR), reporter plasmid (LXREx1-Tk-Luciferase), and control (pCMX-Galactosidase expression vector) (Willey et al. Genes & Development 9 1033-1045 (1995)). Transfection reagent such as FuGENE6 (Roche). 1x Cell lysis buffer (1 % Triton X 100 (JT Baker X200-07), 10% Glycerol (JT Baker M778-07), 5 mM Ditriotreitol (Quantum Bioprobe DTT03; add fresh before lysing), 1 mM EGTA (Ethylene Glycol-bis (B-Amino ethyl ether)-N,N,N',N'-Tetracetic Acid) (Sigma E-4378), 25 mM Tricine (ICN 807420) pH 7.8) 1x Luciferase assay buffer (pH at 7.8) (0.73 mM ATP, 22.3 mM Tricine, 0.11 mM EDTA, 33.3 mM DTT) 1x Luciferrin/CoA (11 mM Luciferin, 3.05 mM Coenzyme A, 10 mM HEPES)

Preparation of Screening Reagents

CV-1 cells were prepared 24 hours prior to the experiment by plating them into T-175 flasks or 500 cm^2 dishes in order to achieve 70-80% confluency on the day of the transfection. The number of cells to be transfected was determined by the number of plates to be screened. Each 384 well plate requires 1.92x106 cells or 5000 cells per well. DNA Transfection Reagent was prepared by mixing the

required plasmid DNAs with a cationic lipid transfection reagent FuGENE6 (Roche) by following the instructions provided with the reagents. Optimal DNA amounts were determined empirically per cell line and size of vessel to be transfected. 10-12 mL of media was added to the DNA Transfection Reagent and this mixture was added to the cells after aspirating media from the T175 cm^2 flask. Cells were then incubated at least 5 hours at 37°C to prepare screening cells.

Luciferase assay reagent was prepared by combining before use (per 10 mL): 10 mL 1x Luciferase assay buffer; 0.54 mL of 1x Luciferrin/CoA; 0.54 mL of 0.2 M Magnesium sulfate

Procedure

Assay plates were prepared by dispensing 5 µL of compound per well of a 384 well plate to achieve final compound concentration of 10 µM and no more than 1% DMSO. Media was removed from the screening cells, the cells trypsinized, harvested cells by centrifugation, counted, and plated at a density of approximately 5000 cells per well in the 384 well assay plate prepared above in a volume of about 45 µL. Assay plates containing both compounds and screening cells (50 µL in total volume) were incubated for 20 hours at 37°C.

After incubation with compounds, media was removed from the cells and lysis buffer (30 µL/well) added. After 30 minutes at ambient temperature, luciferase assay buffer (30 µL/well) was added and the assay plates read on a luminometer (PE Biosystems Northstar reader with on-board injectors, or equivalent). Plates were read immediately after addition of luciferase assay buffer.

The LXR/LXRE co-transfection assay can be used to establish the EC_{50}/IC_{50} values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control ((*N*-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)amino)propyl)-2,2-dimethylpropionamide)) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate.

The data from this assay is fitted to the following equation, from the EC_{50} value may be solved:

$$Y = \text{Bottom} + (\text{Top-Bottom})/(1+10^{((\log EC50-X)*\text{HillSlope})})$$

The EC_{50}/IC_{50} is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC_{50}/IC_{50} values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or % control for an agonist is by comparison to the maximum response achieved by ((*N*-(3-((4-fluorophenyl)-(naphthalene-2-sulfonyl)-amino)propyl)-2,2-dimethylpropionamide) that is measured individually in each dose response experiment.

For the antagonist assay, a LXR agonist can be added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the

activity of the agonist. In this example, 100% inhibition would indicate that the activity of a specific concentration of LXR agonist has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

Compounds of the invention, when tested in this assay, demonstrated the ability to modulate the activity of LXRα and/or LXRβ. Preferably, the active compounds modulate the activity of LXR with a EC50 or IC50 of about 10μM or less. More preferably, the EC50 or IC50 of the preferred active compounds is about 1 μM or less.

Example 34

In vivo Studies

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at various time points. Male C57BL/6 mice (n=8) are dosed by oral gavage with vehicle or compound. At various time points after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for a lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice (LXRα-/- or LXRβ-/-) and C57BL/6 wild-type controls are used in this same protocol.

Plasma Lipid Evaluation:

To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice (n=8) are dosed daily by oral gavage with vehicle or compound. Plasma samples are taken on day –1 (in order to group animals), day 1, 3, and 7. Samples are collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by LXR subtypes, LXR deficient mice (LXRα-/- or LXRβ-/-) and C57BL/6 wild-type controls are used in this same protocol.

Example 35

Measured EC_{50} or IC_{50} for LXR for compounds of the invention

Compounds of the invention, when tested as described in Example 33, demonstrated the ability to modulate the activity of LXR_α and/or LXR_β. LXR activities for various compounds of the invention are presented in the following table; those compounds with EC_{50} or IC_{50} values < 10 μM for at least one of LXR_α and LXR_β are considered to be active. In the following Table, IC_{50} or EC_{50} data is represented as follows: A = < 1 μM, B = 1 – 10 μm, and C= > 10 μM

Cpd #	activity	44	B	100	B	142	A	186	A	379	A	443	A
		45	B	101	A	143	A	187	A	380	B	444	A
1	A	58	A	102	A	144	A	188	A	381	B	445	A
2	A	59	A	103	B	145	A	189	A	382	A	448	C
3	A	60	A	104	A	146	A	190	A	383	A	449	A
4	A	61	A	105	A	147	A	191	A	384	B	450	A
5	A	62	A	106	B	148	A	192	A	385	B	451	A
6	A	63	A	107	A	149	A	193	A	386	A	452	A
7	A	64	A	108	A	150	A	194	A	387	B	453	B
8	A	65	A	109	A	151	A	195	A	388	B	454	B
9	A	66	A	110	A	152	A	196	A	389	B	455	A
10	A	67	A	111	A	153	A	197	A	390	B	456	A
11	A	68	A	112	A	154	A	198	A	391	B	457	A
12	A	69	A	113	A	155	A	199	B	392	A	458	B
13	A	70	A	114	A	156	A	200	A	393	A	459	A
14	A	71	A	115	A	157	A	201	A	394	A	460	A
15	A	72	A	116	A	158	A	220	A	395	B	461	C
16	A	73	A	117	A	159	A	274	B	396	B	462	A
17	A	74	A	118	A	160	A	281	A	397	A	463	A
18	A	75	A	119	A	161	A	344	A	398	A	464	A
19	A	76	A	120	A	162	A	357	A	399	B	465	A
20	A	77	A	121	A	163	A	358	A	400	A	466	C
21	A	78	A	122	A	164	B	359	A	401	B	467	A
22	A	80	B	123	A	165	B	360	A	402	A	468	A
23	A	82	A	124	A	168	B	361	B	403	A	469	B
24	A	83	B	125	A	169	A	362	A	404	B	470	A
25	A	84	A	126	A	170	A	363	B	405	B	471	A
26	A	85	A	127	B	171	A	364	A	406	A	472	A
27	A	86	A	128	A	172	A	365	A	407	A	473	A
28	A	87	A	129	A	173	A	366	B	408	A	474	A
29	A	88	A	130	B	174	A	367	A	409	B	475	B
30	A	89	A	131	B	175	A	368	B	410	B	476	B
31	A	90	A	132	B	176	A	369	A	411	A	477	B
32	A	91	B	133	A	177	A	370	A	412	A	479	A
33	A	92	B	134	A	178	A	371	A	413	A	480	A
34	A	93	A	135	A	179	A	372	A	415	B	481	A
35	B	94	A	136	A	180	A	373	A	416	B	482	A
36	B	95	A	137	A	181	A	374	B	417	A		
37	C	96	A	138	A	182	A	375	A	418	A		
38	C	97	B	139	A	183	A	376	A	419	B		
41	B	98	A	140	A	184	A	377	B	420	B		
42	A	99	A	141	A	185	A	378	B	421	B		

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be incorporated within the spirit and purview of this application and scope of

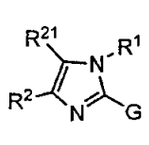
the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated herein by reference for all purposes.

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet,are incorporated herein by reference, in their entirety.

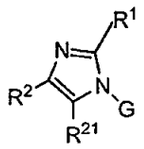
From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any and all other elements from any of the embodiments to describe additional embodiments.

We claim:

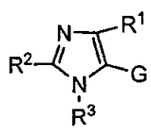
1. A compound according to one of the following formulas,



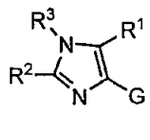
IIa



IIb



IIc



IId

or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein,

(A) R^1 is $-L^1-R^5$, wherein

L^1 is a bond, L^5, L^6, $-L^5-L^6-L^5-$, or $-L^6-L^5-L^6-$, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_6)haloalkyl; and

each L^6 is independently -CS-, -CO-, $-SO_2-$, -O-, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, or $-C(=NN(R^{11})_2)-$, -aryl-, $-C_3-C_8$cycloalkyl-, -heteroaryl-, or -heterocyclyl-;

wherein the aryl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more R^{14};

or each L^6 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, or $-SO_2N(R^{10})$; and

R^5 is aryl, heterocyclyl, heteroaryl, $-(C_3-C_6)$cycloalkyl, -C, or -B-C,

wherein

B is $-[C(R^{15})_2]_m-$ or $-C_3-C_8$ cycloalkyl-; and

C is halogen, $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, or $-N(R^{11})_2$,

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, $(C_3-C_8$ cycloalkyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkenyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$,

$SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, -C_1-C_6 alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, C_1-C_6 haloalkyl, -SO_2R^{11}, -OR^{11}, -SR^{11}, -N_3, -SO_2R^{11}, -COR^{11}, -$SO_2N(R^{11})_2$, -$SO_2NR^{11}COR^{11}$, -C≡N, -$C(O)OR^{11}$, -$CON(R^{11})_2$, -$CON(R^{11})OR^{11}$, -$OCON(R^{11})_2$, -$NR^{11}COR^{11}$, -$NR^{11}CON(R^{11})_2$, -$NR^{11}COOR^{11}$, or -$N(R^{11})_2$;

R^2 and R^{21} are -L^3-R^7, wherein

each L^3 is independently a bond or -$(CH_2)_m$-V^1-$(CH_2)_n$-, wherein

n is 0-6; and

V^1 is –$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, –$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -NR^{11}-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -OCO-, -CO-, -CS-, -$CONR^{10}$-, -C(=N-R^{11})-, -C(=N-OR^{11})-, -C[=N-$N(R^{11})_2$], -CO_2-, -OC(=O)-, -$OC(=O)N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, -$SO_2N(R^{10})$-, -$NR^{10}CONR^{10}$-, -$NR^{10}CSNR^{10}$-, C_3-C_6cycloalkyl, or C_3-C_6 cyclohaloalkyl;

or each L^3 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, –$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -NR^{11}-, -$CON(R^{10})$-, -CO-, -CO_2-, -OC(=O)-, -$OC(=O)N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$-; and

each R^7 is independently hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, -Y-Z, or –X-Y-Z, wherein

X is –O-;

Y is -$[C(R^{15})_2]_m$-, C_2-C_6alkenyl, or -C_3-C_8cycloalkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -C(=N-OH)R^{11}, -$C(=S)N(R^{11})_2$, -CN, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, -OC(=O)-$R^{11}$, or -OC(=O)-$N(R^{11})_2$,

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen, haloaryl, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, $C(R^{11})$=$C(R^{11})$-COOH, aryl, heteroaryl, heterocyclyl, heterocyclyloxy, heteroaryloxy, -Z', -Y'-Z', or –X'-Y'-Z', wherein

X' is –O-;

Y' is -$[C(R^{15})_2]_m$- or -C_3-C_8cycloalkyl; and

Z' is –H, halogen, –OR^{11}, -SR^{11}, -$S(=O)_2R^{11}$, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -$N(R^{11})C(=O)$ R^{11}, -$S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, -$OC(=O)$-$R^{11}$, -$OC(=O)$-$OR^{11}$, -$N(R^{11})C(=O)$-$R^{11}$, or -$N(R^{11})S(O=)_2R^{11}$,

wherein each R^{7a} is optionally substituted with one or more R^8,

wherein each R^8 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyl(OR^{11}), C_0-C_6 alkylOR^{11}, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, or C_0-C_6 alkylSO_2R^{11},

provided that R^2 and R^{21} are not simultaneously hydrogen;

R^3 is –L-R^6, wherein

L is a bond, –X^3-$(CH_2)_n$-X^3-, -$(CH_2)_m$-X^3-$(CH_2)_n$- or -$(CH_2)_{1+w}$-Y^3-$(CH_2)_w$-, wherein

n is 0-6; each w is independently 0 – 5; and

each X^3 is independently a bond, -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -C≡C-, -CO-, -CS-, -$CONR^{10}$-, -$C(=N)(R^{11})$-, -$C(=N$-$OR^{11})$-, -$C[=N$-$N(R^{11})_2]$, -CO_2-, -SO_2-, or -$SO_2N(R^{10})$-; and

Y^3 is -O-, -S-, -NR^7-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -OCO-, -$OC(=O)N(R^{10})$-, -$NR^{10}CONR^{10}$-, -$N(R^{10})SO_2$-, or -$NR^{10}CSNR^{10}$-;

or L is C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -CO-, -CO_2-, -$OC(=O)$-, -$OC(=O)N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$; and

R^6 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, -CN, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, or -$C(=O)N(R^{11})(OR^{11})$, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with with one or more R^{6a}, wherein

each R^{6a} is independently -Z", –Y"-Z", or–X"-Y"-Z", wherein

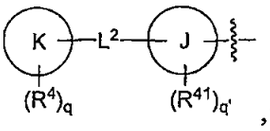
X" is –O-;

Y" is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with at least one group which is each independently Z";

$Z^{"}$ is -H, -CN, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, $-OC(=O)-OR^{11}$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, or $-N(R^{11})COOR^{11}$; and

G is a group of the formula,



, wherein

J is aryl, heteroaryl, or absent;

K is aryl, heteroaryl, or absent;

provided that

(i) if K is absent, then q is 1 and R^4 is bonded directly to L^2; and

each R^4 and R^{41} is independently halogen, oxo, nitro, $CR^{11}=CR^{11}COOR^{11}$, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, $-G^1$, $-E-G^1$ or $-D-E-G^1$, wherein

D is –O-;

E is $-[C(R^{15})_2]_m-$ or $-C_3$-C_8cycloalkyl; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCON(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, $-SOR^{11}$, or $-SR^{11}$;

wherein each R^4 is optionally substituted with one or more R^{4a},

wherein each R^{4a} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, C_1-C_6 alkoxyaryl, arylC_0-C_6 alkylcarboxy, -G', -E'-G', or –D'-E'-G', wherein

D' is –O-;

E' is $-[C(R^{15})_2]_m-$ or $-C_3$-C_8cycloalkyl-; and

G' is –H, -halogen, $-COR^{11}$, $-COOR^{11}$, $-C\equiv N$, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$;

L^2 is a bond or $-[C(R^{15})_2]_m-V^2-[C(R^{15})_2]_n-$, wherein

V^2 is independently $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, -O-, -S-, $-SO_2-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, -CS-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, C_3-C_6cycloalkyl-, or C_3-C_6cyclohaloalkyl,

or V^2 is C_{2-6} alidiyl,

wherein alidiyl chain is optionally interrupted by $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$ or $-SO_2N(R^{10})-$;

or V^2 is aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more R^9, wherein

each R^9 is independently halogen, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkyloxy, C_0-C_6 alkyl or C_1-C_6 alkyl$COOR^{11}$;

each m is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, or 5,

provided that q is 0 if and only if K is not phenyl; and

q' is 0, 1, 2, 3, or 4,

each R^{10} is independently $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, or $-SO_2R^{11}$;

each R^{11} is independently -hydrogen, $-C_1$-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, $-C_1$-C_6 haloalkyl, $-N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, C_{0-6}alkoxyaryl, arylC_{0-6} alkylcarboxy, $-C_0$-C_6 alkyl$N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, or $-OC_{0-6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1.C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$; and

(B) provided that

(i) when L^2 is a bond, both J and K are not absent;

(ii) if the compound if defined by formula IIa, then

a) if J is phenyl and K is thienyl, furyl, or thiazoyl and q is 0, then R^1 is not 4-(NH_2SO_2)phenyl, 4-(NH_2SO_2)-3-fluorophenyl, p-(CH_3SO_2)phenyl-, or 4p-(CH_3SO_2)-3-fluorophenyl-; and

b) if R^5 is pyridyl or phenyl optionally substituted with one or more R^{5a} and L^1 is a bond, then G is not p-(NH_2SO_2)phenyl or p-(CH_3SO_2)phenyl-;

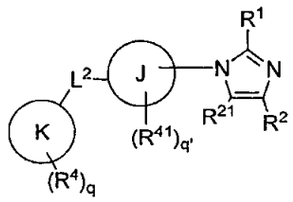
(iii) if the compound is defined by formula IIc or IId, then G is not p-(NH_2SO_2)phenyl or p-(CH_3SO_2)phenyl-;

(iv) the compound is not 1-(biphenyl-4-yl)-2,5-diphenyl-1H-imidazole.

2. The compound according to claim 1, wherein L^1 is a bond

3. The compound according to claim 2, wherein R^5 is aryl optionally substituted with one or more R^{5a}.

4. The compound according to claim 3, of the formula,



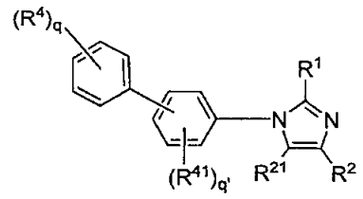
or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

5. The compound according to claim 4, wherein L^2 is a bond.

6. The compound according to claim 4, wherein at least one of J and K is phenyl.

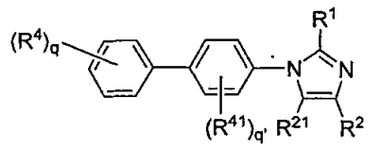
7. The compound according to claim 6, wherein J and K are both phenyl.

8. The compound according to claim 7, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

9. The compound according to claim 8, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^{21} is –H, -halogen, -C_1-C_6alkyl, or –C_1-C_6haloalkyl.

10. The compound according to claim 9, wherein each R^{41} is independently halogen, -G^1, -E-G^1, or –D-E-G^1, wherein

D is –O-;

E is -$[C(R^{15})_2]_m$-;

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$NR^{11}COR^{11}$, -$NR^{11}SO_2R^{11}$, -$N(R^{11})_2$, -SO_2R^{11}, or -$SO_2N(R^{11})_2$.

11. The compound according to claim 10, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

12. The compound according to claim 9, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$N(R^{11})_2$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11}.

13. The compound according to claim 12, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

14. The compound according to claim 9, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl;

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, –CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, or $-OC(=O)-N(R^{11})_2$.

15. The compound according to claim 14, wherein

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3\text{-}C_6)$cycloalkyl-, or $C_2\text{-}C_6$alkenyl,

wherein each R^{15} is independently H, halogen, or $(C_1\text{-}C_6)$alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

16. The compound according to claim 11, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E\text{-}G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

17. The compound according to claim 13, wherein R^2 is $-L^3\text{-}R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or $C_2\text{-}C_6$alkenyl,

wherein each R^{15} is independently H, halogen, or $(C_1\text{-}C_6)$alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

18. The compound according to claim 15, wherein

each R^{41} is independently halogen, $-G^1$, or $-E\text{-}G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1\text{-}C_6$alkyl, $-C_1\text{-}C_6$haloalkyl, or halogen.

19. The compound according to claim 16, wherein

R^2 is $-L^3\text{-}R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3\text{-}C_6)$cycloalkyl-, or $C_2\text{-}C_6$alkenyl,

wherein each R^{15} is independently H, halogen, or $(C_1\text{-}C_6)$alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

20. The compound according to claim 9, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8cycloalkyl, OR^{11}, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $NR^{11}COR^{11}$, or $N(R^{11})_2$.

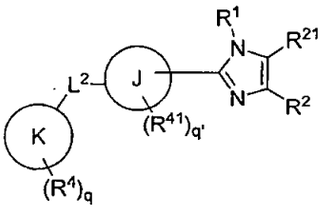
21. The compound according to claim 9, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

22. The compound according to claim 17, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

23. The compound according to claim 18, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

24. The compound according to claim 19, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

25. The compound according to claim 3, of the formula,



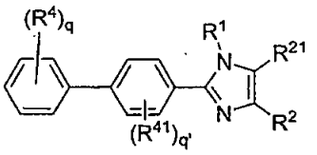
or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

26. The compound according to claim 25, wherein K is phenyl or pyridyl.

27. The compound according to claim 25, wherein J is phenyl.

28. The compound according to claim 27, wherein K is phenyl.

29. The compound according to claim 28, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

30. The compound according to claim 29, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, OR^{11}, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $NR^{11}COR^{11}$, or $N(R^{11})_2$.

31. The compound according to claim 30, wherein each R^{5a} is independently halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

32. The compound according to claim 29, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl;

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, or $-OC(=O)-N(R^{11})_2$.

33. The compound according to claim 32, wherein

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

34. The compound according to claim 29, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

35. The compound according to claim 34, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

36. The compound according to claim 31,

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

37. The compound according to claim 33, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

38. The compound according to claim 36, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

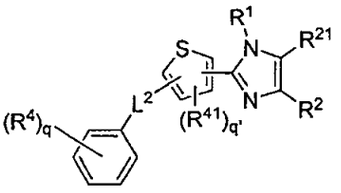
E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is –H, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

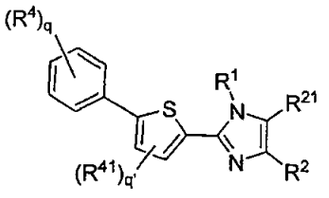
39. The compound according to claim 25, wherein J is thienyl.

40. The compound according to claim 39, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

41. The compound according to claim 40, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

42. The compound according to claim 41, wherein each R^{5a} is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, cycloC_{3-6} alkyl, OR^{11}, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $NR^{11}COR^{11}$, or $N(R^{11})_2$.

43. The compound according to claim 42, wherein each R^{5a} is independently halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl.

44. The compound according to claim 41, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl;

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, or $-OC(=O)-N(R^{11})_2$.

45. The compound according to claim 44, wherein

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently -H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

46. The compound according to claim 41, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

47. The compound according to claim 46, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

48. The compound according to claim 43,

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

49. The compound according to claim 45, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

50. The compound according to claim 48, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

51 The compound according to claim 39, wherein K is pyridinyl.

52. The compound according to claim 2, wherein R^1 is heteroaryl optionally substituted with one or more R^{5a}.

53. The compound according to claim 52, wherein R^1 is thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazidinyl, pyrazolyl, quinolinyl, or isoquinolinyl, all of which are optionally substituted with one or more R^{5a}.

54. The compound according to claim 53, wherein at least one of J and K is phenyl.

55. The compound according to claim 54, wherein J and K are both phenyl.

56. The compound according to claim 55, wherein L^2 is a bond.

57. The compound according to claim 56, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$- or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$.

58. The compound according to claim 56, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

59. The compound according to claim 56, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl or halogen.

60. The compound according to claim 1, wherein

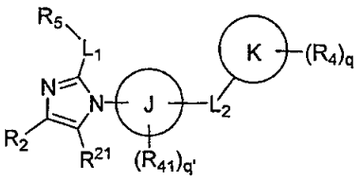
L_1 is–$[C(R^{15})_2]_{m'}$- or –C_3-C_8 cycloalkyl; wherein

m' is any of 1 to 3; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

R^{21} is hydrogen, halogen, nitro, cyano, C_1-C_6alkyl, or C_1-C_6haloalkyl.

61. The compound according to claim 60, of the formula,



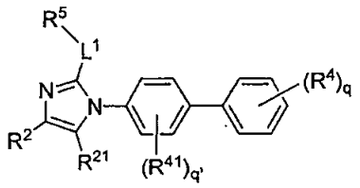
or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

62. The compound according to claim 61, wherein at least one of J and K is phenyl.

63. The compound according to claim 62, wherein J and K are both phenyl.

64. The compound according to claim 63, wherein L_2 is a bond.

65. The compound according to claim 64, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

66. The compound according to claim 65, wherein

each R^{15} is independently –H or –(C_1-C_2)alkyl;

m' is 1 or 2; and

R^5 is phenyl optionally substituted with one or more R^{5a}.

67. The compound according to claim 66, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$- or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$.

68. The compound according to claim 66, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

69. The compound according to claim 66, wherein

each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

70. The compound according to claim 65, wherein

R^{15} is –H;

m is 1, 2, or 3; and

R^5 is heterocyclyl optionally substituted with one or more R^{5a}.

71. The compound according to claim 70, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

72. The compound according to claim 70, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

73. The compound according to claim 70, wherein

each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

74. The compound according to claim 1, wherein

R^1 is $-L^1-R^5$, wherein

L^1 is a bond, -$[C(R^{15})_2]_m$-, or -C_3-C_8 cycloalkyl-; and

R^5 is phenyl or pyridyl, each optionally substituted with one or two R^{5a}, wherein

each R^{5a} is independently –halogen, -C_1-C_6 alkoxy, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl;

R^2, R^{21}, and R^3 are each independently –H, –$[C(R^{15})_2]_m$-OH, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, halogen, -$C(O)N(R^{11})_2$, or -$COOR^{11}$;

L^2 is a bond;

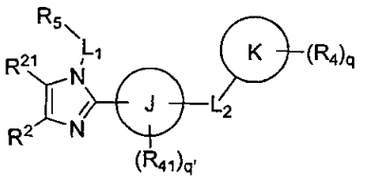
J is phenyl, pyridyl, or thienyl;

K is phenyl, or pyridyl;

each R^{41} is -halogen, -C_1-C_6 alkyl, or C_1-C_6 -haloalkyl; and

each R^4 is -halogen, –$[C(R^{15})_2]_m$-OH, –SO_2R^{11}, –$SO_2N(R^{11})_2$, -$C(O)N(R^{11})_2$, -$COOR^{11}$, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl.

75. The compound according to claim 60, of the formula,



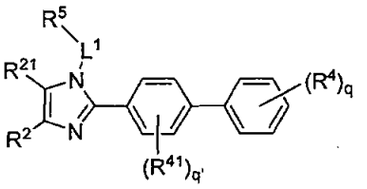
or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

76. The compound according to claim 75, wherein at least one of J and K is phenyl.

77. The compound according to claim 76, wherein J and K are both phenyl.

78. The compound according to claim 77, wherein L_2 is a bond.

79. The compound according to claim 78, of the formula,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof.

80. The compound according to claim 79, wherein

each R^{15} is independently –H or –(C_1-C_2)alkyl;

m' is 1 or 2; and

R^5 is phenyl optionally substituted with one or more R^{5a}.

81. The compound according to claim 80, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

82. The compound according to claim 80, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

83. The compound according to claim 80, wherein

each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, or halogen.

84. The compound according to claim 79, wherein

R^{15} is –H;

m is 1, 2, or 3; and

R^5 is heterocyclyl optionally substituted with one or more R^{5a}.

85. The compound according to claim 84, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

86. The compound according to claim 84, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

87. The compound according to claim 84, wherein

each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

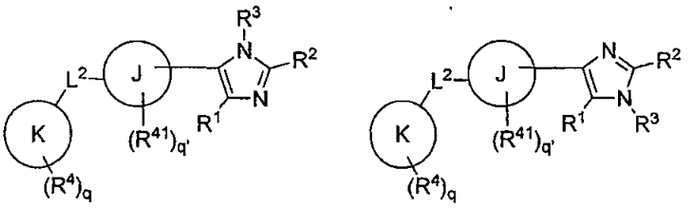
E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

88. The compound according to claim 1 which is one of the species listed in Table 1.

89. The compound according to claim 3, one of the formulas,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^3 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

90. The compound according to claim 89, wherein

J is aryl;

K is aryl; and

L^2 is a bond.

91. The compound according to claim 90, wherein

J is phenyl; and

K is phenyl.

92. The compound according to claim 91, wherein

R^1 is phenyl optionally substituted with one or more R^{5a}.

93. The compound according to claim 92, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

94. The compound according to claim 92, wherein

each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

95. The compound according to claim 92, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$, $-(C_3-C_6)$cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

96. The compound according to claim 92, wherein

each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

97. The compound according to claim 89, wherein

J is heteroaryl;

K is aryl; and

L^2 is a bond.

98. The compound according to claim 97, wherein

J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; and

K is phenyl.

99. The compound according to claim 98, wherein

R^1 is phenyl optionally substituted with one or more R^{5a}.

100. The compound according to claim 99, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m-$; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, halogen, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$.

101. The compound according to claim 99, wherein

each R^{41} is independently halogen, $-G^1$, or -E-G^1, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1-C_6$alkyl, $-C_1-C_6$haloalkyl, or halogen.

102. The compound according to claim 99, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -[C(R^{15})$_2$]$_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C(=N-OH)R^{11}, or -C(=S)N(R^{11})$_2$.

103. The compound according to claim 99, wherein

each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

104. The compound according to claim 89, wherein

J is heteroaryl;

K is heteroaryl; and

L^2 is a bond.

105. The compound according to claim 94, wherein

J is thienyl, pyrrolyl, furanyl, pyridyl, pyrimidyl, or pyrazinyl; and

K is pyridyl, pyrimidyl, or pyrazinyl.

106. The compound according to claim 95, wherein

R^1 is phenyl optionally substituted with one or more R^{5a}.

107. The compound according to claim 96, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -[C(R^{15})$_2$]$_m$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -CON(R^{11})$_2$, -C≡N, -OR^{11}, -N(R^{11})$_2$, -SO_2R^{11}, -SO_2N(R^{11})$_2$, or -SR^{11}.

108. The compound according to claim 96, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -[C(R^{15})$_2$]$_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

109. The compound according to claim 96, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -[C(R^{15})$_2$]$_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl, ,

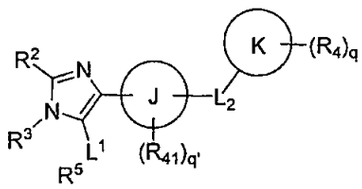
wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

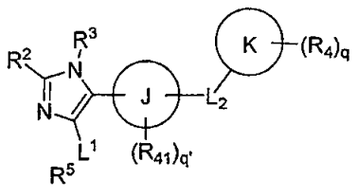
Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C(=N-OH)R^{11}, or -C(=S)N(R^{11})$_2$.

110. The compound according to claim 96, wherein

each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

111. The compound according to claim 60, of one of the formulas,





or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein R^3 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

112. The compound according to claim 111, wherein

J is aryl;

K is aryl; and

L^2 is a bond.

113. The compound according to claim 112, wherein

J is phenyl; and

K is phenyl.

114. The compound according to claim 113, wherein

each R^{15} is independently –H or –(C_1-C_2)alkyl;

m' is 1 or 2; and

R^5 is phenyl optionally substituted with one or more R^{5a}.

115. The compound according to claim 114, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$N(R^{11})_2$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11}.

116. The compound according to claim 114, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

117. The compound according to claim 114, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl, ,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$.

118. The compound according to claim 114, wherein

each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

119. The compound according to claim 113, wherein

R^{15} is –H;

m is 1, 2, or 3; and

R^5 is heterocyclyl optionally substituted with one or more R^{5a}.

120. The compound according to claim 119, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$N(R^{11})_2$, -SO_2R^{11}, -$SO_2N(R^{11})_2$, or -SR^{11}.

121. The compound according to claim 119, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -$[C(R^{15})_2]_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

122. The compound according to claim 119, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, -(C_3-C_6)cycloalkyl-, or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=N-OH)R^{11}, or -C(=S)$N(R^{11})_2$.

123. The compound according to claim 119, wherein

each R^{5a} is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

124. The compound according to claim 65, wherein

each R^{15} is independently –H or –(C_1-C_2)alkyl;

m' is 1 or 2; and

R^5 is heteroaryl optionally substituted with one or more R^{5a}.

125. The compound according to claim 124, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

126. The compound according to claim 124, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, halogen, $-OR^{11}$, or $-SO_2R^{11}$.

127. The compound according to claim 124, wherein

each R^{41} is independently halogen, $-G^1$, or $-E-G^1$, wherein

E is $-[C(R^{15})_2]_m-$,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is $-C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, or halogen.

128. The compound according to claim 79, wherein

each R^{15} is independently –H or –(C_1-C_2)alkyl;

m' is 1 or 2; and

R^5 is heteroaryl optionally substituted with one or more R^{5a}.

129. The compound according to claim 128, wherein

R^2 is $-L^3-R^7$, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, $–OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, or $-C(=S)N(R^{11})_2$.

130. The compound according to claim 128, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, $-G^1$, or $-E-G^1$, wherein

E is -[C(R^{15})$_2$]$_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

131. The compound according to claim 128, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -[C(R^{15})$_2$]$_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

132. The compound according to claim 113, wherein

each R^{15} is independently –H or –(C_1-C_2)alkyl;

m' is 1 or 2; and

R^5 is heteroaryl optionally substituted with one or more R^{5a}.

133. The compound according to claim 132, wherein

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

R^7 is hydrogen, halogen, -Z, or -Y-Z, wherein

Y is -[C(R^{15})$_2$]$_m$- or C_2-C_6alkenyl,

wherein each R^{15} is independently H, halogen, or (C_1-C_6)alkyl; and

Z is –H, halogen, –OR^{11}, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N(R^{11})$_2$, -C(=N-OH)R^{11}, or -C(=S)N(R^{11})$_2$.

134. The compound according to claim 132, wherein

each R^4 is independently halogen, aryl, heteroaryl, heterocyclyl, -G^1, or -E-G^1, wherein

E is -[C(R^{15})$_2$]$_m$-, wherein

each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, halogen, -OR^{11}, or -SO_2R^{11}.

135. The compound according to claim 132, wherein

each R^{41} is independently halogen, -G^1, or -E-G^1, wherein

E is -[C(R^{15})$_2$]$_m$-,

wherein each R^{15} is independently hydrogen or halogen; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, or halogen.

136. The compound according to claim 1, wherein

R^1 is -L^1-R^5, wherein

L^1 is a bond, L^5, L^6, –L^5-L^6-L^5-, or –L^6-L^5-L^6-, wherein

each L^5 is independently $-[C(R^{15})_2]_m-$, wherein

m is 0, 1, 2, 3, or 4; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

L^6 is -CO-, $-SO_2-$, -O-, $-CON(R^{11})-$, $-C_3-C_6$cycloalkyl-, or -heterocyclyl-,

wherein the cycloalkyl, or heterocyclyl is optionally substituted with one or more R^{14}; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C, wherein

B is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl-; and

C is halogen, $-C_1-C_6$alkyl, or $-C_1-C_6$haloalkyl;

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(C_3-C_8$ cycloalkyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkenyl)-C_1-C_6 alkyl-, $(C_3-C_8$ cycloalkyl)-C_2-C_6 alkenyl-; aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, $-C_1-C_6$ alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, $-C_1-C_6$ haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 is-L^3-R^7, wherein

L^3 is a bond wherein and

R^7 is, halogen, aryl, heteroaryl, heterocyclyl, -Z, or -Y-Z, wherein

Y is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl; and

Z is $-H$, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, or $-C(=O)N(R^{11})(OR^{11})$;

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen -Z', -Y'-Z', or $-X'-Y'-Z'$, wherein

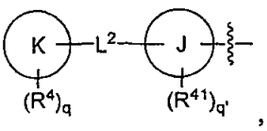
X' is -O-;

Y' is $-[C(R^{15})_2]_m-$ or $-C_3-C_6$cycloalkyl; and

Z' is –H, halogen, –OR^{11}, -SR^{11}, -$S(=O)_2R^{11}$, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -$N(R^{11})C(=O)R^{11}$, -CN, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, or -$N(R^{11})S(O=)_2R^{11}$;

R^{21} and R^3 are each independently hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl; and

G is a group of the formula,



, wherein

J is aryl or heteroaryl;

K is aryl or heteroaryl;

each R^4 and R^{41} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, -G^1, -E-G^1, or –D-E-G^1, wherein

D is –O-;

E is -$[C(R^{15})_2]_m$- or -C_3-C_6cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, -COR^{11}, -$COOR^{11}$, -$CON(R^{11})_2$, -C≡N, -OR^{11}, -$OCON(R^{11})_2$, -$NR^{11}COR^{11}$, -$NR^{11}SO_2R^{11}$, -$N(R^{11})_2$, -$NR^{11}COOR^{11}$, -SOR^{11}, -SO_2R^{11}, -$SO_2NR^{11}COR^{11}$, -$SO_2N(R^{11})_2$, or -SR^{11},

L^2 is a bond;

q is 1, 2, or 3; and

q' is 0, 1, 2, or 3;

each R^{10} is independently -R^{11}, -$C(=O)R^{11}$, -CO_2R^{11}, or -SO_2R^{11};

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-; C_1.C^6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_3-C_8 cycloalkyl, -C_1-C_6 haloalkyl, -$N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_0-C_6alkylN$(R^{13})_2$, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy,

aryloxyalkyl, C_{0-6}alkoxyaryl, arylC_{0-6} alkylcarboxy, C_0-C_6 alkyl, -$NR^{13}SO_2$ R^{13}, or -OC_{0-6} alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-; and

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$.

137. The compound according to claim 1, wherein

R^1 is -L^1-R^5, wherein

L^1 is a bond, -C_3-C_8 cycloalkyl- or L^5, wherein

each L^5 is independently –$[C(R^{15})_2]_m$-, wherein

m is 0, 1, 2, or 3; and

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C, wherein

B is –$[C(R^{15})_2]_m$-, -C_3-C_6cycloalkyl-; and

C is –C_1-C_6alkyl or -C_1-C_6haloalkyl;

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, -C_1-C_6 alkyl, aryloxy, C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, -C_1-C_6 haloalkyl, -SO_2R^{11}, -OR^{11}, -SR^{11}, -N_3, -SO_2R^{11}, -COR^{11}, -$SO_2N(R^{11})_2$, -$SO_2NR^{11}COR^{11}$, -C≡N, -$C(O)OR^{11}$, -$CON(R^{11})_2$, -$CON(R^{11})OR^{11}$, -$OCON(R^{11})_2$, -$NR^{11}COR^{11}$, -$NR^{11}CON(R^{11})_2$, -$NR^{11}COOR^{11}$, or -$N(R^{11})_2$;

R^2 is -L^3-R^7, wherein

L^3 is a bond; and

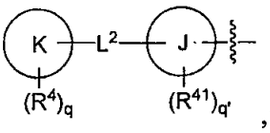
R^7 is –Z or -Y-Z, wherein

Y is -$[C(R^{15})_2]_m$-, or -C_3-C_6cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-OC(=O)\text{-}R^{11}$, or $-OC(=O)\text{-}N(R^{11})_2$;

R^{21} and R^3 are each independently hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

G is a group of the formula,



, wherein

J is aryl or heteroaryl;

K is aryl or heteroaryl;

each R^4 and R^{41} is independently halogen, heteroaryl, heterocyclyl, - G^1, -E- G^1, or –D-E- G^1, wherein

D is –O-;

E is $-[C(R^{15})_2]_m$- or -C_3-C_6cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$,

L^2 is a bond;

q is 1, 2, or 3, and

q' is 0, 1, 2 or 3,

each R^{10} is independently $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, or $-SO_2R^{11}$;

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_3-C_8 cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_8)cycloalkyl, -C_1-C_6 haloalkyl, $-N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

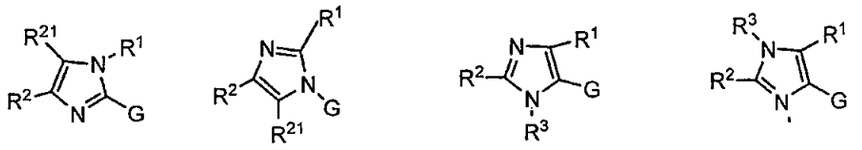
each R^{12} is independently halogen, OR^{13}, $N(R^{13})_2$, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, C_0-C_6 alkyl, $-NR^{13}SO_2$ R^{13}, or -$OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkylCON(R^{11})$_2$, C_0-C_6 alkylCONR^{11}OR^{11}, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkylCOOR^{11}.

138. The compound according to claim 1 which is one of the species listed in Table 1.

139. A compound according to one of the formulas,



or a pharmaceutically acceptable salt, isomer, or prodrug thereof, wherein,

R^1 is -L^1-R^5, wherein

L^1 is a bond, L^5, L^6, –L^5-L^6-L^5-, or –L^6-L^5-L^6-, wherein

each L^5 is independently –[C(R^{15})$_2$]$_m$-, wherein

each R^{15} is independently hydrogen, halogen, (C_1-C_6)alkyl, or (C_1-C_6)haloalkyl; and

each L^6 is independently -CS-, -CO-, -SO_2-, -O-, -CON(R^{11})-, -CONR^{11}N(R^{11})-, -C(=NR^{11})-, -C(=NOR^{11})-, or -C(=NN(R^{11})$_2$)-, -aryl-, -C_3-C_8cycloalkyl-, -heteroaryl-, or -heterocyclyl-

wherein the aryl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more R^{14};

or each L^6 is independently C_2-C_6 alidiyl

wherein the alidiyl chain is optionally interrupted by –C(R^{11})$_2$-, -C(R^{11})$_2$C(R^{11})$_2$-, -C(R^{11})=C(R^{11})-, –C(R^{11})$_2$O-, -C(R^{11})$_2$NR^{11}-, -C≡C-, -O-, -S-, -N(R^{10})CO-, -N(R^{10})CO_2-, -CON(R^{10})-, -CO-, -CO_2-, -OC(=O)-, -OC(=O)N(R^{10})-, -SO_2-, -N(R^{10})SO_2-, or -SO_2N(R^{10}); and

R^5 is aryl, heterocyclyl, heteroaryl, -C, or -B-C

wherein

B is –[C(R^{15})$_2$]$_m$- or -C_3-C_8 cycloalkyl-; and

C is halogen, –C_1-C_6alkyl, -C_1-C_6haloalkyl, -SO_2R^{11}, -SR^{11}, -SO_2N(R^{11})$_2$, -SO_2NR^{11}COR^{11}, -C≡N, -C(O)OR^{11}, -CON(R^{11})$_2$, or -N(R^{11})$_2$,

wherein R^5 is optionally substituted with one or more R^{5a}, wherein

each R^{5a} is independently halogen, nitro, heteroaryl, heterocyclyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, aryl, arylalkyl, aryloxy, aryloxyaryl, arylC_{1-6} alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, SO_2N(R^{11})$_2$,

$SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$ $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, or $N(R^{11})_2$, wherein

each R^{5a} is optionally substituted with one or more groups which independently are -halogen, -C_1-C_6 alkyl, aryloxy C_{0-6} alkylSO_2R^{11}, C_{0-6} alkyl$COOR^{11}$, C_{0-6} alkoxyaryl, C_1-C_6 haloalkyl, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, or $-N(R^{11})_2$;

R^2 and R^{21} are $-L^3$-R^7, wherein

each L^3 is independently a bond or $-(CH_2)_m$-V^1-$(CH_2)_n$- wherein

n is 0-6; and

V^1 is $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, $-NR^{11}$-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, -OCO-, -CO-, -CS-, $-CONR^{10}$-, $-C(=N-R^{11})$-, $-C(=N-OR^{11})$-, $-C[=N-N(R^{11})_2]$, $-CO_2$-, $-OC(=O)$-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, $-SO_2N(R^{10})$-, $-NR^{10}CONR^{10}$-, $-NR^{10}CSNR^{10}$-, C_3-C_6cyclo alkyl, or C_3-C_6 cyclohaloalkyl;

or each L^3 is independently C_2-C_6 alidiyl,

wherein the alidiyl chain is optionally interrupted by $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, $-NR^{11}$-, $-CON(R^{10})$-, -CO-, $-CO_2$-, $-OC(=O)$-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, or $-SO_2N(R^{10})$-; and

each R^7 is independently hydrogen, halogen, nitro, aryl, heteroaryl, heterocyclyl, -Z, -Y-Z, or –X-Y-Z, wherein

X is –O-;

Y is $-[C(R^{15})_2]_m$- or C_2-C_6alkenyl, -C_3-C_8cycloalkyl; and

Z is –H, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$,

wherein R^7 is optionally substituted with one or more R^{7a}, wherein

R^{7a} is halogen, haloaryl, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, $C(R^{11})=C(R^{11})$-COOH, aryl, heteroaryl, heterocyclyl, heterocyclyloxy, heteroaryloxy, -Z', -Y'-Z', or –X'-Y'-Z', wherein

X' is –O-;

Y' is -$[C(R^{15})_2]_m$- or -C_3-C_8cycloalkyl; and

Z' is –H, halogen, –OR^{11}, -SR^{11}, -$S(=O)_2R^{11}$, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -$N(R^{11})C(=O)$ R^{11}, -$S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, -$OC(=O)$-$R^{11}$, -$OC(=O)$-$OR^{11}$, -$N(R^{11})C(=O)$-$R^{11}$, -$N(R^{11})S(O=)_2R^{11}$,

wherein each R^{7a} is optionally substituted with one or more R^8,

wherein each R^8 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyl(OR^{11}), C_0-C_6 alkylOR^{11}, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, or C_0-C_6 alkylSO_2R^{11},

provided that R^2 and R^{21} are not simultaneously hydrogen

R^3 is –L-R^6, wherein

L is a bond, –X^3-$(CH_2)_n$-X^3-, -$(CH_2)_m$-X^3-$(CH_2)_n$- or -$(CH_2)_{1+w}$-Y^3-$(CH_2)_w$- wherein

n is 0-6; each w is independently 0 – 5; and

each X^3 is independently a bond, -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -C≡C-, -CO-, -CS-, -$CONR^{10}$-, -$C(=N)(R^{11})$-, -$C(=N$-$OR^{11})$-, -$C[=N$-$N(R^{11})_2]$, -CO_2-, -SO_2-, or -$SO_2N(R^{10})$-; and

Y^3 is -O-, -S-, -NR^7-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -OCO-,-$OC(=O)N(R^{10})$-, -$NR^{10}CONR^{10}$-, -$N(R^{10})SO_2$-, or -$NR^{10}CSNR^{10}$-;

or L is C_{2-6} alidiyl chain wherein the alidiyl chain is optionally interrupted by -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C-, -O-, -S-, -$N(R^{10})CO$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -CO-, -CO_2-, -$OC(=O)$-, -$OC(=O)N(R^{10})$-, -SO_2-, -$N(R^{10})SO_2$-, or -$SO_2N(R^{10})$; and

R^6 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, -CN, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$, -$N(R^{11})_2$, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})(OR^{11})$, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with with one or more R^{6a}, wherein

each R^{6a} is independently -Z",–Y"-Z", or–X"-Y"-Z", wherein

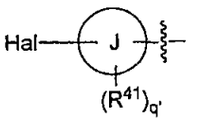
X" is –O-;

Y" is -$[C(R^{15})_2]_m$-, -C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein

the aryl, heteroaryl, cycloalkyl, or heterocyclyl is optionally substituted with at least one group which is each independently Z";

$Z^{"}$ is -H, -CN, halogen, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, $-OC(=O)-OR^{11}$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, or $-N(R^{11})COOR^{11}$; and

G is a group of the formula,



wherein

Hal is halogen;

J is aryl or heteroaryl;

each R^{41} is independently -halogen, nitro, $CR^{11}=CR^{11}COOR^{11}$, aryloxy, aralkyloxy, aryloxyalkyl, arylC_0-C_6 alkylcarboxy, aryl, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, $-G^{1'}$, $-E-G^{1'}$ or $-D-E-G^{1}$, wherein

D is –O-;

E is $-[C(R^{15})_2]_m-$ or -C_3-C_8cycloalkyl; and

G^1 is -C_1-C_6alkyl, -C_1-C_6haloalkyl, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-OCON(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$

wherein each R^4 is optionally substituted with one or more R^{4a},

wherein each R^{4a} is independently halogen, aryloxy, aralkyloxy, aryloxyalkyl, C_1-C_6 alkoxyaryl, arylC_0-C_6 alkylcarboxy, -G', -E'-G', or –D'-E'-G', wherein

D' is –O-;

E' is $-[C(R^{15})_2]_m-$ or -C_3-C_8cycloalkyl-; and

G' is –H, -halogen, $-COR^{11}$, $-COOR^{11}$, -C≡N, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, or $-SR^{11}$;

each m is 0, 1, 2, 3, 4, 5, or 6; and

q' is 0, 1, 2, 3, or 4,

each R^{10} is independently $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, or $-SO_2R^{11}$;

each R^{11} is independently -hydrogen, -C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-, -C_1-C_6 haloalkyl, $-N(R^{12})_2$, aryl, -(C_1-C_6)alkyl-aryl, heteroaryl, -(C_1-C_6)alkyl-heteroaryl, heterocyclyl, or -(C_1-C_6)alkyl-heterocyclyl,

wherein any of R^{11} is optionally substituted with one or more radicals of R^{12};

each R^{12} is independently halogen, C_1-C_6haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, (C_0-C_6 alkyl)C=O(OR^{13}); C_0-C_6 alkylOR^{13}, C_0-C_6 alkylCOR^{13}, C_0-C_6 alkylSO_2R^{13}, C_0-C_6 alkyl$CON(R^{13})_2$, C_0-C_6 alkyl$CONR^{13}OR^{13}$, C_0-C_6 alkyl$SO_2N(R^{13})_2$, C_0-C_6 alkylSR^{13}, C_0-C_6 haloalkylOR^{13}, aryloxy, aralkyloxy, aryloxyalkyl, $C_{0\text{-}6}$alkoxyaryl, aryl$C_{0\text{-}6}$ alkylcarboxy, -C_0-C_6 alkyl$N(R^{13})_2$, -$NR^{13}SO_2R^{13}$, or -$OC_{0\text{-}6}$ alkyl$COOR^{13}$;

each R^{13} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)-C_1-C_6 alkyl-, (C_3-C_8 cycloalkenyl)-C_1-C_6 alkyl-, or (C_3-C_8 cycloalkyl)-C_2-C_6 alkenyl-;

each R^{14} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_0-C_6 alkyl$CON(R^{11})_2$, C_0-C_6 alkyl$CONR^{11}OR^{11}$, C_0-C_6 alkylOR^{11}, or C_0-C_6 alkyl$COOR^{11}$.

140. The compound according to claim 139 which is one of the species listed in Table 2.

141. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable derivative thereof in a pharmaceutically acceptable carrier.

142. A method of treating, preventing, inhibiting or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to part (A) of claim 1.

143. The method of claim 142 wherein the disease or disorder is hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, orcardiovascular disorders.

144. A method of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound according to part (A) of claim 1.

MODULADORES DE LXR BASADOS EN IMIDAZOL

Referencia cruzada a solicitudes de patentes relacionadas

Esta solicitud de patente reivindica prioridad de la Solicitud Provisoria de Patente Estadounidense Número 60/694.372, presentada el 27 de junio de 2005, y de la Solicitud Provisoria de Patente Estadounidense Número 60/736.120, presentada el 10 de noviembre de 2005, ambas incorporadas en la presente como referencia en su totalidad.

Campo de la invención

Esta invención se relaciona con compuestos que modulan la actividad de los receptores X del hígado (LXR). La invención también proporciona composiciones farmacéuticas que comprenden los compuestos de la invención y métodos para utilizar esas composiciones para modular la actividad de los receptores X del hígado. En particular, se proporcionan isómeros y derivados de imidazol para modular la actividad de los LXR.

ANTECEDENTES DE LA INVENCIÓN

Receptores Nucleares

Los receptores nucleares son una superfamilia de proteínas reguladoras que están relacionadas estructural y funcionalmente y son receptores para, por ejemplo, esteroides, retinoides, vitamina D y hormonas tiroides (véase, por ejemplo, Evans (1988) *Science* 240:889-895). Estas proteínas se unen a elementos que actúan *cis* en los promotores de sus genes blanco y modula la expresión de genes en respuesta a ligandos para los receptores.

Los receptores nucleares se pueden clasificar basado en sus propiedades de unión al ADN (véase, por ejemplo, Evans, *supra* y Glass (1994) *Endocr. Rev.* 15:381-407). Por ejemplo, una clase de receptores nucleares incluye los receptores de glucocorticoides, estrógeno, progestina y corticoide mineral que se unen como homodímeros a elementos de respuesta a hormonas (HRE) organizados como repeticiones invertidas (véase, por ejemplo, Glass, *supra*). Una segunda clase de receptores, que incluyen aquellos activados por el ácido retinoico, la hormona tiroides, la vitamina D_3, los ácidos grasos/proliferadores de peroxisoma (por ejemplo, receptores activados por proliferadores de peroxisoma o PPAR) y ecdisona, se unen a las HRE como heterodímeros con un compañero común, los receptores X de retinoide (es decir, los RXR, también denominados receptores de ácidos 9-*cis* retinoicos; véase, por

ejemplo, *Levin et al* (1992), *Nature* 335:359-361 y Heyman et al (1992) *Cell* 68:397-406).

Los RXR son únicos entre los receptores nucleares porque se unen al ADN como un homodímero y son necesarios como un compañero heterodímero para que numerosos receptores adicionales se unan al ADN (véase, por ejemplo, Mangelsdorf *et al.* (1995) *Cell 83*:841-850). Los últimos receptores, denominados la subfamilia de los receptores nucleares de la clase II, incluyen muchos a los que se han establecido o implicado como reguladores importantes de la expresión de genes.

Existen tres genes RXR (véase por ejemplo, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), que codifican RXRα, -ß, y -γ, la totalidad de los cuales pueden heterodimerizarse con cualquiera de los receptores de la clase II, aunque aparentemente hay preferencias por subtipos de RXR distinguibles por receptores compañeros in vivo (véase por ejemplo, Chiba *et al.* (1997) *Mol. Cell. Biol. 17*:3013-3020). En el hígado de un adulto, RXRα es el más abundante de los tres RXRs (véase, por ejemplo, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), lo cual sugiere que cumpliría una función prominente en las funciones hepáticas que participan en la

regulación por los receptores nucleares de la clase II. Véase también, Wan *et al.* (2000) *Mol. Cell. Biol 20*:4436-4444.

Receptores Nucleares Huérfanos

En la superfamilia de los receptores nucleares de las proteínas reguladoras están incluidos los receptores nucleares para los cuales se conoce el ligando y aquellos que carecen de ligandos conocidos. Los receptores nucleares que no están en esta última categoría se denominan receptores nucleares huérfanos. La búsqueda de activadores para receptores huérfanos ha derivado en el descubrimiento de vías de señalización que previamente se desconocían (véase, por ejemplo, Levin *et al.*, (1992), *supra* y Heyman *et al.*, (1992), *supra*). Por ejemplo, se ha informado que los ácidos biliares, que participan procesos fisiológicos tales como el catabolismo del colesterol, son ligandos del receptor farnesoide X (*infra*).

Dado que se sabe que los productos del metabolismo de productos intermedios actúan como reguladores de la transcripción en bacterias y levadura, esas moléculas pueden cumplir funciones similares en organismos superiores (véase, por ejemplo, Tomkins (1975) *Science 189*:760-763 y O'Malley (1989) *Endocrinology 125*:1119-1120). Por ejemplo, una vía

biosintética en eucariotes superiores es la vía de mevalonato, que deriva en la síntesis del colesterol, los ácidos biliares, la porfirina, dolicol, ubiquinona, carotenoides, retinoides, vitamina D, hormonas esteroides y proteínas farnesiladas.

LRXα y LXRβ

LRXα se halla predominantemente en el hígado, se halla a niveles menores en el riñón, el intestino, el bazo y el tejido adrenal (véase, por ejemplo, Willy et al (1995) Gene Dev. 9(9):1033-1045. LXRβ es ubicuo en los animales se lo encontró en casi todos los tejidos examinados. Los LXR son activados por ciertos derivados oxidados naturales del colesterol (véase, por ejemplo, Lehrmann et al (1997) J. Biol. Chem. 272(6):3137-3140). LXRα es activado por el oxicolesterol y promueve el metabolismo del colesterol (Peet et al (1998) Cell 93:693-704). Por lo tanto, los LXR parecen cumplir una función, por ejemplo, en el metabolismo del colesterol (véase, por ejemplo, Janowski et al (1996) Nature 383:728-731).

Receptores Nucleares y Enfermedad

La actividad de los receptores nucleares ha sido implicada en una variedad de enfermedades y trastornos, que incluyen, en

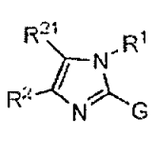
forma no taxativa, hipercolesterolemia (véase, por ejemplo, La Publicación de la Solicitud de Patente Internacional N° WO 00/57915), osteoporosis y falta de vitaminas (véase, por ejemplo, la Patente Estadounidense N° 6.316.5103), hiperlipoproteinemia (véase, por ejemplo, la Publicación de la Solicitud de Patente Internacional N° WO 01/60818), hipertrigliceridemia, lipodistrofia, hiperglucemia y diabetes mellitus (véase, por ejemplo, Publicación de Solicitud de Patente Internacional N° WO 01/82917), aterosclerosis y cálculos biliares (véase, por ejemplo, la Publicación de la Solicitud de Patente Estadounidense N° WO 00/37077), trastornos de la piel y de las membranas mucosas (véase, por ejemplo, las Patentes Estadounidenses N° 6.184.215 y 6.187.814 y la Publicación de la Solicitud de Patente Internacional N° WO 98/32444), acné (véase, por ejemplo, la Publicación de Solicitud de Patente Internacional N° WO 00/49992), y cáncer, enfermedad de Parkinson y enfermedad de Alzheimer (véase, por ejemplo, la Publicación de la Solicitud de Patente Internacional N° WO 00/17334). La actividad de los receptores nucleares, que incluyen los LXR, FXR y PPAR, y los receptores nucleares huérfanos, ha sido implicada en procesos fisiológicos que incluyen, en forma no taxativa, la biosíntesis de los ácidos biliares, el metabolismo o el catabolismo del colesterol y la modulación del colesterol, la modulación de la transcripción del gen de 7α-hidroxilasa

(CYP7A1) del colesterol (véase, por ejemplo, Chiang et al. (2000) J. Biol. Chem. 275:10918-10924), el metabolismo de HDL (véase, por ejemplo, Urizar et al. (2000) J. Biol. Chem. 275:39313-39317 y la Solicitud de Patente Internacional N° WO 01/03705), y el flujo de colesterol aumentado y la expresión aumentada de la proteína de transporte del cassette de ATP (ABC1) (véase por ejemplo, la Publicación de la Solicitud de Patente Internacional N° WO 00/78972).

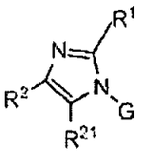
Por lo tanto, existe una necesidad de compuestos, composiciones y métodos para modular la actividad de los receptores nucleares, que incluyen los LXR, FXR, PPAR y los receptores nucleares huérfanos. Esos compuestos son útiles para el tratamiento, la prevención, la inhibición o el mejoramiento de uno o más síntomas de enfermedades o trastornos en los cuales está implicada la actividad de los receptores nucleares.

Resumen de la invención

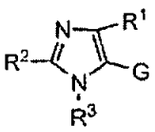
En un aspecto, la presente invención proporciona un compuesto de acuerdo con las siguientes fórmulas IIa-d:



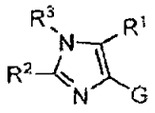
IIa



IIb



IIc



IId

O una sal farmacéuticamente aceptable, isómero o profármaco de él, que son útiles como moduladores de la actividad de los receptores X del hígado (LXR), en donde R^1, R^2, R^{21}, R^3 y G son lo definido anteriormente.

Se proporcionan compuestos para su uso en composiciones y métodos para modular la actividad de los receptores nucleares. En particular, se proporcionan compuestos de la invención que son útiles para modular los receptores X del hígado, LXRα, LXRβ, FXR, PPAR y/o ciertos receptores nucleares huérfanos.

En una realización, los compuestos provistos en la presente son agonistas de LXR. En otra realización, los compuestos provistos en la presente son antagonistas de LXR. Los agonistas que presentan baja eficacia son, en ciertas realizaciones, antagonistas.

Otro aspecto de la invención se refiere a métodos para tratar, prevenir, inhibir o mejorar los síntomas de una enfermedad o un trastorno modulado o afectado de otro modo por la actividad de los receptores nucleares o en donde está implicada la

actividad de los receptores nucleares, que comprenden administrar a un sujeto que necesita de ellos una cantidad terapéuticamente eficaz de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos para reducir los niveles de colesterol en un sujeto que lo necesita, que comprenden administrar una cantidad eficaz que reduce el nivel de colesterol de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de la invención se refiere a un método para tratar, prevenir, inhibir o mejorar uno o más síntomas de una enfermedad o un trastorno que es afectado por los niveles de colesterol, triglicéridos o ácido biliar, que comprende administrar a un sujeto que lo necesita una cantidad terapéuticamente eficaz de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos para modular la actividad de los receptores nucleares, que comprenden poner en contacto al receptor nuclear con un

compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos para modular el metabolismo del colesterol, que comprenden administrar una cantidad eficaz para modular el metabolismo del colesterol de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos para tratar, prevenir, inhibir o mejorar uno o más síntomas de la hipercolesterolemia en un sujeto que lo necesita, que comprenden administrar una cantidad terapéuticamente eficaz de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos para aumentar el flujo de colesterol desde células de un sujeto, que comprenden administrar una cantidad eficaz para aumentar el flujo del colesterol de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de la invención se refiere a métodos para aumentar la expresión del Cassette de Unión a ATP (ABC1) en

las células de un sujeto, que comprenden administrar una cantidad eficaz para aumentar la expresión de ABC1 de un compuesto de las fórmulas IIa, IIb, IIc o IId o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos in vitro para alterar la actividad de los receptores nucleares, que comprenden poner en contacto al receptor nuclear con un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a métodos para reducir los niveles de colesterol en un sujeto que lo necesita, que comprenden administrar una cantidad eficaz para reducir los niveles del colesterol de un compuesto de las fórmulas IIa, IIb, IIc y IId, o un derivado farmacéuticamente aceptable de él.

Otro aspecto de esta invención se refiere a composiciones farmacéuticas que comprenden un portador, excipiente y/o diluyente farmacéuticamente aceptable de las fórmulas IIa, IIb, IIc o IId.

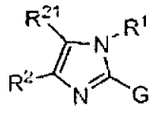
Otro aspecto de la invención se refiere a la regulación del transporte del colesterol y las vías de señalización

inflamatorias que están implicadas en la enfermedad humana que incluye aterosclerosis y enfermedades asociadas tales como el infarto de miocardio y el ataque isquémico en un sujeto que lo necesita, que comprende administrar una cantidad eficaz que regula el transporte de colesterol y las vías de señalización inflamatorias de un compuesto de las fórmulas IIa, IIb, IIc y IId, o un derivado farmacéuticamente aceptable de él.

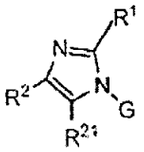
Otro aspecto de la invención se refiere al tratamiento del síndrome metabólico que comprende una constelación de trastornos del metabolismo corporal que incluyen obesidad, hipertensión y resistencia a la insulina y diabetes que incluye el tratamiento de enfermedades que son el resultado del metabolismo y la inmunidad comprometidos que incluyen aterosclerosis y diabetes así como trastornos y enfermedades autoinmunes en un sujeto que lo necesita, que comprende administrar una cantidad terapéuticamente eficaz de un compuesto de las fórmulas IIa, IIb, IIc o IId, o un derivado farmacéuticamente aceptable de él.

Descripción Detallada de la invención

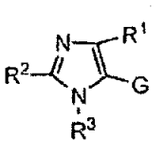
En una primera realización, la presente invención proporciona un compuesto de acuerdo con una de las siguientes fórmulas:



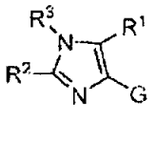
IIa



IIb



IIc



IId

O una sal farmacéuticamente aceptable, isómero, o profármaco de él, en donde:

(A) R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$ o $-L^6-L^5-L^6-$, en donde:

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno, alquilo (de C_1-C_6), cicloalquilo (de C_3-C_6) o haloalquilo (de C_1-C_6); y

Cada L^6 es independientemente $-CS-$, $-CO-$, $-SO_2-$, $-O-$, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, o $-C(=NN(R^{11})_2)-$, -arilo-, -cicloalquilo de C_3-C_8-, -heteroarilo-, o -heterociclilo-,

En donde el arilo, cicloalquilo, heteroarilo, o heterociclilo se sustituye optativamente con uno o más R^{14};

O cada L^6 se selecciona independientemente de alquilo de C_2-C_6,

En donde la cadena de alquilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})$; y

R^5 es arilo, heterociclilo, heteroarilo, cicloalquilo (de C_3-C_6), -C o -B-C-, en donde

B es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8-; y

C es halógeno, -alquilo de C_1-C_6, -haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, o $-N(R^{11})_2$,

En donde R^5 se sustituye optativmente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalqulo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, arilalcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquiloCOOR^{11}, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SON(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 y R^{21} son $-L^3-R^7$, en donde

Cada L^3 es independientemente un enlace o $-(CH_2)_m-V^1-(CH_2)_n-$, en donde

n es 0-6; y

V^1 es $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-OCO-$, $-CO-$, $-CS-$, $-CONR^{10}-$, $-C(=N-R^{11})-$, $-C(=N-OR^{11})-$, $-C[=N-N(R^{11})_2]$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, cicloalquilo de C_3-C_6 o ciclohaloalquilo de C_3-C_6;

O cada L^3 es independientemente alquilo de C_2-C_6,

En donde la cadena de alquilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-CON(R^{10})-$, $-CO-$, $-CO-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$; y

Cada R^7 es independientemente hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z-, -Y-Z-, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$,

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, haloarilo, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, $C(R^{11})=C(R^{11})$-COOH, arilo, heteroarilo, heterociclilo, heterocicliloxi, heteroariloxi, -Z', -Y'-Z', o -X'-Y'-Z', en donde

X' es -O-;

Y' es $-[C(R^{15})_2]_m$ o cicloalquilo de C_3-C_8; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})$, $-N(R^{11})C(=O)R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-OR^{11}$, $-N(R^{11})C(=O)-R^{11}$, o $-N(R^{11})S(O=)_2R^{11}$,

En donde cada R^{7a} se sustituye optativamente con uno o más R^8,

En donde cada R^8 es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, haloalquilo de C_1-$C_6(OR^{11})$, alquilo de C_0-C_6OR^{11}, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6COR^{11}, alquilo de C_0-C_6COOR^{11}, o alquilo de C_0-$C_6SO_2R^{11}$,

Siempre que R^2 y R^{21} no sean simultáneamente hidrógeno,

R^3 es $-L-R^6$, en donde

L es un enlace, $-X^3-(CH_2)_n-X^3-$, $-(CH_2)_m-X^3-(CH_2)_n-$ o $-(CH_2)_{1+w}-Y^3-(CH_2)_w-$, en donde

n es 0-6; cada w es independientemente 0-5; y

cada X^3 es independientemente un enlace, $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C\equiv C-$, -CO-, -CS-, $-CONR^{10}-$, -

$C(=N)(R^{11})-$, $-C(=N-OR^{11})-$, $-[=N-N(R^{11})_2]$, $-CO_2-$, $-SO_2-$, o $-SO_2N(R^{10})-$; y

Y^3 es $-O-$, $-S-$, $-NR^7-$, $-N(R^{10})CO-$, $N(R^{10})CO_2-$, $-OCO-$, $-OC(=O)N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-N(R^{10})SO_2-$, o $-NR^{10}CSNR^{10}-$;

o L es una cadena de alidilo en donde la cadena de alidilo está optativamente interrumpida por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO-$, o $-SO_2N(R^{10})$; y

R^6 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, arilo, cicloalquilo de C_3-C_8, heteroarilo, heterociclilo, $-CN$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2-$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})N(OR^{11})$, en donde el arilo, heteroarilo, cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{6a}, en donde

cada R^{6a} es independientemente $-Z''$, $-Y''-Z''$, o $-X''-Y''-Z''$, en donde

X'' es $-O-$;

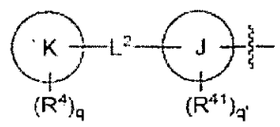
Y'' es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, heterociclilo, arilo o heteroarilo, en donde

El arilo, heteroarilo, cicloalquilo, o heterociclilo optativamente se sustituye con por lo menos un grupo que es cada uno independientemente Z'';

Z'' es $-H$, $-CN$, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)n(R^{11})_2$, $-N(R^{11})_2$, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-$

$N(R^{11})C(=O)N(R^{11})_2$, $-OC(=O)-OR^{11}$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$; y

G es un grupo de la fórmula



, en donde

J es arilo, heteroarilo, o está ausente;

K es arilo, heteroarilo, o está ausente;

Siempre que

(i) si K está ausente, entonces q es 1 y R^4 está unido a L^2; y cada R^4 y R^{41} es independientemente halógeno, oxo, nitro, $CR^{11}=CR^{11}COOR^{11}$, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCN(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, $-SOR^{11}$, o $-SR^{11}$,

En donde cada R^4 se sustituye optativamente con uno o más R^{4a},

En donde cada R^{4a} es independientemente halógeno, ariloxi, analquiloxi, ariloxialquilo, alcoxiarilo de C_1-C_6, aril alquilcarboxi de C_0-C_6, -G', -E'-G', o -D'-E'-G', en donde

D' es -O-;

E' es $-[C(R^{15})]_m-$ o cicloalquilo de C_3-C_8; y

O' es -H, halógeno, $-COR^{11}$, $-COOR^{11}$, $-C\equiv N$, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace o $-[C(R^{15})_2]_m-V^2-[C(R^{15})_2]_n-$, en donde

V^2 es independientemente $-C(R^{11})_m$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, -O-, -S-, $-SO_2-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, -CS-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, cicloalquilo de C_3-C_8, o ciclohaloalquilo de C_3-C_6,

o V es alidilo de C_{2-6},

en donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2O-$, $-C(R^{11})NR^{11}$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$;

o V^2 es arilo, heteroarilo, o heterociclilo, cada uno de los cuales se sustituye optativamente con uno o más R^9, en donde cada R^9 es independientemente halógeno, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alquiloxi de C_1-C_6, alquilo de C_0-C_6COOR^{11};

cada me es 0, 1, 2, 3, 4, 5 o 6;

q es 0, 1, 2, 3, 4, o 5;

siempre que q sea 0 si y sólo si K no es fenilo; y

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SOR^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-, -haloalquilo de C_1-C_6, $-N(R^{12})_2$, arilo, alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, haloalquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C{=}O(OR^{13})$; alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, aluqilo de C_0-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{0-6}, arilalquilcarboxi de C_{0-6}, alquilo de C_0-$C_6N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-;

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, alquilo de C_1-$C_6CON(R^{11})_2$, alquilo de C_0-$C_6CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}; y

(B) siempre que

(i) cuando L^2 es un enlace, tanto J como K no están ausentes;

(ii) si el compuesto definido por la fórmula IIa, entonces

a. si J es fenilo y K es tienilo, furilo o tiazoilo y q es 0, entonces R^1 no es 4-(NH_2SO_2)fenilo, 4-(NH_2SO_2)-3-fluorofenilo-, y

b. si R^5 es piridilo o fenilo optativamente sustituido con uno o más R^{5a} y L^1 es un enlace, entonces G no es p-(NH_2SO_2)fenilo o p-(CH_3SO_2)fenilo-;

(iii) si el compuesto se define con la fórmula IIc o IId, entonces G no es p-(NH_2SO_2)fenilo o p-(CH_3SO_2)fenilo;

(iv) el compuesto no es 1-(bifenil-4-il)-2,5-difenil-1H-imidazol.

En una realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIa, IIb, IIc o IId, en donde:

R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$, o $-L^6-L^5-L^6-$, en donde

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

m es 0, 1, 2, 3, o 4; y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

L^6 es $-CO-$, $-SO_2-$, $-O-$, $CON(R^{11})-$, cicloalquilo de C_3-C_6, o -heterociclilo-,

En donde el cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{14}; y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C, en donde

B es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6-; y

C es halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6;

En donde R^5 se sustituye optativamente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, aril alcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C{\equiv}N$, $C(O)OR^{11}$, $CON(R^{11})$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}COOR^{11}$, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C{\equiv}N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 es $-L^3$-L^7, en donde L^3 es un enlace; y

R^7 es halógeno, arilo, heteroarilo, heterociclilo, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, o $-C(=O)N(R^{11})(OR^{11})$;

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, -Z', -Y'-Z' o -X'-Y'-Z', en donde

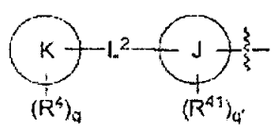
X' es -O-;

Y' es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, o $-N(R^{11})S(O=)R^{11}$;

R^{21} y R^3 son cada uno independientemente hidrógeno, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; y

G es un grupo de la fórmula



, en donde

J es arilo o heteroarilo;

K es arilo o heteroarilo,

Cada R^4 y R^{41} es indpendientemente halógeno, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6,

arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es $-O-$;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}SOR^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace;

q es 1, 2 o 3; y

q' es 0, 1, 2, o 3;

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_2-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (ciloalquenilo de C_3-C)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, haloalquilo de C_1-C_6, $-N(R^{11})_2$, arilo, -alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)-heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{11} es independientemente halógeno, alquilo de C_0-$C_6N(R^{13})_2$, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C{=}O(OR^{13})$, alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_9-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alquilarilo de C_{0-6}, aril alquilcarboxi de C_{0-6}, alquilo de C_0-C_6, $-NR^{13}SO_2$, R^{13}, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6), (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, y

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, halógeno, haloalquilo de C_1-C_6, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6 $CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

En una realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa, IIb, IIc, o IId, en donde:

R^1 es $-L^1$-R^5, en donde

L^1 es un enlace, cicloalquilo de C_3-C_8, o L^5, en donde

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

m es 0, 1, 2, o 3; y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C, en donde

B es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6-; y

C es halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6;

En donde R^5 se sustituye optativamente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, aril alcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}COOR^{11}$, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 es $-L^3-L^7$, en donde L^3 es un enlace; y

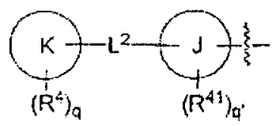
R^7 es -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$;

R^{21} y R^3 son cada uno independientemente hidrógeno, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; y

G es un grupo de la fórmula



, en donde

J es arilo o heteroarilo;

K es arilo o heteroarilo,

Cada R^4 y R^{41} es independientemente halógeno, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace;

q es 1, 2 o 3; y

q' es 0, 1, 2, o 3;

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_2-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o

(cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (ciloalquenilo de C_3-C)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, haloalquilo de C_1-C_6, $-N(R^{11})_2$, arilo, -alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)-heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{11} es independientemente halógeno, OR^{13}, $N(R^{13})_2$, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C{=}O(OR^{13})$, alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_9-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alquilarilo de C_{0-6}, aril alquilcarboxi de C_{0-6}, alquilo de C_0-C_6, $-NR^{13}SO_2$, R^{13}, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6), (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, y

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, halógeno, haloalquilo de C_1-C_6, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6 $CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

En una realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIa, IIb, IIc o IId, en donde:

R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$, o $-L^6-L^5-L^6-$, en donde

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

m es 0, 1, 2, 3, o 4; y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

L^6 es $-CO-$, $-SO_2-$, $-O-$, $CON(R^{11})-$, cicloalquilo de C_3-C_6, o -heterociclilo-,

En donde el cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{14}; y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C, en donde

B es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6-; y

C es halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6;

En donde R^5 se sustituye optativamente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, aril alcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})$,

$CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}COOR^{11}$, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 es $-L^3-L^7$, en donde

L^3 es un enlace; y

R^7 es halógeno, arilo, heteroarilo, heterociclilo, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, o $-C(=O)N(R^{11})(OR^{11})$;

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, -Z', -Y'-Z' o -X'-Y'-Z', en donde

X' es -O-;

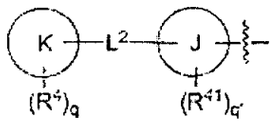
Y' es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, o $-N(R^{11})S(O=)_2R^{11}$;

317

R^{21} y R^3 son cada uno independientemente hidrógeno, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; y

G es un grupo de la fórmula



, en donde

J es arilo o heteroarilo;

K es arilo o heteroarilo,

Cada R^4 y R^{41} es indpendientemente halógeno, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es $-O-$;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace;

q es 1, 2 o 3; y

q' es 0, 1, 2, o 3;

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_2-C_8)-

alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, haloalquilo de C_1-C_6, $-N(R^{11})_2$, arilo, -alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)-heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{11} es independientemente halógeno, alquilo de C_0-$C_6N(R^{13})_2$, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C{=}O(OR^{13})$, alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_9-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{0-6}, aril alquilcarboxi de C_{0-6}, alquilo de C_0-C_6, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6), (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, y

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, halógeno, haloalquilo de C_1-C_6, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6 $CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

En una realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIa, IIb, IIc o IId, en donde:

R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, cicloalquilo de C_3-C_8, o L^5, en donde

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

m es 0, 1, 2, o 3; y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C, en donde

B es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6-; y

C es alquilo de C_1-C_6, o haloalquilo de C_1-C_6;

En donde R^5 se sustituye optativamente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, aril alcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}COOR^{11}$, alcoxiarilo de C_{0-6},

320

haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 es $-L^3-L^7$, en donde L^3 es un enlace; y

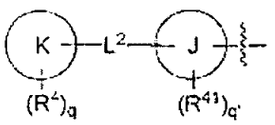
R^7 es -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$;

R^{21} es hidrógeno, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; y

G es un grupo de la fórmula



, en donde

J es arilo o heteroarilo;

K es arilo o heteroarilo,

Cada R^4 y R^{41} es independientemente halógeno, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace;

q es 1, 2 o 3; y

q' es 0, 1, 2, o 3;

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_2-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-cicloalquilo de C_3-C_8, haloalquilo de C_1-C_6, $-N(R^{11})_2$, arilo, -alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)-heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{11} es independientemente halógeno, OR^{13}, $N(R^{13})_2$, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C=O(OR^{13})$, alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_9-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alquilarilo de C_{0-6}, aril alquilcarboxi de C_{0-6}, alquilo de C_0-C_6, $-NR^{13}SO_2$, R^{13}, o -Oalquilo de $C_{0-6}COOR^{13}$;

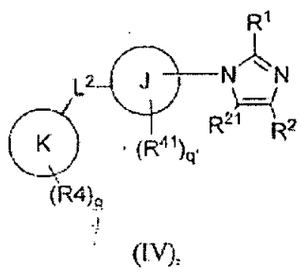
cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6), (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, y

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, halógeno, haloalquilo de C_1-C_6, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6 $CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

En una realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa, IIb, IIc y IId, en donde R^1 es L^1-R^5, en donde L^1 es un enlace, y R^2, R^{21}, R^3, R^5 y G son los definidos para las fórmulas IIa-d; dichos compuestos se denominan en adelante fórmulas IIIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIa-d, en donde R^1 es L^1-R^5,
En donde L^1 es un enlace; y R^5 es arilo optativamente sustituido con uno o más R^{5a},
Y R^2, R^{21}, R^3 y G son los definidos para las fórmulas IIa-d; dichos compuestos se denominan en adelante fórmulas IVa-d.

En otra realización, la invención proporciona el compuesto de la fórmula IV,



(IV).

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, J, K, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IV, en donde L^2 es un enlace.

En otra realización, el inventor proporciona el compuesto de acuerdo con la fórmula IV, en donde K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IV, en donde L^2 es un enlace y K es fenilo.

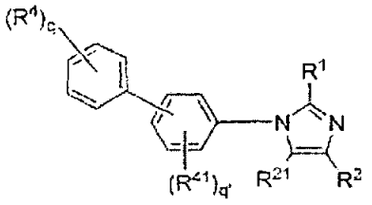
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IV, en donde L^2 es un enlace y J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IV, en donde J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IV, en donde J es fenilo, y K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IV, en donde J es fenilo, K es fenilo y L^3 es un enlace.

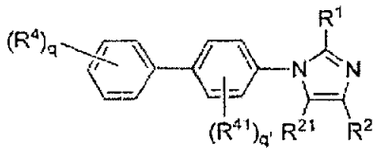
En otra realización, la invención proporciona un compuesto de la fórmula V,



(V),

O una sal farmacéuticamente aceptable, un isómero o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, q, y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de la fórmula VII,



(VII),

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^{21} es -H, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; R^1 es lo definido para la fórmula

IVa-d; y R^2, R^4, R^{41}, q y q' son lo definido para la fórmula IIa-d.

En otra realiazación, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde cada R^{41} es independientemente halógeno, $-G^1-E-G^1$ o $-D-E-G^1$, en donde

D es $-O-$;

E es $-[C(R^{15})_2]_m-$;

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, o $-SO_2N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno,

Dichos compuestos en adelante se denominan fórmula VIIa.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerd con la fórmula VII, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, G^1 o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$,

Dichos compuestos en adelante se denominan fórmula VIIb.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde R es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6);

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{15})_2$, $-CN$, $-S(O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^3 es hidrógeno, halógeno, -Z- o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6), y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$,

Tales compuestos en adelante se denominan fórmula VIIc.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIa, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$,

Dichos compuestos en adelante se denominan fórmula VIId.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIb, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlce y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})$,

Dichos compuestos en adelante se denominan fórmula VIIe.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIc, en donde cada R^{41} es independientemente halógeno, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno,

Dichos compuestos en adelante se denominan fórmula VIII.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIId, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R_{15} es independientemente H, halógeno, o alquilo (de C_1-C_6), y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, o $-C(=S)N(R^{11})$,

Dichos compuestos en adelante se denoninan fórmula VIIg.

En otra reazliación, la invención proporciona el compuesto de acuerdo con la fórmula VIIe, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, $-OR^{11}$, $-SOR^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-NR^{11}COR^{11}$, o $-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIc, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_8, $-OR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})^2$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, o $-N(R^{11})_2$; y R^{21} es -H.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIf, en donde R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIf, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; y R^{21} es -H.

En otra realización, la invención proporciona un compuesto de acuerdo con la fórmula VII, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de

C_1-C_6, cicloalquilo de C_3-C_8, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, o $-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6 y R^{21} es -H.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIg, en donde cada R^{5a} es independientemente alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIIg, en onde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6; y R^{21} es -H.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, arilo, heteroarilo, heterociclilo, alquilo de C_1-C_6-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C_6-arilo, -Z, -Y-Z, o -X-Y-Z, en donde

X es -O-,

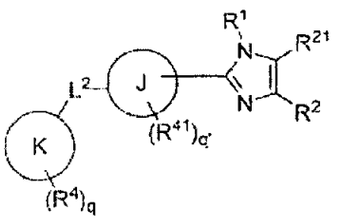
Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, o cicloalquilo de C_3-C_8; y

Z es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VII, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas VIIa-VIIg, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de la fórmula VIII,



(VIII),

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula

IVa-d, y R^2, R^{21}, R^4, R^{41}, J, K, L^2, q, y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmual VIII en donde K es fenilo o piridilo.

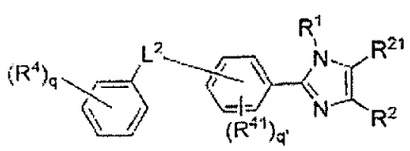
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII en donde K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII en donde K es piridilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII en donde J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII en donde J es fenilo y K es fenilo.

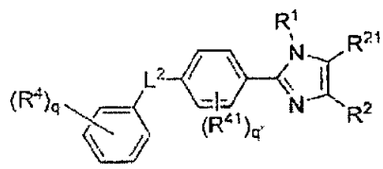
En una realización, la invención proporciona el compuesto de la fórmula IX,



(IX),

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de la fórmula X,



(X),

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula X, en donde L^2 es un enlace; dichos compuestos se denominan en adelante fórmula XI.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_8, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, o $-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, o halquilo de C_1-C_6,

Dichos compuestos se denominan en adelante fórmula XIa.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace, y

R^7 es hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6;

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6;

En donde cada R^{11} es independientemente H, halógeno, alquilo (de C_1-C_6) y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$,

Dichos compuestos se denominan en adelante fórmula XIb.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde cada R es independientemente halógeno, arilo, heteroarilo, heteroaciclilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIa, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6;

En donde cada R^{15} es independientemente H, halógeno, o alquilo de (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$,

Dichos compuestos se denominan en adelante fórmula XId.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIb, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compeusto de acuerdo con la fórmula XId, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, hetarociclilo, $-G^1$, o $-E-G^1-$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, arilo, heteroarilo, heterociclilo, alquilo de C_1-C_1-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C_6-arilo, -Z, -Y-Z, -X-Y-Z, en donde

X es -O-,

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), alquenilo de C_2-C_6, o cicloalquilo de C_3-C_8; y

Z es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2-$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$.

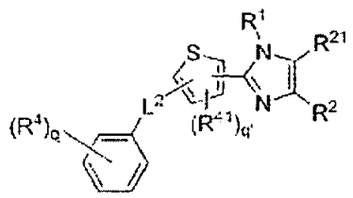
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XI, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de lsa fórmulas XIa-XId, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII, en donde J es tienilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII, en donde J es tienilo y K es fenilo.

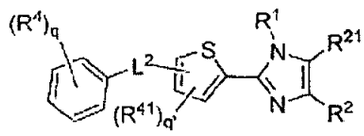
En otra realización, la invención proporciona el compuesto de la fórmula XII,



(XII),

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de la fórmula XIII,

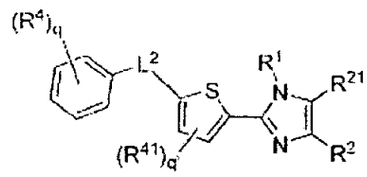


(XIII)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula

IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de la fórmual XIV,



(XIV)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIV, en donde L es un enlace, dichos compuestos se denominan en adelante fórmula XV.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_8, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, o $-N(R^{11})_2$.

340

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6,o haloalquilo de C_1-C_6, dichos compuestos se denoninan en adelante fórmula XVa.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, nitro, arilo, heteroarilo, hetarociclilo, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6;

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$,

Dichos compuestos se denominan en adelante XVb.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CONR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde cada R^4 es independientemente halógeno, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XVa,

R^2 es $-L^3-R^7$, en donde L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$,

Dichos compuestos se denominan en adelante fórmula XVd.

En otra realización, la invención proporciona el compuesto de la fórmula XVb, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XVd, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{11} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde R^{11} es hidrógeno, halógeno, nitro, ciano, arilo, heteroarilo, heterociclilo, alquilo de C_1-

C_6-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C_6-arilo, -Z, -Y-Z, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, o cicloalquilo de C_3-C_8; y

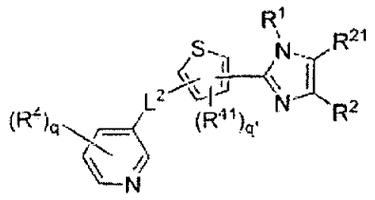
Z es H, -CN, halógeno, $-OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, $-N(R^{11})$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$ o $-N(R^{11})COOR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XV, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas XVa-XVd, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6, haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula VIII, en donde K es piridinilo.

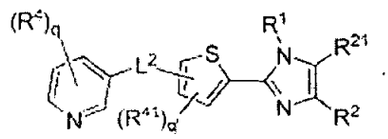
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XVI,



(XVI)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

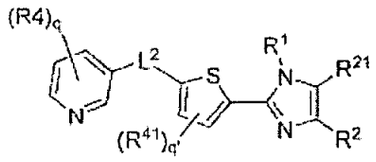
En otra realización, la invención proporciona el compuesto que tiene la fórmula XVII,



(XVII)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XVIII,



(XVIII)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es lo definido para la fórmula IVa-d, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XVIII, en donde L^2 es un enlace, dichos compuestos se denominan en adelante fórmula XIX.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIX, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, $-OR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-NR^{11}COR^{11}$, o $-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIX, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, dichos compuestos se denominan en adelante fórmula XIXa.

En otra realización, a invención proporciona el compuesto de acuerdo con la fórmula XIX, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo de C_2-C_6) o alquenilo de C_2-C_6; y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$ o $-OC(=O)-N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIX, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z-, en donde

Y $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6; y

En donde cada R^{15} es independientemente H, halógeno o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$,

Dichos compuestos se denominan en adelante fórmula XIXb.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIX, en donde cada R^4 es

independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIX, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno, o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6), $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo cno la fórmula XIXa, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_2-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente, H, halógeno, o alquilo de (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{11})_2$, o $-C(=S)N(R^{11})_2$

Dichos compuestos se denominan en adelante fórmula XIXd.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIXb, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde Cada R^{15} es independientemente hidrógeno o halógeno y G^1 es alquilo de C_1-C_6, haloalquilo de C_2-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIXd, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1-$, $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde Cada R^{15} es independientemente hidrógeno o halógeno; y G^1 es alquilo de C_1-C_6, haloalquilo de C_2-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XIX, en dnde R^{21} es hidrógeno, halógeno, nitro, ciano, arilo, heteroarilo, heterociclilo, alquilo de C_1-C_6-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C_6-arilo, -Z, -Y-Z, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C-C_6, cicloalquilo de C_3-C_8; y

Z es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, -

$C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$ o $-N(R^{11})COOR^{11}$.

En otra realización, la invención proprociona el compuesto de acuerdo con la fórmula XIX, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas XIXa-XIXd, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es heteroarilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIIa-d, en donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, porazolilo, quinolinilo, o isoquinolinilo, la totalidad de los cuales optativamente se sustituyen con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIIa-d, en donde R_1 es tienilo, furilo, pirrolilo, pirimidinilo, pirazidinilo, pirazolilo,

quinolinilo, o isoquinolinilo, la totalidad de los cuales se sustituyen optativamente con uno o más R^{5a} y J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, n donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo o isoquinolinilo, la totalidad de los cuales se sustituyen optativamente con uno o más R^{5a}, y K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es tienilo, furilo, piridilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo, o isoquinolinilo, la totalidad de los cuales se sustituyen optativamente con uno o más R^{5a}, J es fenilo, y K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo, o isoquinolinilo, la totalidad de los cuales se sustituye con R^{5a}, J es fenilo, K es fenilo y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es tienilo, furilo, pirrolilo, pirdinilo, pirimidinilo, pirazidinilo, pirazolilo,

quinolinilo, o isoquinolinilo, la totalidad de los cuales se sustituyen optativamente con por lo menos uno o más R^{5a};

J es fenilo; K es fenilo; L^2 es un enlace;

y R^2 es $-L^3-R^7$, en donde L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, $-(=N-OH)R^{11}$, o $-C(=S)N(R^{11})$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo, o isoquinolinilo, la totalidad de los cuales se sustituyen otptativamente con uno o más R^{5a},

J es fenilo; K es fenilo; L^3 es un enlace;

Y cada R^4 es indendependientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independiemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo, o isoquinolinilo, la totalidad de los cuales se sustituyen optativamente con uno o más R^{5a};

J es fenilo; K es fenilo; L^3 es un enlace;

Y cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno y G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIIa-d, en donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo o isoquinolinilo, la totalidad de los cuales se sustituye optativamente con uno o más R^{5a};

J es fenilo, K es fenilo; L^2 es un enlace;

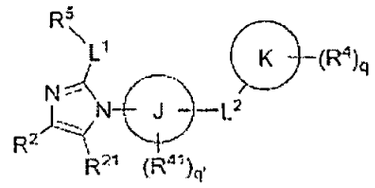
Y R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o cicloalquilo de C_3-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d,

en donde L^1 es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8, en donde m' es cualquiera de 1 a 4, y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6), y R^2, R^{21}, R^3, R^5 y G son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de la fórmula XX,



(XX),

O una sal farmacéuticamente aceptable de él, un isómero o un profármaco de él, en donde

L^1 es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8, en donde

m' es cualquiera de 1 a 3; y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6) o haloalquilo (de C_1-C_6),

y R^2, R^{21}, R^4, R^{41}, R^5, L^2, J, K, q y q' son lo definido para la fórmula IIa-d.

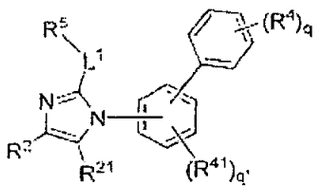
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XX, en donde J. es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XX, en donde K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XX, en donde J es fenilo y K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XX, en donde J es fenilo, K es fenilo, y L^2 es un enlace.

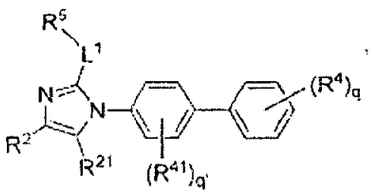
En otra realización, la invención proporciona el compuesto de la fórmula XXI



(XXI)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde L^1 es lo definido para la fórmula XX, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII,



(XXII)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde L^1 es lo definido para la fórmula XX, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_6; m' es 1 o 2; y R^5 es fenilo optativamente sustituido con uno o más R^{5a},
Dichos compuestos se denominan en adelante fórmula XXIII.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIII, en donde R^7 es $-L^3-R^7$, en donde L^3 es un enlace; y
R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde
Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_8), o alquenilo de C_2-C_6,
En donde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_3-C_8), o alquilo (de C_1-C_6); y
Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=O)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIII, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo,

heterociclilo, $-G^1$, o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIII, en donde cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$

En donde R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIII, en odnde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde R^{15} es -H; m es 1, 2 o 3; y R^3 es heterociclilo optativamente sustituido con uno o más R^{5a}, dichos compuestos se denominan en adelante fórmula XXIV.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIV, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_8) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_3-C_8), o alquilo de C_1-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIV, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde E es $-[C(R^{15})_2]-$, en donde

Cada R^{15} es independienmente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIV, en donde cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$

En donde cada R^1 es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIV, en donde R^{21} es hidrógeno,

halógeno, nitro, ciano, alquilo de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde R^{15} es independientemente -H o alquilo (de C_1-C_6), m es 1, 2, 3, o 4; y R^5 es heterociclilo optativamente sustituido con uno más R^{5a}, dichos compuestos se denominan en adelante fórmula XXIVa.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIVa, en donde R^2 es $-L^3-R^7$, en donde L es un enlace, y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_8), o alquenilo de C_2-C_6,

En donde R^1 es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIVa, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIVa, en donde cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

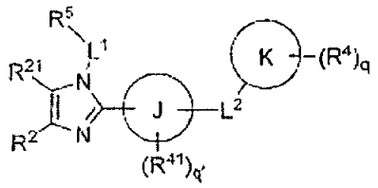
E es $-[C(R^{15})_2]_m-$,

En donde cada R^1 es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIVa, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de la fórmula XXVI



(XXVI),

O una sal farmacéuticamente aceptable, un isómero o un profármaco de él, en donde

L^1 es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8, en donde

m' es cualquiera de 1 a 3; y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), cicloalquilo (de C_3-C_8), o haloalquilo (de C_1-C_6),

y R^2, R^2, R^4, R^{41}, R^5, L^2, J, K, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde J es arilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde J es heteroarilo, dichos compuestos en adelante se denominan compuestos de la fórmula XXVIa.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIa en donde K es arilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIa en donde K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde K es arilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI, en donde K es heteroarilo, dichos

compuestos en adelante se denominan compuestos de la fórmula XXVIb. En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIb, en donde J es arilo.

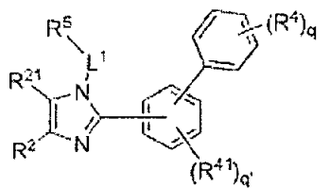
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIb en donde J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde J es fenilo y K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVI en donde J es arilo, K es fenilo y L^2 es un enlace.

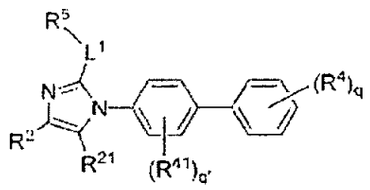
En otra realización, la invención proporciona el compuesto de la fórmula XXVII,



(XXVII)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde L^1 es lo definido para la fórmula XXVI, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIII,



(XXVIII)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde L^1 es lo definido para la fórmula XXVI, y R^2, R^{21}, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIII, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$, cicloalquilo (de C_3-C_8) o alquenilo de C_2-C_6,
En donde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_2-C_8) o alquilo (de C_1-C_6); y
Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIII, en donde cada R es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m$, en donde
Cada R^1 es independientemente hidrógeno o halógeno, y
G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIII, en donde cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_mm$,
En donde cada R^{15} es independientemente hidrógeno o halógeno; y
G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVII, en donde cada R^1 es independientemente -H, alquilo (de C_1-C_6) o cicloalquilo (de C_3-C_8); m' es 1 o 2; y R^5 es fenilo optativamente sustituido

con uno o más R^{5a}, dichos compuestos se denominan en adelante fórmula XXIX.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIX,

En donde R^2 es $-L^3-R$, en donde L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$, cicloalquilo (de C_3-C_8), o alquenilo de C_2-C6),

En donde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_3-C_8) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_3-C_8) o alquilo (de C_1-C_6); y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIX, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIX, en donde cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXIX, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIII, en dnde R^{15} es -H; m es 1, 2, o 3; y R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}, dichos compuestos se denominan en adelante fórmula XXX.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXX, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_8), o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_3-C_8), o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona le compuesto de acuerdo con la fórmula XXX, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, $-G^1$, o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXX, en donde cada R^{41} es independientemente $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

En otra realización, la invención proporciona le compuesto de acuerdo con la fórmula XXX, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVIII, en donde cada R^{15} es independientemente -H, o alquilo (de C_1-C_2); m es 1, 2, 3 o 4; y R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}, dichos compuestos se denominan en adelante fórmula XXXI.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXXI, en donde R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

En dnde cada R^{15} es independientemente H, halógeno, cicloalquilo (de C_3-C_8), o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-O(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXXI, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXXI, en donde cada R^{41} es independientemente $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R_{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXXI, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}; y R^2 es $-L^3$-R^7, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2;

R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}; y

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_2), m' es 1 o 2; R es heteroarilo optativamente sustituido con uno o más R^{5a}; y cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVII, en donde cada R^{15} es independientemente -H, o alquilo (de C_1-C_2); m' es 1 o 2; R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}, y

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVII, en donde cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}, y cada R^4 es independientemente halógeno, arilo, hetaroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

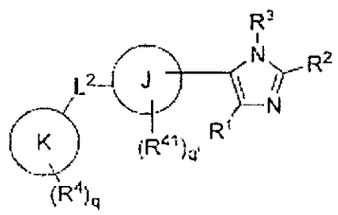
En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVII, en donde cada R^{15} es independientemente -H o alquilo de (C_1-C_2); m' es 1 o 2; R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}; y

Cada R^{41} es independientemente halógeno, $-G^1$, o $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$,

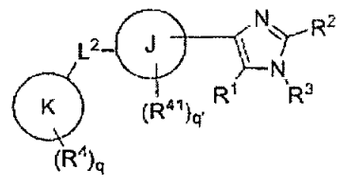
En donde R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII,



(XXXII)



(XXXIII)

o una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^1 es hidrógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6, y R^1, R^2, R^4, R^{41}, L^2, q y q' son lo definido para la fórmula IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXII, en donde J es arilo, K es arilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo, K es fenilo y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo, K es fenilo, L^2 es un enlace; y R^1 es es fenilo optativamente sustituido uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo, K es fenilo, L^2 es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a} y cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$ y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$.

En otra realización la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo; K es fenilo; L^2 es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a} y cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo, K es fenilo, L^2 es un enlace, R^1 se sustituye optativamente con uno o más R^{5a} y R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(O)OR^{11}$, $-C(=O)N(R^{11})$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo; K es fenilo; L^3 es un enlace, R^1 es fenilo, optativamente sustituido con uno o más R^{5a} y cada R^{5a} es independientemente halógeno, alquilo de C_1-C, alcoxi de C_1-C_6, alcoxi de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, esta invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es heteroarilo; K es arilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K es fenilo y L^3 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K es fenilo, L^2 es un enlace, y R^1 es fenilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es fenilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K es fenilo; L^2 es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo, K es fenilo, L^2 es un enlace, R^1 es fenilo optativamente sustituido con uno o más R^{5a}, y cada R^{5a} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmualas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo, K es fenilo, L^2 es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a}; y R^2 es $-L^3-R^7$, en donde

L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o -alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K es fenilo, L^2 es un enlace, R^1 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es heteroarilo; K es heteroarilo y L es un enlace.

En otra realización, la ivención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo, K es piridilo, pirimidilo, o pirazinilo, L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K es fenilo, pirimidilo, o pirazinilo; L^2 es un enlace; y R^1 es fenilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K piridilo, pirimidilo, o pirazinilo; L^2 es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2-$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo, K es piridilo, pirimidilo, o pirazinilo; L^2 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o

pirazinilo; K es piridilo, pirimidilo, o pirazinilo; L es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a}; y R^2 es $-L^3-R^3$, en donde

L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

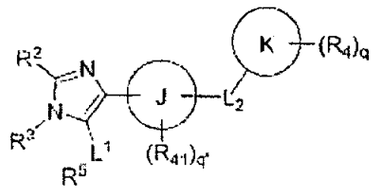
Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6), y

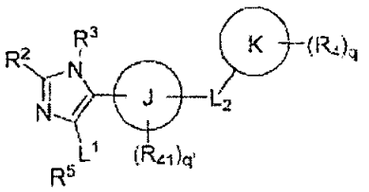
Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-O(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXII y XXXIII, en donde J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo; K es piridilo, pirimidilo, o pirazinilo; L^2 es un enlace; R^1 es fenilo optativamente sustituido con uno o más R^{5a}, y cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV,



(XXXIV)



(XXXV)

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^3 es hidrógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6 y R^1, R^2, R^4, R^{41}, L^2, q y q' son lo definido para las fórmulas IIa-d.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es arilo; K es arilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; y L^2 es un enlace; cada R^{15} es independientemente -H o aluqilo (de C_1-C_2); m' es 1 o 2; y R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; y L^2 es un enlace; cada R^{15} es independientemente -H o aluqilo (de C_1-C_2); m' es 1 o 2; y R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}; y R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo, y L^2 es un enlace; cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; R^5 es heteroarilo optativamente sustituido con uno o más R^{5a} y cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-OR^{11}$, o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; y L^2 es un enlace; cada R^{15} es independientemente -H o alquilo (de C_1-C_2), m' es 1 o 2; R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}; y cada R^{41} es independientemente halógeno, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$;

en donde cada R_{15} es independientemente hidrógeno o halógeno; y G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; y cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es fenilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; y cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^{41} es independientemente halógeno, $-G^1$ es $-E-G^1$, en donde

E es $-[C(R^{11})_2]_m-$,

En donde R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es fenilo optativamente sustituido con uno o más R^{5a}; y R^2 es $-L^3-R^7$, en donde L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, haloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; y cada R^{15} es independientemente -H o alquilo (de C_1-C_2); m' es 1 o 2; y R^5 es fenilo optativamente sustituido con uno o más R^{5a}; y cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; R^{15} es -H; m es 1, 2 o 3; y R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; R^{15} es -H; m es 1, 2 o 3;
R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}; y cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{15})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; R^{15} es -H; m es 1, 2 o 3; R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}; y cada R^{5a} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; R^{15} es -H; m es 1, 2 o 3; R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}; y R es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_8) o alquenilo de C_2-C_6),

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXXIV y XXXV, en donde J es fenilo; K es fenilo; L^2 es un enlace; R^{15} es -H; m es 1, 2 o 3; R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}; y cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es arilo o heteroarilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pizainilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo, piridilo, tienilo, pirrolilo, o furanilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo, piridilo o tienilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es piridilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es tienilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde K es arilo o heteroarilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde K es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde K es fenilo, piridilo, tienilo, pirrolilo, o furanilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde K es fenilo o piridilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde K es piridilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde K es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es arilo o heteroarilo, y K es arilo o heteroarilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es arilo o heteroarilo; K es arilo o heteroarilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde

J es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo,

K es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo,

tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo; y

L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo, piridilo, tienilo, pirrolilo o furanilo; K es fenilo, piridilo, tienilo, pirrolilo, o tienilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo, piridilo, o tienilo; K es fenilo o piridilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo; K es fenilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es piridilo; K es fenilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es tienilo; K es fenilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es fenilo; K es piridilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde J es tienilo; K es piridilo; y L^2 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^5 es arilo, heterociclilo, o heteroarilo, en donde R^5 optativamente se sustituye con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^5 es arilo o heteroarilo, en onde R^5 se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^5 es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo, en donde R^5 se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde L^1 es un enlace; y R^5 es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo, en donde R^5 se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde L^1 es un enlace; R^5 es fenilo, piridilo, tienilo, pirrolilo o furanilo, en donde R^5 se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde L^1 es un enlace, y R^5 es fenilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde L^1 es un enlace, y R^5 es piridilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde L^1 es un enlace, y R^5 es tienilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, arilo, heteroarilo, heterociclilo, alquilo de C_1-C_6-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C_6-arilo, -Z, -Y-Z o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m$, alquenilo de C_2-C_6 o cicloalquilo de C_3-C_8; y

Z es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6, o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^1 es hidrógeno, arilo, heteroarilo, heterociclilo, alquilo de C_1-C_6-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C_6-arilo, -Z o -Y-Z en donde

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6 o cicloalquilo de C_3-C_8; y

Z es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, -

$C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^3 es hidrógeno, alquilo de C_1-C_6, o haloalquilo (de C_1-C_6).

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV y XXVI-XXXV, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno o $-[C(R^{15})_2]-Z$, en donde

Cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_2) y

Z es -H, halógeno, $-OR^{11''}$, $-C(=O)R^{11''}$, $-C(=O)OR^{11''}$, $-C(=O)N(R^{11''})_2$, $-C(=N-OH)R^{11''}$, o $-C(=S)N(R^{11''})_2$,

En donde $R^{11''}$ es -H o (alquilo de C_1-C_6).

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV y XXVI-XXXV, en donde R^2 es -halógeno, $-CF_3$, $-CH_2OH$, $-CH_3SO_2Me$, $-C(CH_3)_2OH$ o $-C(CH_3)_2SO_2Me$.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV y XXVI-XXXV, en donde R^2 es -halógeno, $-CF_3$, $-CH_2OH$, o $-C(CH_3)OH$.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV y XXVI-XXXV, en donde R^2 es $-CF_3$, o $-C(CH_3)OH$.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXXVI-XXXV, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde:

Cada R^4 es independientemente halógeno, $-CH_2-G^1$, $-C(H)(F)-G^1$, $-CF-G^1$, en donde

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, -F, $-OR^{11'}$ o $-SO_2R^{11'}$

En donde $R^{11'}$ es -H o alquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde cada R^4 es independientemente $-CH_3$, $-CF_3$, $-CF_2H$, $-CH_2F$, -OH, $-CH_2OH$ o $-SO_2$(alquilo de C_1-C_3).

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde cada R^{41} es independientemente halógeno, metilo o trifluorometilo.

En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, arilo, heteroarilo, heterociclilo, alquilo de C_1-C_6-heterociclilo, alquilo de C_1-C_6-heteroarilo, alquilo de C_1-C-arilo, -Z, -Y-Z, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6 o cicloalquilo de C_3-C_8;

Z es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-(=O)N(R^{11})_2$, $-N(R^{11})_2$, -CN, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas IIa-d, IIIa-d, IVa-d, IV-XXIV, y XXVI-XXXV, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IIa-d, en donde R^1 es $-L^1-R^5$, en donde R^1 es un enlace, $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8; y

R^5 es fenilo o piridilo, cada uno optativamente sustituido con uno o dos R^{5a}, en donde

Cada R^{5a} es independientemente -halógeno, alcoxi de C_1-C, alquilo de C_1-C_6 o haloalquilo de C_1-C_6;

R^2, R^{21} y R^3 son cada uno independientemente -H, $-[C(R^{15})_2]_m$-OH, -alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-C(O)N(R^{11})_2$- o $-COOR^{11}$;

L^2 es un enlace;

J es fenilo, piridilo, o tienilo;

K es fenilo o piridilo;

Cada R^{41} es halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6; y

Cada R^4 es halógeno, $-[C(R^{15})_2]_m$-OH, $-SO_2N(R^{11})_2$, $-C(O)N(R^{11})_2$, $-COOR^{11}$, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula IVa-d, en donde

R^1 es $-L^1$-R^5, en donde

L^1 es un enlace, $-[C(R^{15})_2]_m$-, o cicloalquilo de C_3-C_8; y

R^5 es fenilo o piridilo, cada uno optativamente sustituido con uno o dos R^{5a}, en donde

Cada R^{5a} es independientemente -halógeno, alcoxi de C_1-C_6, alquilo de C_1-C_6, o haloalquilo de C_1-C_6;

R^2, R^{21} y R^3 son cada uno independientemente -H, $-[C(R^{15})_2]_m$-OH, alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-C(O)N(R^{11})_2$ o $-COOR^{11}$;

L^2 es un enlace;

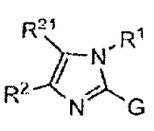
J es fenilo, piridilo, o tienilo;

K es fenilo o piridilo;

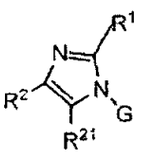
Cada R^{41} es halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6; y

Cada R^4 es halógeno, $-[C(R^{15})_2]_m-OH$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, $-C(O)N(R^{11})_2$, $-COOR^{11}$, alquilo de C_1-C_6 o haloalquilo de C_1-C.

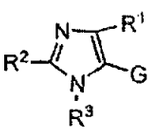
En un segundo aspecto, la invención proporciona compuestos intermedios de acuerdo con una de las fórmulas XXVa-d,



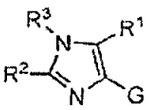
XXVa



XXVb



XXVc



XXVd

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde

R^1 es $-L^1-R^5$, en donde

L^1 es un enlace; L^5, L^6, $-L^5-L^6-L^5$ o $-L^6-L^5-L^6$, en donde

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

cada L^6 es -CS-, -CO-, $-SO_2-$, -O-, $CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$ o $-C(=NN(R^{11})_2)-$, arilo, cicloalquilo de C_3-C_6, heteroarilo o -heterociclilo-,

En donde el arilo, cicloalquilo, heteroarilo o heterociclilo se sustituye optativamente con uno o más R^{14}; y

398

O cada L^6 es independientemente alidilo de C_2-C_6;

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$ o $-SO_2N(R^{10})$; y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C, en donde

B es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6-; y

C es halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$ o $-N(R^{11})_2$,

En donde R^5 se sustituye optativamente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, aril alcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi

alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}COOR^{11}$, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 y R^{21} son $-L^3-R^7$, en donde

Cada L^3 es independientemente un enlace o $-(CH_2)_m-V^1-(CH_2)_n-$

n es 0-6; y

V^1 es $-C(R^{11})_2$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})O-$, $-C(R^{11})_2NR^{11}$, $-C\equiv C-$, $-O-$, $-S-$, $-NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-OCO-$, $-CO-$, $CS-$, $-CONR^{10}-$, $-C(=N-R^{11})-$, $-C(=N-OR^{11})-$, $-C(=N-N(R^{11})_2]$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, alquilo de C_3-C_6, o ciclohaloalquilo de C_3-C_6;

O cada L^3 es independientemente alidilo de C_2-C_6,

En donde la caden ade alidilo está optativamente interrumpida por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$ o $-SO_2N(R^{10})-$; y

Cada R^7 es independientemente hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z, o -Y-Z, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, cicloalquilo de C_3-C_8; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, o $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$,

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, haloarilo, ariloxi, aralquiloxi, ariloxialquilo, arilalquilcarboxi (de C_0-C_6), $C(R^{11})=C(R^{11})-COOH$, arilo, heteroarilo, heterociclilo, heterocicliloxi, heteroariloxi, -Z', -Y'-Z' o -X'-Y'-Z', en donde

X' es -O-;

Y' es $-[C(R^{15})_2]_m-$ o -cicloalquilo de C_3-C_6; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-OR^{11}$, $-N(R^{11})S(O=)R^{11}$, o $-N(R^{11})S(O=)_2R^{11}$,

En donde cada R^{7a} se sustituye optativamente con uno o más R^8,

En donde cada R^8 es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, haloalquilo de C_1-$C_6(OR^{11})$, alquilo de C_0-C_6OR^{11}, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_1-C_6COR^{11}, alquilo de C_0-C_6COOR^{11} o alquilo de C_0-$C_6SO_2R^{11}$,

Siempre que R^2 y R^{21} no sean simultáneamente hidrógeno

R^3 es $-L-R^6$, en donde

L es un enlace, $-X^3-(CH_2)_n-X^3$, $-(CH_2)_m-X^3-(CH_2)_n-$ o $-(CH_2)_{1+w}-Y^3-(CH_2)_w-$ en donde

n es 0-6; cada w es independientemente 0-5; y

cada X^3 es independientemente un enlace, $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})-$, $-C(R^{11})=C(R^{11})-$, $-C\equiv C-$, $-CO-$, $-CS-$, $-CONR^{10}-$, $-C(=N)(R^{11})-$, $C(=N-OR^{11})-$, $-C[=N-N(R^{11})_2]$, $-CO_2-$, $-SO_2-$ o $-SO_2N(R^{10})-$; y

Y^3 es $-O-$, $-S-$, $-NR^7-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-OCO-$, $-OC(=O)N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-N(R^{10})SO_2-$, o $-NR^{10}CSNR^{10}-$;

O L es una cadena de alidilo de C_{2-6} en donde la cadena de alidilo está optativamente interrumpida por $-C(R^{11})-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}$, $-C\equiv C$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})$; y

R^6 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, arilo, cicloalquilo de C_2-C_6, heteroarilo, heterociclilo, $-CN-$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, o $-C(=O)N(R^{11})(OR^{11})$, en donde

El arilo, heteroarilo, cicloalquilo, o heterociclilo se sustituye optativamente con unoo más R^{6a}, en donde

Cada R^{6a} es independientemente $-Z''$, $-Y''-Z''$, o $-X''-Y''-Z''$, en donde

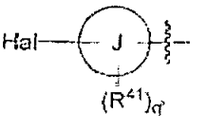
X'' es $-O-$;

Y" es $-[C(R^{15})_2]_m-$, alquenilo de C-C_6, cicloalquilo de C_3-C_8, heterociclilo, arilo o heteroarilo, en donde

El arilo, heteroarilo, cicloalquilo o heterociclilo se sustituye optativamente con por lo menos un grupo que es cada uno independientemente Z";

Z" es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})$, $-C(=O)N(R^{11})N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, $-OC(=O)-OR^{11}$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$; y

G es un grupo de la fórmula



, en donde

Hal es halógeno;

J es arilo o heteroarilo;

Cada R^{41} es indpendientemente halógeno, nitro, $CR^{11}=CR^{11}COOR^{11}$, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCON(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

En donde cada R^4 es optativamente halógeno, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_1-C_6, aril-alquilcarboxi de C_0-C_6, -G', -E'-G', o -D'-E'-G', en donde

D' es -O-,

E' es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8; y

G' es -H, halógeno, $-COR^{11}$, $-COOR^{11}$, -C≡N, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$;

Cada m es 0, 1, 2, 3, 5, 5 o 6; y

q' es 1, 2, 3 o 4; y

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, haloalquilo de C_1-C_6, $-N(R^{11})_2$, arilo, -alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)-heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)C=O(OR^{13}), alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_9-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de

C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alquilarilo de C_{0-6}, aril alquilcarboxi de C_{0-6}, alquilo de C_0-C_6, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6), (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6,

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, halógeno, haloalquilo de C_1-C_6, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6 $CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde Hal es Cl, Br o I.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde Hal es Cl.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde Hal es Br.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde Hal es I.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es arilo o heteroarilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es fenilo, piridilo, tienilo, pirrolilo o furanilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es fenilo, piridilo, o tienilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es fenilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es piridilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde J es tienilo.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^5 es arilo, heterociclilo, o heteroarilo, en donde R^5 optativamente se sustituye con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^5 es arilo o heteroarilo, en donde R^5 optativamente se sustituye con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^5 es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo, en donde R^5 optativamente se sustituye con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde L^1 es un enlace.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde L^1 es un enlace, y R^5

es fenilo, piridilo, tienilo, pirrolilo, furanilo, pirimidinilo, pirazinilo, imidazoilo, pirazoilo, oxazoilo, tiazoilo, isoxazoilo, isotiazoilo, triazoilo, triazinilo, tetrazoilo, o tetrazinilo, en donde R^5 se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde L^1 es un enlace, y R^5 es fenilo, piridilo, tienilo, pirrolilo, o furanilo, en donde R^5 se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^5 es fenilo se sustituye optativamente con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde L^1 es un enlace; y R^5 es piridilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde L^1 es un enlace; y R^5 es tienilo optativamente sustituido con uno o más R^{5a}.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, o $-[C(R^{15})_2]-Z$, en donde

Cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_2); y

Z es -H, halógeno, $-OR^{11''}$, $-C(=O)R^{11''}$, $-C(=O)OR^{11''}$, $-C(=O)N(R^{11''})_2$, $-C(=O)N(R^{11''})_2$, $-C(=N-OH)R^{11''}$, o $-C(=S)N(R^{11''})_2$,

En donde $R^{11''}$ es -H, o (alquilo de C_1-C_6).

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^2 es halógeno, $-CF_3$, $-CH_2OH$, $-CH_2SO_2Me$, $-C(CH_3)_2OH$, o $-C(CH_3)_2SO_2Me$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^2 es halógeno, $-CF_3$, $-CH_2OH$, o $-C(CH_3)_2OH$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^2 es $-CF_3$ o $-C(CH_3)_2OH$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^{41} es independientemente $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde R^1 es L^1-R^5, en donde L^1 es un enlace; y

R^5 es fenilo o piridilo, cada uno optativamente sustituido con uno o dos R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, $-CH_3$ o $-CF_3$;

R^2 es $-H$, $-C(R^{20})_2OH$, $-CH_3$, $-CF_3$ o halógeno, en donde

Cada R^{20} es independientemente $-H$, $-F$, CH_3 o $-CF_3$;

J es fenilo, piridilo, o tienilo; y

Cada R^{41} es halógeno, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2CF_3$ o $-CH_2CF_3$.

En otra realización, la invención proporciona el compuesto de acuerdo con la fórmula XXVa-d, en donde q`es 0 o 1; R^1 es L^1-R^5, en donde L^1 es un enlace; y

R^5 es fenilo optativamente sustituido con uno o dos R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, $-CH_3$ o $-CF_3$;

Cada R^2 es -H, $-C(R^{20})_2OH$, $-CH_3$, $-CF_3$, o halógeno, en donde

Cada R^{20} es independientemente -H, -F, $-CH_3$, o $-CF_3$; y

R^{41} es halógeno, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2CF_3$ o $-CH_2CF_3$.

En otra realización, la invención proporciona el compuesto de acuerdo con las fórmulas XXVa-d, en donde cada R^{41} es independientemente halógeno, metilo o trifluorometilo. En otra realización, la invención proporciona el compuesto de acuerdo con cualquiera de las realizaciones previas en donde R^{21} es hidrógeno.

En un tercer aspecto, la invención proporciona una composición farmacéutica que comprende un compuesto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d, o IV-XXXV, o un derivado farmacéuticamente aceptable de él, en un portador farmacéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula IV, o un

derivado farmacéuticamente aceptable de él, en un portador faramcéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula V, o un derivado farmacéuticamente aceptable de él, en un portador faramcéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula VI, o un derivado farmacéuticamente aceptable de él, en un portador faramcéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula VII, o un derivado farmacéuticamente aceptable de él, en un portador faramcéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula IIa-d, o un derivado farmacéuticamente aceptable de él, en un portador faramcéuticamente aceptable.

En un cuarto aspecto, la invención proporciona un estuche, que comprende un material de empaquetado y un compuesto de

cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV, o un derivado farmacéuticamente aceptable de él, que es eficaz para modular la actividad de un receptor nuclear o para el tratamiento, la prevención, la inhibición o el mejoramiento de uno o más síntomas de enfermedades o trastornos mediados por un receptor nuclear.

En otra realización, la invención proporciona un estuche, que comprende un material de empaquetado y un compuesto de la fórmula IIa-d, o un derivado farmacéuticamente aceptable de él, que es eficaz para modular la actividad de un receptor nuclear o para el tratamiento, la prevención, la inhibición o el mejoramiento de uno o más síntomas de enfermedades o trastornos mediados por un receptor nuclear.

En otra realización, la invención proporciona un estuche, que comprende un material de empaquetado y un compuesto de la fórmula IIa-d, o un derivado farmacéuticamente aceptable de él, que es eficaz para modular la actividad de un receptor nuclear o para el tratamiento, la prevención, la inhibición o el mejoramiento de uno o más síntomas de enfermedades o trastornos mediados por un receptor nuclear, que también comprende una etiqueta que indica que el compuesto de la fórmula IIa-d, o un derivado farmacéuticamente aceptable de él, se usa para modular la actividad de un receptor nuclear o

para el tratamiento, la prevención o el mejoramiento de uno o más síntomas de enfermedades o trastornos mediados por un receptor nuclear, o enfermedades o trastornos en donde está involucrada la actividad de un receptor nuclear.

En un sexto aspecto, la invención proporciona un método para tratar, prevenir, inhibir o mejorar los síntomas de una enfermedad o un trastorno que se modula o está afectada de otro modo por la actividad de un receptor nuclear o en la cual está implicaa la actividad del receptor nuclear, que comprende administrar a un sujeto que lo necesita una cantidad terapéuticamente eficaz de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En una realización preferida del sexto aspecto, la invención proporciona un método para tratar, prevenir, inhibir, o mejorar los síntomas de una enfermedad o un trastorno que está modulada o afectada de otro modo por la actividad de un receptor nuclear o en la cual está implicada la actividad de un receptor nuclear, que comprende administrar a un sujeto que lo necesita una cantidad terapeúticamente eficaz de un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

Cuando se hace referencia a la parte (A) de las fórmulas IIa-d con respecto a los métodos para usar compuestos de la

invención, tal como para el tratamiento, la prevención, la inhibición o el mejoramiento de la enfermedad, o para su uso en la preparación de un medicamento para el tratamiento, la prevención, o el mejoramiento de la enfermedad, se entiende que todos los compuestos definidos por la parte (A) están incluidos y no se deben considerar las condiciones de la parte (B) de las mismas fórmulas cuando se determina el el alcance de los compuestos definidos para los usos de la presente.

En una realización preferida del sexto aspecto, la invención proporciona el método en donde la enfermedad o el trastorno es hipercolesterolemia, hiperlipoproteinemia, hipertrigliceridemia, lipodistrofia, hiperglucemia, diabetes mellitus, dislipidemia, aterosclerosis, enfermedad de cálculos biliares, acné comùn, condiciones de piel acneiforme, diabetes, enfermedad de Parkinson, cáncer, enfermedad de Alzheimer, inflamación, trastornos inmunológicos, trastornos de lípidos, obesidad, condiciones caracterizadas por una función de barrera epidérmica perturbada, condiciones de diferenciación interrumpida o exceso de proliferación de la epidermis o de la membrana mucosa, o trastornos cardiovasculares.

En un séptimo aspecto, la invención proporciona un método para reducir los niveles de colesterol en un sujeto que lo

necesita, que comprende administrar una cantidad reductora del nivel de colesterol eficaz de un compuesto de acuerdo con cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En una realización preferida del séptimo aspecto, la invención proporcina un método para reducir los niveles de colesterol en un sujeto que lo necesita, que comprende administrar una cantidad eficaz para reducir los niveles de colesterol de un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

En un octavo aspecto, la invención proporciona un método para tratar, prevenir, o mejorar uno o más síntomas de una enfermedad o trastorno que está afectado por los niveles del colesterol, los triglicéridos, o el ácido biliar, que comprende administrar a un sujeto que lo necesita una cantidad terapéuticamente eficaz de un compuesto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En una realización preferida del octavo aspecto, la invención proporciona un método para tratar, prevenir o mejorar uno o más síntomas de una enfermedad o trastorno que está afectado por los niveles de colesterol, triglicéridos, o ácido biliar, que comprende administrar a un sujeto que lo necesita una

cantidad terapéuticamente eficaz de un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

En un noveno aspecto, la invención proporciona un método para modular la actividad de los receptores nucleares, que comprende poner en contacto al receptor nuclear con un compuesto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En una realización preferida del noveno aspecto, la invención proporciona un método para modular la actividad de los receptores nucleares, que comprende poner en contacto el receptor nuclear con un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

En una realizaación del noveno aspecto, la invención proporciona el método en donde el receptor nuclear es un receptor nuclear huérfano.

En una realización del noveno aspecto, la invención proporciona el método en donde el receptor nuclear es un receptor X del hígado.

En una realización del noveno aspecto, la invención proporciona el método en donde el receptor nuclear es un

receptor X de hígado, en donde el receptor X de hígado es LXRα o LXRβ.

En un décimo primer aspecto, la invención proporciona un método para modular el metabolismo del colesterol, que comprende administrar una cantidad eficaz para modular el metabolismo del colesterol de un compuesto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En una realización preferida del décimo primer aspecto, la nvención proporciona un método para modular el metabolismo del colesterol, que comprende administrar una cantidad eficaz que modula el mestabolismo del colesterol de un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

En un décimo segundo aspecto, la invención proporciona un método para tratar, prevenir o mejorar uno o más síntomas de la hipocolesterolemia en un sujeto que lo necesita, que comprende administrar una cantidad terapéuticamente eficaz de un compeusto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En una realización preferida del décimo segundo aspecto, la invención proporciona un método para tratar, prevenir o

mejorar uno o más síntomas de la hipercolesterolemia en un sujeto que lo necesita, que comprende administrar una cantidad terapéuticamente eficaz de un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

En un décimo tercer aspecto, la invención proporciona un método para aumentar el flujo del colesterol fuera de las células de un sujeto, que comprende administrar una cantidad eficaz para aumentar el flujo del colesterol hacia fuera de un compuesto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d, o IV-XXXV.

En una realización preferida del décimo tercer aspecto, la invención proporciona un método para aumentar el flujo del colesterol fuera de las células de un sujeto, que comprende administrar una cantidad eficaz para aumentar el flujo hacia fuera del colesterol de un compuesto de acuerdo con la parte (A) de las fórmulas IIa-d.

En un décimo cuarto aspecto, la invención proporciona un método para aumentar la expresión del Cassette de unión a ATP (ABC1) en las células de un sujeto, que comprende administrar una cantidad eficaz para aumentar la expresión de ABC1 de un compeusto de cualquiera de las fórmulas IIa-d, IIIa-d, IVa-d, XXVa-d o IV-XXXV.

En las siguientes realizaciones del primer aspecto, es entiende que son aplicables las siguientes condiciones:

(i) cuando L^2 es un enlace, tanto J como K no están ausentes;

(ii) si el compuesto está definido por la fórmula IIaa, entonces

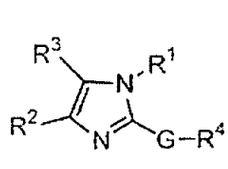
a. si J es fenilo y K es tienilo, furilo o tiazoilo y q es 0, entonces R^1 no es 4-(NH_2SO_2)fenilo, 4-(NH_2SO_2)-3-fluorofenilo, p-(CH_3SO_2)fenilo, o 4p-(CH_3SO2)-3-fluorofenilo y

b. si R^5 es piridilo optativamente sustituido con uno o más R^{5a} y L^1 es un enlace, entonces G no es p-(NH_3SO_2)fenilo o p-(CH_3SO_2)fenilo;

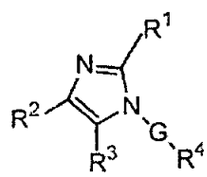
(iii) si el compuesto está definido por la fórmula IIcc o IIdd, entonces G no es p-(NH_3SO_2)fenilo,

(iv) el compuesto no es 1-(bifenil-4-il)-2,5-difenil-1H-imidazol.

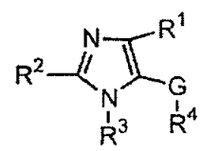
Una realización de la invención se relaciona con compuestos reprsentados por las fórmulas IIaa, IIbb, IIcc o IIdd:



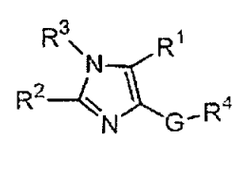
IIaa



IIbb



IIcc



IIdd

Como un isómero, una mezcla de estereoisómeros, una mezcla racémica de ellos de estereoisómeros, o un tautómero, o como una sal, farmacéuticamente aceptable, profármaco, solvato o polimorfo de él.

Cada sustituyente de R^1 se selecciona independientemente del grupo formado por R^5 y $-L^1-R^5$.

Otra realización es que el sustituyente de R^1 es R^5; R^5 preferido se selecciona del grupo formado por un anillo aromático o no aromático de 5-12 miembros, heterociclilo o o heteroarilo de 5-12 miembros que tiene uno o más heteroátomos N, O, o S; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a}. R^5 es preferentemente tienilo, furanilo, piperidinilo, pirrolidinilo, piperazinilo, morfolinilo, tiazolilo, indolilo, isoxazolilo, piridinilo, pirimidinilo, imidazolilo y fenilo.

Ejemplos de grupos de R^{6a} incluyen halógeno, haloalquilo de C_{1-6}, hidroxi, nitro, grupo alifático de C_{1-6}, alcoxi de C_{1-6}, alquilo de $C_{0-6}OR^{11}$, $OCOR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}SR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, arilalquilo, ariloxiarilo, arilo alcoxi de C_{1-6}, Oalquilo de $C_{1-6}COR^{11}$, Oalquilo de $C_{1-6}N(R^{11})_2$, alquilo de $C_{0-6}N(R^{11})_2$, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}N(R^{11})_2$, alquilo de

$C_{0-6}COOR^{11}$, alquilo de $C_{0-6}COON(R^{11})_2$, alquilo de $C_{0-6}CON(R^{11})_2$, alquilo de $C_{0-6}C{\equiv}N$, Oalquilo de $C_{0-6}COOR^{11}$, alquilo de $C_{0-6}OCON(R^{11})_2$, o alquilo de C_{0-6}Oalquilo de C_{0-6}. R^{5a} optativamente se sustituye en la posición sustituible con SO_2R^{11}, alcoxiarilo de C_{0-6}, anillo aromático o no aromático de 5-12 miembros, o heterociclilo o heteroarilo de 5-12 miembros que tiene uno o más heteroátomos N, O o S. Preferentemente, R^{5a} es Cl, Br, F, alquilo de C_{1-6}, haloalquilo de C_{1-6}, alcoxi de C_{1-6}, Oalquilo de $C_{1-6}COOR^{11}$, $NR^{11}COR^{11}$, alquilo de $C_{0-6}CON(R^{11})_2$, NO_2 y Oalquilo de $C_{1-6}CON(R^{11})_2$. Ejemplos de R^{5a} incluyen $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2,-$OCOCH(CH_3)_2$, $OCOC(CH_3)_3$, $NHCOCH_3$, $OCON(CH_3)_2$, $OCONHCH_3$, $OCON(CH_2)_2CH_3$, $OCONHCH(CH_3)_2$, $O(CH_2)_2$, $CONH_2$, $O(CH)(CH_3)_2$, alquilo de C_{1-5}, OCH_2COOH, $OCH_2COOC(CH_3)_3$, $O(CH_2)_2N(CH_2CH_3)_2$, $OC(CH_3)_2COOC(CH_3)_3$, o OCH_2CH_2OH. Más preferentemente, R^{5a} es Cl, F, o CF_3.

Otra realización es que el sustituyente de R^1 es $-L_1-R^5$. R^5 preferido se selecciona del grupo formado por un anillo aromático o no aromático de 5-12 miembros, heterociclilo o heteroarilo de 5-12 miembros que tiene uno o más heteroátomos N, O o S; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a}. Ejemplos de R^{5a} preferidos incluyen fenilo, piridinilo, oxazolilo, tienilo, tiazolilo, morfolinilo, furanilo, imidazolilo, piperazinilo,

pirimidinilo, isoxazolilo, o piperidinlo, más preferentemente, oxazolilo, piridinilo, fenilo, furanilo, tienilo o tiazolilo.

Las realizaciones para L_1 incluyen un enlace directo, alcoxi de C_{1-6}, carbonilo, SO_2, CS, $CON(R^{11})_2$, $CONR^{11}OR^{11}$, $CONR^{11}N(R^{11})_2$, $-C(=NR^{11})-$, $-C(=NOR^{11})_2)-$, un anillo aromático o no aromático de 5-12 miembros, heterociclilo o heteroarilo de 5-12 miembros que tiene uno o más heteroátomos N, O, o S, que se sustituye optativamente en una posición sustituible con uno o más radicales de R^{14}. Otra realización para L_1 es $-(CH_2)_m-V-(CH_2)_n-$ o $V-(CH_2)_n-V$; m es 0-6, V es independientemente $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-OC(=O)$, $-OC(=O)N(R^{10})-$, $-CONR^{11}OR^{11}-$, $-CONR^{11}NR^{11}-$, $-CONR^{11}-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, cicloalquilo de C_{3-6}, $-NR^{10}CSNR^{10}-$, ciclo haloalquilo de C_{3-6} o $-NR^{10}CONR^{10}-$. Un L_1 preferido se selecciona del grupo formado por CONH, alidilo de C_{1-6}, CO, SO_2, CH_2, CH_2O, CH_2CH_2, C=O, CONH, $CONHC(CH_3)_2$, $CONHC(CH_2)_3OCH_2$, OCH_2CH_2, OCH_2CO, $OCH_2CH_2N(CH_2)_2$ y $CONHCH_2CH_2N(CH_3)_2$. L_1 más preferido se selecciona del grupo formado por CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, $CONHCH_2CH_2N(CH_3)_2$; OCH_2 y OCH_2CH_2. R^5 preferido se selecciona del grupo formado por fenilo, piridinilo, oxazolilo, tienilo, tiazolilo, furanilo, morfolinilo, imidazolilo, piperazinilo, pirimidinilo, isoxazolilo, y piperidinilo. Otro R^{5a} preferido incluye halógeno, haloalquilo,

$OCH_2CON(CH_3)_2$, $OCH_2COOC(CH_3)_3$, $OCH_2CH_2N(CH_2CH_3)_2$, OCH_2COOH, $OC(CH_3)_2COOC(CH_3)_2$, $OCON(CH_3)_2$, $OCONHCH_3$, OCH_2CH_2OH, $OCONHCH_2CHCH_3$, o $NHCOCH_3$.

Otra realización es que R^2 se selecciona independientemente del grupo formado por R^7 y L_3-R^7. Cada R^7 se selecciona de hidrógeno, alquilo de C_{1-6}, halógeno, haloalquilo de C_{1-6}, alcoxi de C_{1-6}, haloalquilo de $C_{1-6}OR^{11}$, alquilo de $C_{0-6}COOR^{11}$, alquilo de $C_{0-6}CON(R^{11})_2$, alquilo de $C_{0-6}N(R^{11})_2$, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}C{\equiv}N$, alquilo de C_{0-6} $CONR^{11}N(R^{11})_2$, alquilo de $C_{0-6}OCR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, cicloalquilo de $C_{3-6}OR^{11}$, un anillo aromático o no aromático de 5-12 miembros o heteroarilo y heterociclilo de 5-12 miembro que tiene uno o más heteroátomos N, O, o S; R^7 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{7a}.

Otra realización es que R^2 es R^7, seleccionado del grupo formado por un anlllo aromático o no aromático de 5-12 miembros; heteroarilo y heterociclilo que tiene 5-12 miembros que tiene uno o más heteroátomos N, O, S. R^7 se sustituye optativamente en una posición sustituible con uno o má radicalesde R^{7a}.

R^7 preferido es fenilo, piridinilo, tienilo, furanilo, piperidinilo, pirrolidinilo, piperazinilo, morfolinilo,

tiazolilo, indolilo, oxazolilo, piridinilo, isoxazolilo, pirimidinilo, naftilo, hidrógeno, CF_3, alquilo de $C_{1-6}C{\equiv}N$, CH_2OH, $COOCH_3$, $COON(R^{11})_2$, o $COOR^{11}$. Otros ejemplos de R^7 incluyen trifluorometilo, $CH_2C{\equiv}N$, $C(CH_3)_2C{\equiv}N$, $COOCH_3$, CH_2OH, $CONHCH_2CH_3$, $CONHOCH_2CH(OH)CH_2OH$, $CONHCH_2CH_3N(CH_3)_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2CH_2OCH_3$, CH_2COOCH_3, $CON(CH_3)_2$, $COOCH(CH_3)_2$, $CONHCH_2CH_2CH_2CH_2OCH_3$, $OCOCH(CH_3)_2$, $OCH_2CON(CH_3)_2$, $CH_2CONCH_2(CH_3)$, $C(CH_3)_2OH$, COOH, nitro, cicloalquilo de C_{3-6}, cicloalquilo de $C_{3-6}OR^{11}$, cicloalquilo de $C_{3-6}C{\equiv}N$, o $COOCH(CH_3)_2$. Más preferentemente, R^7 es CF_3, $COOCH_3$, COOH, o $CONHCH_2CH_3$. Cuando R^7 es fenilo o piridinilo, R^{7a} se selecciona del grupo formado por halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, y haloalquilo de C_{1-6}. Ejemplos de R^{7a} incluyen halógeno, trifluorometilo, alquilo de C_{1-6}, alcoxi de C_{1-6}, CH=CHCOOH, $CH_2CHCOOH$, CH_2COOH, OCH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3 y $OCH(CH_3)_2$.

Otra realización es que R^2 es L_3-R^7. Un L_3 se selecciona independientemente de un enlace directo, -CS-, -CO-, -CONH-, $-CONR^{11}-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, $-C(=NN(R^{11})_2)-$; $(CH_2)_m-V_1-(CH_2)_n-$ o $-V_1-(CH_2)_n-V_1-$, m es es 0-6; V_1 es independientemente $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}$, -C≡C-, -O-, -S-, $-NR^{11}-$, $-CR^{11}NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$,

OCO-, -CO-, $-CO_2-$, -CO(=O)-, OC(=O)N(R^{10})-, SO_2-, -(R^{10})SO_2-, -$NR^{10}CONR^{10}-$, cicloalquilo de C_{3-6}, -$NR^{10}CSNR^{10}-$, ciclohaloalquilo de C_{3-6} o -$SO_2N(R^{10})$. Más preferentemente, L_3 es CH_2, CO, OCH_2, CH_2OCH_2, CONH, CH_2OCOH_2, CH_2NHCH_2, $CH_2NC(CH_3)_2$, $CH_2N(CH_3)CH_2$, CH_2COCH_3, $CH_2N(CH_3)_2CH_2$, ciclohexamina o ciclopropanamina.

Cada R^{7a} es independientemente un halógeno, alquilo de C_{1-6}, $CR^{11}-CR^{11}COOR^{11}$, alcoxi de C_{1-6}, alquilo de $C_{1=6}OR^{11}$, alquilo de $C_{1-6}OCOOR^{11}$, alquilo de $C_{0-6}NR^{11}CO^{11}$, alquilo de $C_{0-6}SO_2NCOR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$; alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})C=O(OR^{11}), $OVOR^{11}$, haloalquilo de C_{1-6}, Oalquilo de C_{1-6}, haloarilo, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6}, arilalquilcarboxi de C_{0-6}, $NR^{11}SO_2R^{11}$, Oalquilo de C_{1-6}, Oalquilo de $C_{1-6}COOR^{11}$, alcoxiheteroarilo de C_{0-6}, alcoxiheterociclilo de C_{0-6}, cicloalquilo de $C_{0-6}COOR^{11}$, cicloalquilamina de C_{3-6}, un anillo aromátido o no aromático de 5-12 miembros o heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, O, o S. Ejemplos de R^{7a} se selecciona del grupo formado por halógeno, trifluorometilo, alquilo de C_{1-6}, alcoxi de C_{1-6}, CH=CHOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2O(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3 y $OCH(CH_3)_2$.

Cada R^{7a} se puede sustituir en una posición sustituible con uno o más radicales de R^8; cada R^8 es independientemente alquilo de

C_{1-6}, alcoxi de C_{1-6}, haloalquilo de C_{1-6}, haloalquilo de $C_{1-6}OR^{11}$, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}CON(R^{11})_2$, alquilo de $C_{0-6}COR^{11}$, alquilo de $C_{0-6}COOR^{11}$, $NR^{11}COOR^{11}$, o alquilo de $C_{0-6}SO_2R^{11}$.

Ejemplos de R^{7a} se seleccionan del grupo formado por halógeno, trifluorometilo, alquilo de C_{1-6}, alcoxi de C_{1-6}, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3, y $OCH(CH_3)_2$.

Cada R^3 se selecciona independiemente, del grupo formado por R^6 y $-L-R^6$. Una realización es que R^3 es R^6 y es independientemente hidrógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, haloalquilo de C_{1-6}, haloalquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}CON(R^{11})_2$, $OCON(R^{11})_2$, alquilo de $C_{0-6}COR^{11}$, $CONR^{11}OR^{11}$, alquilo de $C_{0-6}COOR^{11}$; un anillo aromático o no aromático de 5-12 miembros; hetaroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, O, o S; cada R^6 se puede sustituir en una posición sustituible con uno o más radicales de R^{6a}. R^6 preferido es hidrógeno o fenilo optativamente sustituido.

Cada R^{6a} es independientemente halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, haloalquilo de $C_{0-6}OR^{11}$, $CON(R^{11})_2$, $CONR^{11}OR^{11}$, alquilo de $C_{0-6}COOR^{11}$, $CR^{11}=CR^{11}COOR^{11}$, alquilo de $C_{0-6}OR^{11}$, alquilo de C_{0-}

$_{6}COR^{11}$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}COOR^{11}$, alquilo de $C_{0-6}NR^{11}OR^{11}$, alquilo de $C_{0-6}SO_2NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})C=O(OR^{11}), $OVOR^{11}$, Ohaloalquilo de C_{0-6}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6}, arilo alquilcarboxi de C_{0-6}, $NR^{11}SO_2R^{11}$, Oalquilo de $C_{1-6}COOR^{11}$, alcoxiheteroarilo de C_{0-6}, alcoxiheterociclilo de $C_{0-6}COOR^{11}$.

Otra realización es que R^6 es L-R^6, L se selecciona independientmente de un enlace directo, -CO-, -CONH-, -$CONR^{11}$-, -$C(=NR^{11})$-, -$C(=NOR^{11})$-, -CS-, -$C(=NN(R^{11})_2)$-; una cadena de alidilo de C_{2-6} en donde la cadena de alidilo está optativamente interrumpida por -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -C≡C, -O-, -S-, -$N(R^{10})$CO-, -$N(R^{10})CO_2$, -NR^{11}-, -OR^{11}-, -$CON(R^{10})$-, -CO-, -CO_2-, OC(=O)-, OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})$SO-, o -$SO_2N(R^{10})$-; -$(CH_2)_m$-V_0-$(CH_2)_n$- o -V_0-$(CH_2)_n$-V_0-; m es 0-6; n es 0-6; V_0 es independientemente -$C(R^{11})_2$-, -$C(R^{11})_2C(R^{11})_2$-, -$C(R^{11})$=$C(R^{11})$-, -$C(R^{11})_2O$-, -$C(R^{11})_2O$-, -$C(R^{11})_2NR^{11}$-, -C≡C, -O-, -S-, -NR^{11}, -$CR^{11}NR^{11}$-, -$N(R^{10})CO_2$-, -$CON(R^{10})$-, -OCO-, -COR^{11}-, -$COOR^{11}$-, -CO-, -CO_2, -OC(=O), -OC(=O)$N(R^{10})$-, -SO_2-, -$N(R^{10})$SO-, -$NR^{10}COR^{10}$-, -$NR^{10}CSNR^{10}$-, ciclohaloalquilo de C_{3-6} o -$SO_2N(R^{10})$-. Ejemplos de L incluyen O, CF_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH$, $CONHCH_2CH_2N(CH_3)_2$ o OCH_2CH_2.

Cada R^4 se selecciona independientemente de alquilo de C_{1-6}, $CR^{11}=CR^{11}COOH$, alcoxi de C_{1-6}, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}COR^{11}$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}OCOOR^{11}$, alquilo de $C_{0-6}NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})C=O(OR^{11}), $OVOR^{11}$, halógeno, haloalquilo de C_{1-6}, alquilo de $C_{0-6}C\equiv N$, Ohaloalquilo de C_{1-6}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6}, aril alquilo de $C_{0-6}COOR^{11}$, $NR^{11}SO_2R^{11}$, Oalquilo de C_{1-6}, Oalquilo de $C_{0-6}COOR^{11}$, alcoxiheteroarilo de C_{0-6}, alcoxiheterociclilo de C_{0-6}, ciclooalquiloCOOR^{11}, un anillo aromático o un anillo no aromático de 5-12 miembros, o heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, O, o S. R^4 preferido se selecciona del grupo formado por OH, CN, $C(CH_3)_2OH$, SO_2CH_3, $SO_2C(CH_3)_3$, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{1-6}, CH_3COOH, $C(CH_3)_2COOH$, $NH(SO_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, ciclobutano-COOH, $OC(CH_3)_2COOH$, CF_3, $C(CH_3)_2COOH$, CH_2COOCH_3, CH_2CH_2COOH, OCH_3COCH_3 y $COCH_3$. Más preferentemente, R^4 es SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3 o SCH_3.

Cada R^4 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{4a}. Cada R^{4a} se selecciona independientemente de alquilo de C_{1-6}, (alquilo de C_{1-6})C=O(OR^{11}); alcoxide C_{1-6}; alquilo de $C_{1-6}OR^{11}$, alquilo de $C_{0-6}COR^{11}$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$; alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})C=O(OR^{11}), halógeno, haloalquilo de

C_{1-6}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6} arilo alquilo de $C_{0-6}COOR^{11}$, alquilo de $C_{0-6}C{\equiv}N$, $NR^{11}SO_2R^{11}$, Oalquilo de C_{1-6}, o Oalquilo de $C_{0-6}COOR^{11}$.

Cada R^{10} se selecciona independientemente de R^{11}, $C(=O)R^{11}$, CO_2R^{11}, SO_2R^{11}.

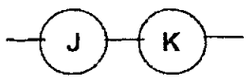
Cada R^{11} se selecciona independientemente de hidrógeno o un grupo alifático de C_{1-8} sustituido o no sustituido; haloalquilo de C_{1-6}, $N(R^{12})_2$; un anillo aromático o no aromático de 5-12 miembros, o heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, S, o O; que se sustituye optativamente en una posición sustituible con uno o más radicales de R^{12}.

Cada R^{12} es independientemente halógeno, haloalquilo de C_{1-6}, alquilo de C_{1-6}, alcoxi de C_{1-6}, (alquilo de C_{1-6})$C{=}O(OR^{13})$; alquilo de $C_{0-6}COR^{13}$, alquilo de $C_{0-6}SO_2R^{13}$, alquilo de $C_{0-6}CON(R^{13})_2$, alquilo de $C_{0-6}CONR^{13}OR^{13}$, alquilo de $C_{0-6}OR^{13}$, alquilo de $C_{0-6}SO_2N(R^{13})_2$, alquilo de $C_{0-6}SR^{13}$, (alquilo de C_{0-6})$C{=}O(OR^{13})$, haloalquilo de $C_{0-6}OR^{13}$, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{0-6}, arilo alquilcarboxi de C_{0-6}, alquilo de $C_{0-6}NR^{13}SO_2R^{13}$, Oalquilo de C_{1-6}, o Oalquilo de $C_{1-6}COOH$.

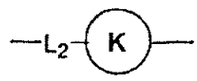
Cada R^{13} es independientemente hidrógeno o un grupo alifático de C_{1-8} sustituido o no sustituido.

Cada R^{14} es independientemente alquilo de C_{1-6}, alcoxi de C_{1-6}, halógeno, haloalquilo de C_{1-6}, alquilo de $C_{0-6}CON(R^{11})_2$, alquilo de $C_{0-6}CONR^{11}OR^{11}$, alquilo de $C_{0-6}OR^{11}$ o alquilo de $C_{0-6}COOR^{11}$.

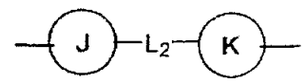
Otra realización de la invención es que G es independientemente G1, G2 o G3;



G1



G2



G3

Cada Anillo J o Anillo K puede estar independientemente ausente, puede ser igual o diferente y se selecciona independientemente de un anillo aromático o no aromático de 5-12 miembros, o heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos, N, S o O.

Cada anillo J o anillo K independientemente se sustituye optativamente en una posición sustituible con uno o más radicales de R^4. El anillo J es preferentemente un anillo de fenilo o un anillo de heteroarilo de 5-6 miembros. Ejemplos del Anillo J incluyen fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, bifenilo,

naftilo, piperidinilo, piperazinilo, o imidazolilo. Un anillo J preferido es tienilo o fenilo. El anillo J se sustituye optativamente en una posición sustituible con uno o más radicales de R^4. Los sustituyentes del anillo J adecuados denominados R^4 incluyen metilsulfonilo, o el grupo alifático de C_{1-6} o sustituyentes seleccionados del grupo formado por $CR^{11}=CR^{11}COOR^{11}$, alquilo de C_{1-6}, alcoxi de C_{1-6}, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{1-6}COR^{11}$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}OCOOR^{13}$, alquilo de $C_{0-6}CON(R^{11})_2$, Oalquilo de $C_{1-6}CON(R^{11})_2$, alquilo de $C_{0-6}C\equiv N$, alquilo de $C_{0-6}NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})$, alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6}) $C\equiv O(OR^{11})$, $OVOR^{11}$, halógeno, haloalquilo de C_{1-6}, Ohaloalquilo de C_{1-6}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6}, arilo alquilo de $C_{0-6}COOR^{11}$, $NR^{11}SO_2R^{11}$, Oalquilo de $C_{1-6}COOR^{11}$, alcoxiheteroarilo de C_{0-6}, alcoxiheterociclilo de C_{0-6}, cicloalquiloCOOR^{11}, un anillo aromático o no aromático de 5-12 miembros y heteroarilo o heterociclilo de 5-12 miembros que tiene unoo má heteroátomos N, O o S. Ejemplos de R^4 preferido incluyen OH, CN, $C(CH_3)_2OH$, SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, $SO_2C(CH_3)_3$, SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{0-6}, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $O(CH_2CH_3)_2COOH$, CH_2COOCH_3, $O(CH_3)_2COOCH_3$, CH_2CH_2COOH, CH=CHCOOH, OCH_2COOCH_3, $COCH_3$, OCH_3, $COOC(CH_3)_3$, ciclobutano-COOH,

$OC(CH_3)_2COOH$, CH_2CH_3, CH_3, $CH(CH_3)_2$, CH_2COOCH_3, $OCON(CH_2CH_3)_2$, $NHCOCH_3$ o CF_3.

Ejemplos del Anillo K incluyen fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, bifenilo, naftilo, piperidinilo, piperazinilo, isoxazolilo, pirimidinilo, o imidazolilo. El anillo K se sustituye optativamente a una posición sustituible con uno o más radicales de R^4. Los sustituyentes del Anillo K adecuados denominados R^4 incluyen metilsulfonilo, o un grupo alifático de C_{1-6} o sustituyentes seleccionados del grupo formado por $CR^{11}=CR^{11}COOR^{11}$, alquilo de C_{1-6}, alcoxi de C_{1-6}, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{1-6}COR^{11}$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}OCOOR^{11}$, alquilo de $C_{0-6}NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})$C=O(OR^{11})$, $OVOR^{11}$, halógeno, haloalquilo de C_{1-6}, Ohaloalquilo de C_{1-6}, alquilo de $C_{0-6}C\equiv N$, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6}, arilo alquilcarboxi de C_{0-6}, $NR^{11}SOR^{11}$, Oalquilo de C_{1-6}, Oalquilo de $C_{0-6}COOR^{11}$, alcoxiheteroarilo de C_{0-6}, alcoxiheterociclilo de C_{0-6}, cicloalquilo $COOR^{11}$, un anillo aromático o un anillo no aromático de 5-12 miembros, y heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, O o S. Preferentemente, el Anillo K es fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo,

bifenilo, naftilo, piperidinilo, piperazinilo, isoxazolilo, pirimidinilo, o imidazolilo. Cuando el Anillo K es un fenilo o o piridinilo, preferentemente se sustituye con metilsulfonilo.

Ejemplos de grupos de R^4 incluyen OH, CN, $O(CH_3)_2OH$, SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, $SO_2C(CH_3)_3$, SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{1-6}, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $C(CH_2CH_3)_2COOH$, $CH_2COOHCH_3$, $C(CH_3)_2COOCH_3$, CH_2CH_2COOH, CH=CHCOOH, OCH_2COOCH_3, $COCH_3$, OCH_3, $COOC(CH_3)_3$, ciclobutano-COOH, $OC(CH_3)_2COOH$, CH_2CH_3, CH_3, $CH(CH_3)_2$, CH_2COOCH_3, $OCON(CH_2CH_3)_2$, $NHCOCH_3$, o CF_3. $-L_2$ es $-(CH_2)_m-V_2-(CH_2)_n-$ o $-V_2-(CH_2)_m-V_2-$; m es 0-6, n es 0-6; V_2 es independientemente $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C$, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $CON(R^{11})O-$, -CO-, $-CO_2-$, $-OR^{11}N-$, $-OR^{11}COO-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-NR^{10}CONR^{10}-$, cicloalquilo de C_{3-6}, $-NR^{10}CSNR^{10}-$, ciclohaloalquilo de C_{3-6} o $-SO_2N(R^{10})-$; un cadena de alidilo de C_{0-6} en donde la cadena de alidilo está optativamente interrumpida por $-O(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C\equiv C-$, -O-, -S-, $-N(R^{10})CO-$, $N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$,-CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, cicloalquilo de C_{3-6} o $-SO_2N(R^{10})-$; un anillo aromático o no aromático de 5-12 miembros, heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, S o O que se sustituye

optativamente en una posición sustituible con uno o más radicales de R^9. Alternativamente, L_2 es un enlace directo, -CS-, alquilo de C_{1-6}, alcoxi de C_{1-6}, alquilo de $C_{1-6}COO$-, -CH=CHCOO-, alquilo de $C_{0-6}CONR^{11}$-, -Oalquilo de $C_{0-6}COO$-, alquilo de $C_{0-6}SO_2$-, alquilo de $C_{0-6}N(R^{11})$-, alquilo de $C_{0-6}N(R^{11})$-, alquilo de $C_{0-6}CO$-, cicloalquilamina, $-C(=NR^{11})$-, $-C(=NOR^{11})$-, $-C(=NN(R^{11})_2)$-; un anillo aromático o no aromático de 5-12 miembros, heteroarilo o oheterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, S o O que se sustituye optativamente en una posición sustituible con uno o más radicales de R^9. Un L_2 preferido se selecciona del grupo formado por -CONH-, $-CONHCH_3$-, $-CH_2O$-, $-OCH_2COOCH_2$-, $-CONHCH_2$- y -C≡C.

Otra realización es que G es G1, R^1 es R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G1, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, isoxazolilo, pirimidinilo, o imidazolilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^{5a} es halógeno, trifluorometilo, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH_2CH_2N(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3 o $OCH(CH_3)_2$;

c) R^2 es trifluorometilo, $COOCH_3$, CH_2OH, $CONHCH_2CH_3$, $CONHOCH_2CH(OH)CH_2OH$, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2CH_2OCH_3$, CH_2COOCH_3, $CON(CH_3)_2$, $COOCH(CH_3)_2$, $CONHCH_2CH_2CH_2OCH_3$, $OCOCH(CH_3)_2$, $OCH_2CON(CH_3)_2$, $CH_2CONHCH_2(CH_3)$, $C(CH_3)_2OH$, COOH, nitro o $COOCH(CH_3)_2$;

d) R^3 es hidrógeno o fenilo optativamente sustituido;

e) El anillo J es tienilo, furanilo, piridinilo o fenilo;

f) El anillo K es fenilo o piridinilo optativamente sustituido; y

g) R^4 es OH, CN, $C(CH_3)_2OH$, SO_2CH_3, $SO_2C(CH_3)_3$, CH_3, SO_2NH_2, SO_2CH_2CH3, SCH_2CH_3, SCH_3, OCH_3, CF_3, OCF_3, CH_2CF_3, alquilo de C_{1-6}, halógeno o CH_2COOH.

Otra realización es que G es G1, R^1 es R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G1, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, imidazolilo, isoxazolilo, pirimidinilo, o fenilo; R^5 se sustituye

optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^{5a} es halógeno, trifluorometilo, $OCONHCH(CH_3)_2$, $OCONH(CH_2CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3 o $OCH(CH_3)_2$;

c) R^2 es R^7 independientemente seleccionado de $CH_2C{\equiv}N$, $C(CH_3)_2C{\equiv}N$, cicloalquilo de $C_{3-6}C{\equiv}N$, tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, imidazolilo, isoxazolilo, pirimidinilo o fenilo; R^7 optativamente se sustituye en una posición sustituible con uno o más radicales de R^{7a};

d) R^{7a} se selecciona del grupo formado por halógeno, trifluorometilo, alquilo de C_{1-6}, alcoxi de C_{1-6}, CH=CHCOOH, CH_2COOH, OCH_2COOH, $OCONHCH(CH_3)_2$, $NHCOCH_3$, OH, OCH_3, COOH, $COOCH_3$, $OCH_2C(CH_3)_2$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2$, $OCONHCH_3$, OCH_2CH_3 y $OCH(CH_3)_2$;

e) R^3 es hidrógeno o fenilo optativamente sustituido;

f) El anillo J es tienilo, tiazolilo, furanilo, piridinilo o fenilo;

g) El anillo K es fenilo o piridinilo optativamente sustituido; y

h) R^4 es OH, CN, $C(CH_3)_2OH$, CH=CHCOOH, SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, SCH_2CH_3, $SO_2C(CH_3)_3$, SCH_3, OCH_3, alquilo de C_{1-6}, CF_3, F, Cl o Br.

Otra realización es que G es G1, R^1 es L_1-R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc o IIdd es G1, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es L_1-R^5; R^5 es fenilo, piridinilo, morfolinilo, oxazolilo, furanilo, tiazolilo o tienilo; R^5 se sustituye optativamente con R^{5a};

b) R^{5a} es halógeno o trifluorometilo;

c) L_1 es CS, CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, OCH_2, OCHCO o OCH_2CH_2;

d) R^2 es trifluorometilo, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2OCH_3$;

e) R^3 es hidrógeno o fenilo optativamente sustituido con R^{6a};

f) El anillo J es tienilo, piridinilo, furanilo, tiazolilo o fenilo; el anillo K es fenilo o piridinilo sustituido; y

g) R^4 es SO_2CH_3, SO_2NH_2, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{1-6}, halógeno o CH_2COOH.

Otra realización es que G es G1, R^1 es R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G1, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es R^5 seleccionado del grupo formado por tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, isoxazolilo, pirimidinilo, y fenilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^{5a} es $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, $OCOCH(CH_3)_2$, $NHCOCH_3$, $OCONHCH(CH_3)_2$, $O(CH_3)_2$, $CONH_2$, $O(CH)(CH_3)_2$, alquilo de C_{1-6}, OCH_2COOH, $OCH_2COOC(CH_3)_3$, $O(CH_2)_2N(CH_2CH_3)_2$, $OCOC(CH_3)_3$, $OC(CH_2)_2COOH$, $OCONH(CH_2)_2COOH$, $OCONH(CH_3)_2$, $OCONCH_3$, $OCONHCH_2CH_2CH$, $OC(CH_3)_2COOC(CH_3)_3$ y $O(CH_2)_2OH$;

c) R^2 es L_3-R^7; R^7 es fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, oxazolilo, piperidinilo, imidazolilo, piperazinilo o piridinlo;

d) L_3 es -CO-, alidilo de C_{1-6}, -CONH-, $-CONR^{11}-$, $-CONR^{11}NR^{11}-$, CH_2OCH_2-, $CH_2OCH_2CH_2-$, $-OCH_2-$, $-CH_2N(CH_3)_2-$, $-CH_2NHCH_2-$, $-CONR^{11}O-$, $-CH_2COOCH_2-$, $-CH_3N(CH_3)(CH_2)-$, $-CH_2N(ciclopropano)CH_2-$, $-CH_2NC(CH_3)_2CH_2-$, $-CH_2N(ciclohexano)CH_2-$, $-CH_2NCH(CH_3)_2CH_2-$, $-CH_2N(CF_3)(CH_2)_2-$,

$-CH_2N(CH_3)(CH_2)CH_2OCOCH_2CH_2-$, $-CONHCH_2CH_2N(CH_3)_2-$ o $-CH_2N(CH_2C{\equiv}N)CH_2-$, $-CS-$;

e) R^{7a} se selecciona del grupo formado por halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, CF_3, OCH_2CH_2COOH, CH_2COOH, $COOCH_3$, CH_2OH y OCH_3,

f) R^3 es hidrógeno o fenilo optativamente sustituido con R^{6a};

g) El anillo J es tienilo, piridinilo, tiazolilo o fenilo;

h) El anillo K es fenilo o piridinilo sustituido; y

i) R^4 es SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, SO_2NH_4, OCH_3, alquilo de C_{1-6}, CH_2COOH, $O(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, CF_3 o $COCH_3$.

Otra realización es que G es G1, R^1 es R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G1, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^5 es L_1-R^5; R^5 se selecciona del grupo formado por tienilo, furanilo, morfolinilo, tiazolilo, indolilo, imidazolilo, piperazinilo, piperidinilo, oxazolilo, piridinilo, isoxazolilo, pirimidinilo, y fenilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^{5a} es alquilo de C_{1-6}, alcoxi de C_{1-6}, COOH, halógeno o trifluorometilo;

c) L_1 es CS, CH_2, CH_2O, CH_2CH_2, OCH_2CH_2, OCH_2CO, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3OCH_2$, o $CONHCH_2CHN(CH_3)_2$;

d) R^2 es L_3-R^7; R^7 se selecciona del grupo formado por fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, oxazolilo, piridinilo, isoxazolilo, pirimidinilo, imidazolilo, CF_3, cicloalquilo de $C_{3-6}C{\equiv}N$, alquilo de $C_{0-6}C{\equiv}N$ y $COOCH_3$; R^7 optativamente se sustituye en una posición sustituible con uno o más radicales de R^{7a};

e) L_3 es CH_3, CS, CH_2OCH_2, $NC(CH_3)_2$, $CH_2NH(CH)_2$, CONH, CO, $CONR^{11}$, OCH_2, $CH_2N(CH_3)_2CH_2$, CH_2OCOCH_2, $CH_2CONHCH_2$, $CH_2CONHCH_2CH_2$, cicloalquilamina, $CHN(CH_3)CH_2$ o $CH_2NCH(CH)_2CH_2$;

f) R^{7a} se selecciona del grupo formado por halógeno, trifluorometilo, alquilo de C_{1-6}, alcoxi de C_{1-6}, CH=CHCOOH, CH_2COOH, OCH2COOH, $OCONHCH(CH_3)$, NHCOCH, OH, OCH, COOH, COOCH, $OCH_2C(CH_3)_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH3)_2$, $OCONHCH_3$, OCH_2CH_3, $CH_2N(CH_2)CH_2CF_3$ y $OCH(CH_3)_2$

g) R^3 es hidrógeno o fenilo optativamente sustituido con R^{6a};

h) El anillo J es tienilo, tiazolilo, piridinilo, furanilo o fenilo; el anillo K es fenilo o piridinilo sustituido; y

i) R^4 es SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{1-6}, CH_2COOH, $O(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl o Br.

Otra realización es que G es G2 y R^1 es R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G2, una realización más preferida de esta invención se relaciona con con un compuesto que tiene una o más características seleccinoadas del grupo formado por:

a) R^1 es R^5 seleccionado del grupo formado por tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, isoxazolilo, pirimidinilo, imidazolilo y fenilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^2 es R^7 seleccionado del grupo formado por fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, oxazolilo, piridinlio, isoxazolilo, pirimidinilo, imidazolilo, CF_3, cicloalquilo de $C_{3-6}C{\equiv}N$, alquilo de $C_{1-6}C{\equiv}N$, y $COOCH_3$, R^7 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{7a};

c) R^3 es hidrógeno o fenilo optativamente sustituido;

d) L_2 se selecciona del grupo formado por -CONH-, -$CONHCH_2$-, -CH_2O-, OCH_2COOCH_2-, -O-, C≡C, OCH_2CH_2- y $CONHOCH_2CH(OH)CH_2O$-, -CS-;

e) El anillo J o K es fenilo sustituido, bifenilo, piridinlo, piperidinilo, piperazinilo, morfolinilo, furanilo, tienilo, o naftilo; y

f) R^4 se selecciona del grupo formado por OH, CN, $C(CH_3)_2OH$, SO_2CH_3, $SO_2CH_2CH_3$, SO_2CH_2, CH_2CH_3, SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{1-6}, CH_2COOH, $C(CH_3)COOCH_3$, CH_2CH_2COOH, $OCH_2CON(R^{11})$, $OCH_2CH_2N(CH_3)_2$, OCH_2COOH, OCH_2COOCH_3, CH_2OH, $COCH_3$, $COOC(CH_3)_3$, ciclobutano-COOH, $OC(CH_3)_2COOH$ y CF_3.

Otra realización es que G es G2, R^1 es L_1-R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G2, una realización más preferida de la invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es L_1-R^5; R^5 es fenilo o piridinilo sustituido;

b) R^{5a} es halógeno, trifluorometilo, alquilo de C_{1-6}, haloalquilo de C_{1-6}, nitro, alcoxi de C_{1-6}, o OCON(alqulo de $C_{1-6})_2$;

c) L_1 es CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, $CONH(CH_2)_3$, $CONHCH_2CH_2N(CH_3)_2$ o OCH_2CH_2, -CS-;

d) R^2 es R^7 que se selecciona del grupo formado por fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo,

oxazolilo, piridinilo, CF_3, cicloalquilo de $C_{3-6}C\equiv N$ o $COOCH_3$;

e) R^3 es hidrógeno o fenilo optativamente sustituido con R^{6a};

f) El anillo J o K es fenilo sustituido, tienilo, furaninlo, piperazinilo, piperidinilo o piridinilo;

g) L_2 es CONH, $CONHCH_2$, CH_2O, OCH_2COOCH_2, O, $C\equiv C$, -CS-, OCH_2CH_2 o $CONHOCH_2CH(OH)CH_2O$; y

h) R^4 se selecciona del grupo formado por halógeno, haloalquilo de C_{1-6}, alquilo de $C_{1-6}COOR^{11}$, y metil sulfonilo.

Otra realización es que G es G2, R^1 es R^5 y R es L_3R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G2, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es R^5 seleccionado del grupo formado por tienilo, furanilo, morflinilo, tiazolilo, indolilo, oxazolilo, piridinilo, imidazolilo, isoxazolilo, pirimidinilo y fenilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^{5a} es halógeno o trifluorometilo;

c) R^2 es L_3-R^7; R^7 se selecciona del grupo formado por fenilo, piridinilo, tienilo, furanilo, morfolinilo,

tiazolilo, oxazolilo, piridinilo, fenilo, imidazolilo, isoxazol, pirimidinilo, CF_3, cicloalquilo de $C_{3-6}C{\equiv}N$, alquilo de $C_{1-6}C{\equiv}N$ y $COOCH_3$, R^7 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

d) L_3 es -CS-, CH_2, CH_2OCH_2, NCH_2, $(CH_2)_2$, $CHN(CH_2)_2$. CJCN, CONH, CO o $CONHCH_2$;

e) R^3 es hidrógeno o fenilo optativamente sustituido;

f) El anillo J o K es fenilo sustituido, furanilo, tienilo, piridinilo, bifenilo o naftilo;

g) L_2 es CONH, CS, $CONHCH_2$, CH_2O, OCH_2COOCH_2, OCH_2CH_2 o OCH_2; y

h) R^4 es SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, SCH_3, OCH_3, alquilo de C_{1-6}, $COOCH_2CO$, OCH_3, CH_2COOH, CH_2COOCH_3, $CH(CH_3)_2COOH$, $OC(CH_3)_2COOH$, $COOC(CH_3)_3$, ciclobutano-COOH, $C(CH_3)_2COOH$, COH_2COOCH y CF_3.

Otra realización es que G es G3, R^1 es R^5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc o IIdd es G3, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es R^5 seleccionado del grupo formado por tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, imidazolilo, isoxazol, pirimidinilo y fenilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^2 es R^7 seleccionado del grupo formado por fenilo, piridinlo, tienilo, furanilo, morfolinilo, tiazolilo, oxazolilo, piridinilo, imidazolilo, isoxazol, pirimidinilo, CF_3, halógeno, cicloalquilo de $C_{3-6}C{\equiv}N$, alquilo de $C_{1-6}C{\equiv}N$ y $COOCH_3$; R^7 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

c) R^3 es hidrógeno o fenilo optativamente sustituido;

d) L_2 se selecciona del grupo formado por -CONH-, $-CONHCH_2-$, -CS-, -CHO-, $-OCH_2COOCH_2-$, $-COOCH_2-$, -CO-, $-OCH_2-$, -OCO-, -NHCON-, -O-, $-OCH_2-$, -OCO-, -NHCON-, -O-, $-OCH_2CH_2-$, -OCON-, y $-SO_2-$;

e) El anillo J o K es fenilo sustituido, bifenilo, piridinilo, piperidinilo, piperazinilo, morfolinilo, tienilo, pirimidinilo o naftilo;

f) R^4 es metilsulfonilo, halógeno, haloalquilo, CH_2COOH, OCH_2-fenilo, CH_2COO-fenilo, OCH_2COOH, o $OCH_2CHN(CH_3)$; y

g) R^{5a} es $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, $OCOCH(CH_3)_2$, $NHCOCH_3$, $OCONHCH(CH_3)_2$,

$O(CH_2)_2$, $CONH_2$, $O(CH)(CH_3)_2$, alquilo de C_{1-6}, OCH_2COOH, $OCH_2COOC(CH_3)_3$, $O(CH_2)_2N(CH_2CH_3)_2$, $OCOC(CH_3)_3$, $OC(CH_2)_2COOH$, $OCNH(CH_3)_2$, $OCONCH_3$, $OCONHCH_2CH_2CG_3$, $OC(CH_3)_2COOC(CH_3)_3$, Y $O(CH_2)_2OH$.

Otra realización es que G es G3, R^1 es L_1-R_5 y R^2 es R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G3, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es L_1-R^5; R^5 es fenilo sustituido o piridinilo;

b) R^{5a} es halógeno o trifluorometilo;

c) L_1 es CH_2, CH_2O, CH_2CH_2, C=O, SO_2, CONH, $CONHC(CH_3)_2$, CS, $CONH(CH_2)_3OCH_2$, $CONHCH_2CH_2N(CH_3)_2$ o OCH_2CH_2;

d) R^2 es halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, carboxialquilo de C_{1-6}, o CF_3;

e) R^3 es hidrógeno o fenilo optativamente sustituido con R^{6a};

f) El anillo J o K es fenilo, piridinilo, tienilo, furanilo, piperidinilo, pirrolidinilo, piperazinilo, morfolinilo, tiazolilo, indolilo, oxazolilo, isoxazolilo, pirimidinilo, imidazolilo, o bifenilo; y

g) L_2 es CS, CONH, $CONHCH_2$, CH_2O, OCH_2COOCH_2, OCH_2 o OCH_2CH_2;

h) R^4 se selecciona del grupo formado por halógeno, haloalquilo de $C_{1-6}COOR^{11}$, y metil sulfonilo.

Otra realización es que G es G3, R^1 es R^5 y R^2 es L_3R^7. Cuando G de las fórmulas IIaa, IIbb, IIcc, o IIdd es G3, una realización más preferida de esta invención se relaciona con un compuesto que tiene una o más características seleccionadas del grupo formado por:

a) R^1 es selecciona del grupo formado por tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, isoxazolilo, pirimidinilo y fenilo; R^5 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{5a};

b) R^2 es L_3-R^7, R^7 es fenilo, piridinilo, tienilo, furanilo, morfolinilo, tiazolilo, oxazolilo, piridinilo, imidazolilo, piperazinilo, piridinilo, isoxazolilo, imidazolilo, pirimidinilo, CF_3, cicloalquilo de $C_{3-6}C{\equiv}N$, alquilo de $C_{0-6}C{\equiv}N$ y $COOCH_3$; R^7 se sustituye optativamente en una posición sustituible con uno o más raidacles de R^{7a};

c) L_3 es -CO-, -CS-, alidilo de C_{1-6}-, -CONH-, -$CONR^{11}$-, -$CONR^{11}NR^{11}$-, -CH_2OCH_2-, -$CH_2OCH_2CH_2$-, -OCH_2-, -$CH_2N(CH_2)_2$-, -CH_2NHCH_2-, -$CONR^{11}O$-, -CH_2OCOCH_2-, -$CH_3N(CH_3)(CH_2)$-, -CH_2N(ciclopropano)CH_2-, -$CH_2NC(CH_3)_2CH_3$-, -CH_2N(ciclohexano)CH_2-, -$CH_2NCH(CH_3)_2CH_2$-, -$CH_2N(CF_3)(CH_2)_2$-, -$CH_2N(CH_3)(CH_2)CH_2OCOCH_2CH_2$-, -$CONHCH_2CH_2N(CH_3)_2$-, o -$CH_2N(CH_2C{\equiv}N)CH_2$-;

d) R^3 es hidrógeno o fenilo optativamente sustituido;

e) El anillo J o K es fenilo sustituido, furanilo, tienilo, piridinlo, bifenilo, o naftilo; y

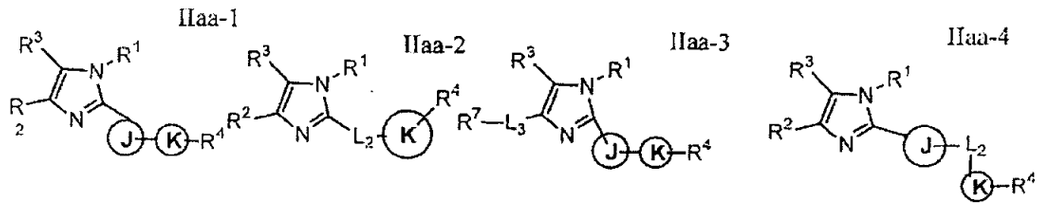
f) L_2 es CONH, $CONHCH_2$, CH_2O, OCH_2COOCH_2, CS, o $CONHCH_2$;

g) R^4 es SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3, SCH_3, SO_2NH, OCH_3, alquilo de C_{1-6}, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, CF_3 o $COCH_3$.

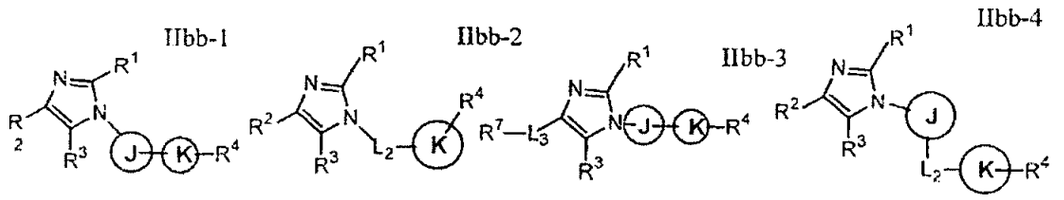
Otra realización de esta invención se relaciona con una composición que comprende un comuesto de la presente invención o un tautómero o una sal farmacéuticamente aceptable de él; y un portador farmacéuticamente aceptable. Se apreciará que que los compuestos de esta invención pueden derivar en grupos funcionales para proporcioanr derivados de profármacos que son capaces de la conversión de regreso a los compuestos padres in vivo. Ejemplos de dichos profármacos incluyen los derivados de ésteres fisiológicamente aceptables y metabólicamente lábiles, tales como ésteres de metoximetilo, ésteres de metiltiometilo, o ésteres de pivaloiloximetilo derivados de un grupo hidroxilo del compuesto o un grupo carbamoilo derivado de un grupo amino del compuesto. Además, cualquier equivalente fisológicamente aceptable de los compuestos de la presente invención, en forma similar a los ésteres o carbamatos metabólicamente lábiles, que son capaces de producir los compuestos parentales de la

presente invención in vivo, están dentro del alcance de esta invención.

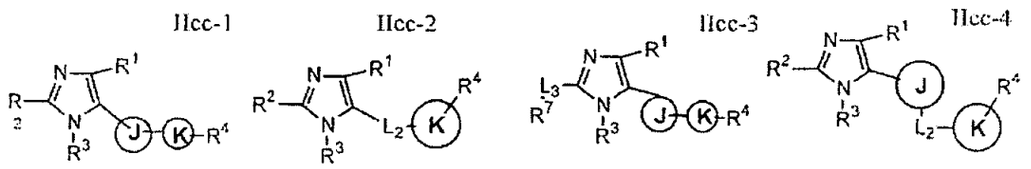
Otra realización de esta invención se relaciona con compuestos representados por la fórmulas IIaa-1, IIaa-2, IIaa-3 o IIaa-4 (Realización IIaa):



Otra realización de esta invención se relaciona con compuestos representados por las fórmulas IIbb-1, IIbb-2, IIbb-3, IIbb-3 o IIbb-4 (Realización IIb):

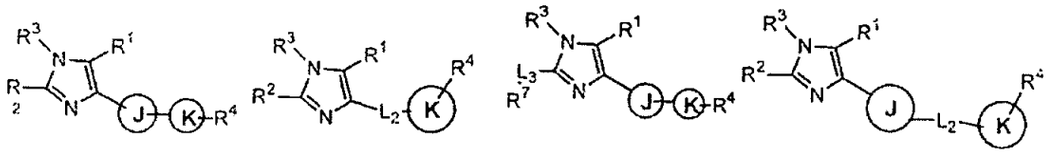


Otra realización de esta invención se relacina con compuestos representados por las fórmulas IIc-1, IIcc-2, IIcc-3 o IIcc-4 (Realización IIcc):



Otra realización de esta invención se relaciona con con compuestos representados por las fórmulas IIdd-1, IIdd-2, IIdd-3 o IIdd-4 (Realización IIdd):

IIdd-1 IIdd-2 IIdd-3 IIdd-4



De las realizaciones precedentes, IIaa-IIdd, R^1 es R^5 seleccionado del grupo formado por tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, isoxazolilo, pirimidinilo, imidazolilo, y fenilo; R^5 optativamente se sustituye en una posición sustituible con uno o más radicales de R^{5a}. R^5 preferido es fenilo o piridinilo optativmente sustituido con R^{5a}.

R^2 es R^7 seleccionado del grupo formado por trifluorometilo, $COOCH_3$, CH_2OH, $CONHCH_2CH_3$, $CONHOCH_2CH(OH)CH_2OH$, $CONHCH_2CH_2N(CH_3)_2$, $CONHCH_2CH_2OCH_3$, $CONHCH_2CH_2OCH_3$, CH_2COOCH_3, $CON(CH_3)_2$, $COOCH(CH_3)_2$, $CONHCH_2CH_2CH_2OCH_3$, $OCOCH(CH_3)_2$, $OCH_2CON(CH_3)_2$, $CH_2CONHCH_2(CH_3)$, $C(CH_3)OH$, COOH, nitro o $COOCH(CH_3)_2$, $CH_2C{\equiv}N$, cicloalquilo de $C_{3-6}C{\equiv}N$, tienilo, furanilo, morfolinilo, tiazolilo, indolilo, oxazolilo, piridinilo, imidazolilo, isoxazolilo, pirimidinilo y fenilo; R^7 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{7a}.

L_1 se selecciona independientemente de un enlace directo, -CO-, -CONH-, $-CONR^{11}-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, $-C(=NN(R^{11})_2)-$; una cadena de alidilo de C_{2-6} en donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})-$, -C≡C-, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO-$, $-NR^{11}-$, $-OR^{11}-$, $-CON(R^{10})-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$; $-(CH_2)_m-V_0-(CH_2)_n-$ o $-V_0-(CH_2)_n-V_0-$; m es 0-6; n es 0-6; V_0 es independientemente $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}$, -C≡C-, -O-, -S-, $-NR^{11}-$, $-CR^{11}NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, -OCO-, $-COR^{11}-$, $-COOR^{11}-$, -CO-, $-CO_2-$, -OC)=O), $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-NR^{10}COR^{10}-$, $-NR^{10}CSNR^{10}-$, ciclohaloalquilo de C_{3-6}, o $-SO_2N(R^{10})-$. Más específicaamente, L_1 se selecciona del grupo formado por -CONH-, alquilo de C_{1-6}, alcoxi de C_{1-6}, -CO-, $-SO_2-$, $-CH_2-$, $-CH_2O-$, $-CH_2CH_2-$, -C=O-, -CONH-, $-CONHC(CH_3)_2-$, $-CONH(CH_2)_3OCH_2-$, $-OCH_2CH_2-$, $-OCH_2CH_2N(CH_3)_2-$, y $-CONHCH_2CH_2N(CH_3)_2-$.

L_3 se selecciona independientemente de un enlace directo, -CO-, -CONH-, $-CONR^{11}-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, $-C(=NN(R^{11})_2-$; una cadena de alidilo de C_{2-6} en donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, -C≡C-, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2$, $-NR^{11}-$, $-OR^{11}-$, $-CON(R^{10})-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$,

$-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$; $-(CH_2)_m-V_0-(CH)_n-$, o $-V_0-(CH_2)_m-V_0-$; m es 0-6; n es 0-6; V_0 es independientemente $-C(R^{11})-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C$, $-O-$, $-S-$, $-NR^{11}-$, $-CR^{11}NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-OCO-$, $-COR^{11}-$, $-COOR^{11}-$, $-CO-$, $-CO_2-$, $-OC(=O)$, $-OC(=O)N(R^{10})-$, $-SO-$, $-N(R^{10})SO_2-$, $-NR^{10}COR^{10}-$, $-NR^{10}CSNR^{10}-$, ciclohaloalquilo de C_{3-6} o $-SO_2N(R^{10})-$. Más específicamente, L_3 es $-CO-$, alidilo de C_{1-6}, $-CONH-$, $-CONR^{11}-$, $-CONR^{11}NR^{11}-$, $-CH_2OCH_2-$, $-CH_2OCH_2CH_2-$, $-OCH-$, $-CH_2N(CH_3)_2-$, $-CH_2N(CH_3)_2-$, CH_2NHCH_2-, $CONR^{11}O-$, $-CH_2OCOCH_2-$, $-CH_3N(CH_3)(CH_2)-$, $-CH_2N(ciclopropano)CH-$, $-CH_2NC(CH_3)_2CH_2-$, $-CH_2N(ciclohexano)CH_2-$, $-CH_2NCH(CH_3)_2CH_2-$, $-CH_2N(CF_3)(CH_2)_2-$, $-CH_2N(CH_3)(CH_2)CH_2OCHCH_2CH_2-$, $-CONHCH_2CH_2N(CH_3)_2-$ o $-CH_2N(CH_2C\equiv N)CH_2-$.

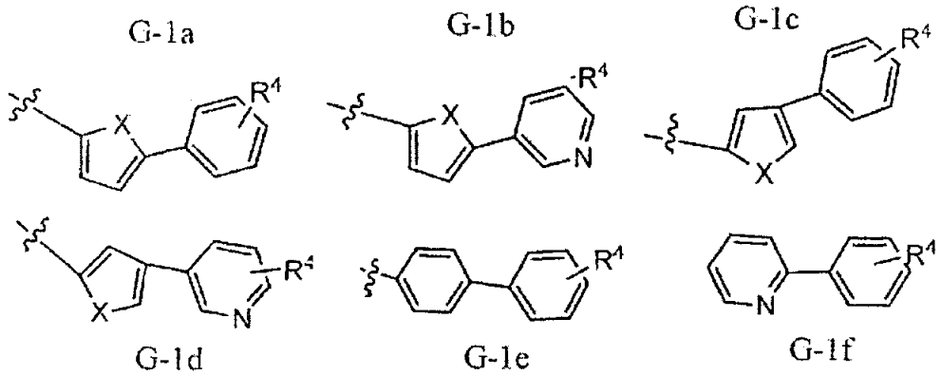
R^{5a} se selecciona del grupo formado por halógeno, trifluorometilo, alquilo de C_{1-6}, alcoxi de C_{1-6}, $CH=CHCOOH$, $-CH_2COOH$, OCH_2COOH, $OCONHCH(CH_3)_2-$, $NHCOCH_3$, OH, OCH_3, $COOH$, $COOCH_3$, $OCH_2C(CH_3)_2$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2OCOCH(CH_3)_2-$, $OCONHCH_3$, OCH_2CH_3 o $OCH(CH_3)_2$.

L_2 se selecciona independientemente de un enlace directo, $-CO-$, $CONH-$, $-CONR^{11}-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, $-C(=NN(R^{11})_2)-$; una cadena de alidilo de C_{2-6} en donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, -

$C(R^{11})=C(R^{11})-$, $-C\equiv C-$, $-C-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-OR^{11}-$, $-CON(R^{11})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$; $-(CH_2)_m-V_0-(CH_2)_n-$, o $-V_0-(CH_2)_n-V_0-$, m es 0-6; n es 0-5; V_0 es independientemente $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-NR^{11}-$, $-CR^{11}NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-OCO-$, $-COR^{11}-$, $-COOR^{11}-$, $-CO-$, $-CO_2-$, $-OC(=O)$, $-OC(=O)NR^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-NR^{10}COR^{10}-$, $-NR^{10}CSNR^{10}-$, ciclohaloalquilo de C_{3-6} o $-SO_2N(R^{10})-$. Más específicamente, L_2 se selecciona del grupo formado por $-CONH-$, $-CONHCH_2-$, $-CH_2O-$, $-OCH_2COOCH_2-$, $-O-$, $C\equiv C$, $-OCHCH_2$ y $-CONHOCH_2CH(OH)CH_2O-$.

R^{5a} se selecciona independientemente del grupo formado por $OCH_2C(CH_3)_3$, Cl, F, Br, $OCH_2CH(CH_3)_2$, OCH_2CH_3, CF_3, COOH, OCH_3, OH, NO_2, $OCOCH(CH_3)_2$, $OCOC(CH_3)$, $NHCOCH_3$, $OCON(CH_3)_2$, $OCONHCH_3$, $OCON(CH_2)_2CH_3$, $OCONHCH(CH_3)_2$, $O(CH_2)_2$, $CONH_2$. $O(CH)(CH_3)_2$, alquilo de C_{1-6}, OCH_2COOH, $OCH_2COOC(CH_3)_2$, $O(CH_2)_2N(CH_2CH_3)_2$, $OC(CH_3)_2COOC(CH_3)_3$ y OCH_2CH_2OH. R^4 se selecciona del grupo formado por SO_2CH_3, $SO_2C(CH_3)_3$, SO_2NH_2, $SO_2CH_2CH_2$, SCH_2CH_3, SCH_2, OCH_3, alquilo de C_{1-6}, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, $O(CH_3)_2COOH$, CH_2COOCH_3, $C(CH_3)_2COOCH_3$, CH_2CH_2COOH, OCH_2COOCH_3, $COCH_3$, $COOC(CH_3)_3$, ciclobutano-COOH, $OC(CH_3)_2COOH$, $COOCH_2CH$, OCF_3 y CF_5.

Otra realiazación de esta invención se relaciona con compuestos descritos anteriormente en donde G se selecciona del grupo formado por:



De los compuestos precedentes, R se selecciona del grupo formado por una cadena de alidilo de C_{0-6} en donde la cadena de alidilo está optativamente interrumpida por $-C(R^{11})_2-$, $C(R^{11})_2C(R^{11})_2-$, $C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}$, $-C\equiv C$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $OC(=O)-$, $-OC(=O)N)R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$.

Cada R^4 se selecciona independientemente de alquilo de C_{1-6}, $CR^{11}=CR^{11}COOR^{11}$, alcoxi de C_{1-6}, alquilo de $C_{0-6}OR^{11}$, alquilo de $C_{0-6}COR^{11}$, alquilo de $C_{0-6}SOR^{11}$, alquilo de $C_{0-6}OCOOR^{11}$, alquilo de $C_{0-6}NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2NR^{11}COR^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})$C=O(OR^{11})$, $OVOR^{11}$, halógeno, haloalquilo de C_{1-6}, haloalquilo de $C_{1-6}OR^{11}$, Ohaloalquilo de C_{1-6}, arioxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6},

aril alquilcarboxi de C_{0-6}, $NR^{11}SO_2R^{11}$, Oalquilo de C_{0-6}, Oalquilo de $C_{0-6}COOR^{11}$, alquilo de $C_{0-6}C\equiv N$, alcoxiheteroarilo de C_{0-6}, alcoxiheterociclilo de C_{0-6}, cicloalquiloCOOR^{11}, un anillo aromático o no aromático de 5-12 miembros, o heteroarilo o heterociclilo de 5-12 miembros que tiene uno o más heteroátomos N, O, o S. R^4 preferido se selecciona del grupo formado por SO_2CH_3, $SO_2C(CH_3)_3$, $SO_2CH_2CH_3$. SCH_2CH_3, SCH_3, OCH_3, alquilo de C_{1-6}, CH_2COOH, $C(CH_3)_2COOH$, $NHSO_2CH_3$, F, Cl, Br, ciclobutan-COOH, $OC(CH_3)_2COOH$, CF_3. $C(CH_3)_2COOH$, $-CH_2COOCH_3$, CH_2CH_2COOH, OCH_2COOCH_3 y $COCH_3$. Más preferentemente R es SO_2CH_3, $SO_2CH_2CH_3$, SCH_2CH_3 o SCH_3.

X se selecciona del grupo formado por S, NR^{11} y O.

Cada R^4 se sustituye optativamente en una posición sustituible con uno o más radicales de R^{4a}. Cada R^{4a} se selecciona independientemente de alquilo de C_{1-6}, (alquilo de C_{1-6})C=O(OR^{11}); alcoxi de C_{1-6}, alquilo de $C_{0-6}OR^{11}$, añquilo de $C_{0-6}COR^{11}$, alquilo de $C_{0-6}SO_2R^{11}$, alquilo de $C_{0-6}SO_2N(R^{11})_2$, alquilo de $C_{0-6}SR^{11}$, (alquilo de C_{0-6})OC=O(OR^{11}), halógeno, haloalquilo de C_{1-6}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{1-6}, aril alquilcarboxi de C_{0-6}, $NR^{11}SO_2R^{11}$, Oalquilo de C_{1-6}, alquilo de $C_{0-6}C\equiv N$, o Oalquilo de $C_{0-6}COOR^{11}$.

Definiciones

Las siguientes definiciones son aplicables a los términos usados en la presente, a menos que se diga de otro modo. Por lo tanto, por ejemplo, "alquilo" se define a continuación como que contiene de 1 a 12 átomos de carbono, pero un sustituyente definido como alquilo de C_{1-6} se limita a ungrupo alquilo de 1 a 6 átomos de caronbo. Todas las selecciones de todas las variables relacionadas con todas las estructuras o fórmulas generales de la presente se entiende que son correctas solamente cuando dicha selección produce una estructura química estable reconocida por un experto en el arte.

Cuando se hace referencia a realizaciones particulares solamente mediante la estructura, todos los grupos químicos no mencionados de otro modo que constituyen esa estructura son los definidos en cada reailzación individual de esa estructura. Por lo tanto, por ejemplo, cuando se dice "En otra realización, la invención proporciona un compuesto de cuerdo con cualquiera de las fórmulas Ia-d, en donde K es fenilo o piridilo", se entiende que otra realización de la invención comprende cada realización de una cualquiera de las fórmulas Ia-d descritas en la memoria descriptiva en donde K es fenilo o piridilo y todos los demás grupos son los definidos en las realizaciones particulares.

Por simplicidad, los grupos químicos se definen y mencionan en toda la memoria descriptiva principalmente como grupos químicos univalentes (por ejemplo, alquilo, arilo, etc). De todos modos, dichos términos también se usan hacer los grupos multivalentes correspondientes en las circunstancias estructurales apropiadas claros para los expertos en el arte. Por ejemplo, si bien un grupo "alquilo" generalmente se refiere a un radical monovalente, (por ejemplo, CH_3-CH_2-), en ciertas circunstancias, un grupo de unión bivalente puede ser "alquilo", en cuyo caso los expertos en el arte entenderán que el alquilo es un radical divalente (por ejemplo, -CH_3-CH_2-), que es equivalente al término "alquileno". (En forma similar, en circunstancias en las cuales se requiere un grupo divalente y se dice que es "arilo", los expertos en el arte entenderán que el término "arilo" se refiere al grupo divalente correspondiente, arileno). Se entiende que todos los átomos tienen su número normal de valencias para la formación de enlaces (es decir, 4 para carbono, 3 para N, 2 para O y 2, 4, o 6 para S, según el estado de oxidación del S). Algunas veces, un grupo se puede definir, por ejemplo, como $(A)_a$-B-, en donde a es 0 o 1. En esas circunstancias, cuando a es 0 el grupo es B- y cuando a es 1 el grupo es A-B-. En forma similar, alquilo de $C_{9-6}OR^{11}$ incluye tanto $-OR^{11}$ como $-C_1-C_6-OR^{11}$ y $-[C(R^{15})_2]_m-$ es un enlace cuando m es 0. En los casos en que un grupo es un radical divalente, no hay una limitación

implícita sobre la ubicación de los dos enlaces que unen el radical de unión a sus dos unidades químicas de soporte. Por ejemplo, para un radical de ciclohexilo divalente, el ciclohexilo puede estar unido a través de dos enlaces químicos separados a dos átomos de carbono distinguibles dnetro del anillo; o los dos enlaces pueden estar unidos al mismo átomo de carbono del anillo. En un ejemplo ilustrativo, si un radical de ciclopropilo divalente une dos anillos de fenilo, seta definición comprende tanto 1,2-difenilciclopropilo como unidades de 1,1-difenilciclopropilo.

Como se usan en la presente, las formas en singular "una", "un" y "el/la" incluyen los referentes plurales a menos que le contexto lo indique claramente de otro modo. Por ejemplo, "un compuesto" se refiere a uno o más de dichos compuestos, mientras que "la enzima" incluye una enzima particular así como otros miembros de la familia y equivalentes de ella como lo saben los expertos en el arte. Como se usa en la memoria descriptiva y en las reivindicaciones adjuntas, a menos que se especifique lo contrario, los siguientes términos tienen la definición indicada.

El término "ausente" como se usa en la presente significa el grupo reemplazado por un enlace simple. Si el reemplazo del grupo con un enlace deriva en dos grupos unidos ambos

definidos como enlaces, entonces los grupos -enlace-enlace- se entiende que se reducen a un enlace simple.

El término "interrumpida por" como se usa en la presente significa que el grupo especificado se inserta en cualquier punto dentro de la cadena especificada, pero no en los extremos. Por ejemplo, si la cadena de alquilo de C_3, definida en la presente, está interrumpida por -O-, entonces estarían comprendidos los siguientes grupos. $-CH_2-O-CH_2-CH_2$, $-CH_2CH_2-O-CH_2$, $-CH(CH_3)-O-CH_2-$ y $-CH_2-O-CH(CH_3)-$.

Los términos "alifático· y "grupo alifático" como se usan en la presente significan hidrocarburos de cadena recta, ramificada o cílica de C_1-C_{12} (a menos que se diga de otro modo) que están completamente saturados o que contienen una o más unidades de insaturación pero que no son aromáticos. Por ejemplo, grupos alifáticos adecuados incluyen grupos alquilo, alquenilo, alquinilo lineales, ramificados o cílicos sustituidos o no sustituidos e híbridos de ellos tales como (cicloalquil)alquilo, (cicloalquenil)alquilo o (cicloalquil)alquenilo.

Los términos "alquilo", "alcoxi", "hidroxialquilo", "alcoxialquilo" y "alcoxicarbonil", usados solos o como parte

de un grupo de mayor tamaño incluyen tanto cadenas rectas como ramificadas que contienen uno a doce átomos de carbono.

Los términos "alquenilo" y "alquinilo" usados solos o como parte de un grupo de mayor tamaño incluyen tanto cadenas rectas como ramificadas que contienen dos a doce átomos de carbono.

El término "alcoxi" se refiere a un radical de -O-alqilo, en dnde el alquilo es lo definido en la presente.

"Alquilo" se refiere a un radical de cadena de hidrocarburo recto o ramificado que comprende exclusivamente átomos de carbono e hidrógeno, que no contiene ninguna insaturación, que tiene de uno a doce átomos de carbono, preferentemente de uno a ocho y que está unido al resto de la molécula por un enlace simple, por ejemplo, metilo, etilo n-propilo, 1-metiletilo (iso-propilo), n-butilo, n-pentilo, 1,1-dimetiletilo (t-butilo), y simiklares. A menos que se diga de otro modo específicamente en la memoria descriptiva, el radical de alquilo se sustituye optativamente con uno o más sustituyentes seleccionados del grupo formado por halo, ciano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$ y $-SO_2N(R^{11})_2$ donde cada R^{10} y R^{11} son lo definido anteriormente en el Primer aspecto de

la invención. A menos que se diga de otro modo específicamente en la memoria descriptiva, se entiende que para los radicales, definidos a continuación, que contienen un grupo alquilo sustituido que la sustitución puede ocurrir en cualquier carbono del grupo alquilo.

"Alquenilo" se refiere a un radical decadena de hidrocarburo recto o ramificado que comprende exclusivamente átomos de carbono y de hidrógeno, que comprende por lo menos un enlace doble, que tiene de dos a ocho átomos de carbono, y que está unido al resto de la molécula por un enlace simple o un enlace doble, por ejemplo, etenilo, prop-1-enilo, but-1-enilo, pent-1-enilo, penta-1,4-dienilo, y similares. A menos que se diga de otro modo específicamente en la memoria descriptiva, el radical de alquenilo optativamente se sustituye con uno o más sustituyentes seleccionados del grupo formado por halo, ciano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $N(R^{11})SO_2R^{11}$, SO_2OR^{11}, $-SO_2R^{11}$ y $-SO_2N(R^{11})_2$ en donde cada R^{10} y R^{11} son los definidos en el Primer aspecto de la invención. A menos que se diga de otro modo específicamente en la memoria descriptiva, se entiende que para los radicales, definidos a continuación, que contienen un grupo alquenilo sustituido que la sustitución puede ocurrir en cualquier carbono del grupo alquenilo.

"Arilo" se refiere a un sistema de anillo monocíclico o multicíclico aromático que contiene de 6 a 19 átomos de carbono, donde el sistema de anillo optativamente está saturado parcial o totalmente. Los grupos arilo incluyen, en forma no taxativa, grupos tales como fluorenilo, fenilo y naftilo. A menos que se diga de otro modo específicamente en la memoria descriptiva, el término "arilo" se entiende que incluye radicales de arilo optativamente sustituidos por uno o más sustituyentes seleccionados del grupo formado por alquilo, alquenilo, halógeno, haloalquilo, ciano, nitro, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, R^0-R^{11}, R^0-$N(R^{11})_2$-, R^0-COR^{11}, R^0-$COOR^{11}$, R^0-$CON(R^{11})_2$, R^0-$N(R^{11})COOR^{10}$, R^0-$N(R^{11})COR^{11}$, R^0-NSO_2R^{11}, R^0-$N(R^{11})SO_2R^{11}$, R^0-SO_2OR^{11}, R^0-SO_2R^{11} y R^0-$SO_2N(R^{11})_2$, donde cada R^0 se selecciona independientemente de un grupo alifático sustituido o no sustituido, un anillo de heteroarilo o heterociclilo no sustituido, fenilo (Ph), Ph sustituido, -OPh, -OPh sustituido, o $-CH_2Ph$ sustituido. Ejemplos de sustituyentes en el grupo alifático o anillo de fenilo de R^0 incluyen amino, alquilamino, dialquilamino, aminocarbonilo, halógeno, alquilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilaminocarboniloxi, idalquilaminocarboniloxi, alcoxi, nitro, ciano, carboxi, alcoxicarbonilo, alquilcarbonilo, hidroxi, haloalcoxi o haloalquilo.

463
463

Un grupo alifático o un anillo heterocíclico no aromático puede contener uno o más sustituyentes. Ejemplos de sustituyentes adecuados en el carbono saturado de un grupo alifático o del anillo heterocíclico no aromático incluyen aquellos enumerados anteriormente para el carbono insaturado de un grupo arilo o heteroarilo e incluyen los siguientes: =O, =S, $=NNHR^0$, $=NN(R^0)_2$, =N, $=NNHC(O)R^0$, $=NNHCO_2$ (alquilo), $=NNHSO_2$(alquilo), o $=NR^0$, donde R^0 se selecciona independientemente de hidrógeno, grupo alifático no sustituido o sustituido, un anillo de heteroarilo o heterocíclico no sustituido, fenilo (Ph), Ph sustituido, -OPh, -OPh sustituido, CH_2Ph o $-CH_2Ph$ sustituido. Ejemplos de sustituyentes en el grupo alifático incluyen amino, alquilamino, dialquilamino, aminocarbonilo, halógeno, alquilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilaminocarboniloxi, dialquilaminocarboniloxi, alcoxi, nitro, ciano, carboxi, alcoxicarbonilo, alquilcarbonilo, hidroxi, haloalcoxi, o haloalquilo.

Sustituyentes adecuados sobre el nitrógeno de un anillo heterocíclico no aromático incluyen $-R^0$, $-N(R^0)_2$-$C(O)R^0$, $COOR^0$, $-C(O)C(O)R^0$, $-SO_2R$, $-SO_2N(R^0)_2$, $-C(=S)N(R^0)_2$, $-C(=NH)-N(R^0)_2$ y $NR^0RSO_2R^0$ en donde cada R^0 se selecciona independientemente de hidrógeno, un grupo alifático no sustituido o sustituido, un anillo de heteroarilo o heterocíclico no sustituido, fenilo

(Ph), Ph sustituido, -OPh, -OPh sustituido, o $-CH_2Ph$ sustituido. Ejemplos de sustituyentes sobre el grupo alifático o el anillo de fenilo incluyen amino, alquilamino, dialquilamino, aminocarbonilo, halógeno, alquilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilaminocarboniloxi, dialquilamioncarboniloxi, alcoxi, nitro, ciano, carboxi, alcoxicarbonilo, alquilcarbonilo, hidroxi, haloalcoxi o haloalquilo.

El término "alcoxiarilo" como se usa aquí significa un grupo arilo, definido aquí, sustituido con uno o más grupos alcoxi, definido aquí. Ejemplos de grupos alcoxiarilo incluyen, en forma no taxativa, metoxifenilo, butiloxifenilo y dimetoxinaftilo.

"Aralquilo" o "arilalquilo" se refiere a un radical de la fórmula -RaRb donde Ra es un radical de alquilo definido anteriormente y Rb es uno o más radicales de arilo definido aquí, por ejemplo, bencilo, difenilmetilo y similares. El radical(es) de arilo y el radical de alquilo optativamente se sustituye como se describió anteriormente.

El término "aralquiloxi" o "arilalcoxi" como se usa aquí, significa un grupo aralquilo, definido aquí, anexado a la molécula madre a través de un átomo de oxígeno. Ejemplos de

aralquiloxi incluyen, en forma no taxativa, benciloxi, 2-feniletoxi, 4-fenilbutoxi, 9-fluorenilmetoxi y similares.

El término "arilalquilcarboxi" como se usa aquí, significa un grupo arilalquilo, definido aquí, anexado a la molécula madre a través de un grupo carboxi, definido anteriormente. El grupo carboxi puede estar enlazado en cualquier sentido, con el carbono de carbonilo enlazado al grupo arilalquilo y el oxígeno enlazado a la molécula madre, o el carbonlo enlazado a la molécula madre y el oxígeno enlazado al grupo arilalquilo. Ejemplos de grupos arilalquilcarboxi incluyen, en forma no taxativa, bencilacetoxi, (benciloxi)carbonilo, (2-feniletoxi)carbonilo, fenil-acetiloxi y 1-oxo-5-fenl-pentiloxi.

El término "ariloxi" como se usa aquí, significa un grupo arilo, definido aquí, anexado a una molécula madre a través de un átomo de oxígeno. Ejemplos de grupos "ariloxi" incluyen, en forma no taxativa, fenoxi, 1-naftiloxi y 2-naftiloxi.

"Alquileno" y "cadena de alquileno" se refieren a una cadena de hidrocarburo divalente recto o ramificado, que une el resto de la molécula a un grupo de radical, que comprende exclusivamente carbono e hidrógeno, que contiene una insaturación y que tiene de uno a doce átomos de carbono,

preferentemente que contiene de uno a ocho carbonos, por ejemplo, metileno, etileno, propileno, n-butileno, y similares. La cadena de alquileno puede estar unida al resto de la molécula y al grupo radical a través de un carbono dentro de la cadena o a través de dos átomos de carbono cualquiera dentro de la cadena. La cadena de alquileno está optativamente sustituida por uno o más sustituyentes seleccionados del grupo que comprende halo, ciano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$ y $SO_2N(R^{11})_2$ donde cada R^{10} y R^{11} son lo definido anteriormente en el Primer aspecto de la invención. La cadena de alquileno puede estar unida al resto de la molécula a través de dos carbonos cualquiera dentro de la cadena.

"Alquenileno" y "cadena de alquenileno" se refieren a una cadena de hidrocarburo divalente recto o ramificado que une el resto de la molécula a un grupo de radical, que comprende exclusivamente carbono e hidrógeno, que contiene por lo menos un enlace doble y que tiene de dos a doce átomos de carbono, por ejemplo etenileno, propenileno, n-butenileno, y similares. La cadena de alquenileno se une al resto de la molécula a través de un enlace simple y al grupo de radical a través de un enlace doble o de un enlace simple. Los puntos de unión de la cadena de alquenileno al resto de la molécula y al grupo de

radical pueden ser a través de un carbono o dos átomos de carbono cualquiera dentro de la cadena. La cadena de alquenileno está optativamente sustituida por uno o más sustituyentes seleccionados del grupo formado por halo, ciano, nitro, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, SO_2OR^{11}, $-SO_2R^{11}$, y $SO_2N(R^{11})_2$ donde cada R^{10} y R^{11} son lo definido anteriormente en el Primer aspecto de la invención.

El término "ariloxialquilo" como se usa aquí, significa un grupo alquilo unido a la molécula madre, endonde el grupo alquilo se sustituye con un grupo ariloxi, definido aquí. Ejemplos de grupos ariloxialquilo incluyen, en forma no taxativa, fenoximetilo, naftiloxibutilo y fenoxihexilo.

El término "ariloxiarilo" como se usa aquí, significa un grupo arilo unido a la molécula madre, en donde el grupo arilo se sustituye con un grupo ariloxi, definido aquí. Ejemplos de grupos ariloxiarilo incluyen, en forma no taxativa, fenoxifenilo, naftiloxifenilo y fenoxinaftilo.

El término "carbonilo" como se usa aquí, significa un grupo -C(=O)-.

El término "carboxi" como se usa aquí, significa un grupo -C(=O)O-.

"Cicloalquilo" se refiere a un radical de hidrocarburo monocíclico o bicíclico monovalente adecuado que comprende exclusivamente átomos de carbono e hidrógeno, que tiene de tres a diez átomos de carbono (a menos que se diga de otro modo), y que está saturado o incluye una o más unidades insaturadas (pero no es aromático) y está unido al resto de la molécula por un enlace simple, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclopent-1-enilo, ciclohexilo, ciclohex-2,4-dienilo, decalinilo y similares. A menos que se diga de otro modo específicamente en la memoria descriptiva, se entiende que el término "cicloalquilo" incluye radicales de cicloalquilo que optativamente se sustituyen con uno o más sustituyentes seleccionados independientemente del grupo formado por alquilo, alquenilo, halo, haloalquilo, haloalquenilo, ciano, nitro, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroarilalquilo, $-OR^{11}$, $-N(R^{11})_2$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2R^{11}$ y $-SO_2N(R^{11})_2$, donde R^{10} y R^{11} son lo definido anteriormente en el primer aspecto de la invención.

"Cicloalquilalquilo" se refiere a un radical de la fórmula -RaRd donde Ra es un radical de alquilo como se definió anteriormente y Rd es un radical de cicloalquilo definido anteriormente. El radical de alquilo y el radical de cicloalquilo pueden optativamente sustituirse como se definió anteriormente.

El término "ciclohaloalquilo" como se usa aquí significa un grupo cicloalquilo, definido aquí que se sustituye con uno o más grupos halo, como se define aquí. Ejemplos de grupos "ciclohaloalquilo" incluyen, en forma no taxativa, heterociclohexilo, trifluorociclopentilo, diclorociclohexilo y similares.

"Halo" o "Halógeno" se refiere a bromo, cloro, flúor o yodo.

"Haloalquilo" se refiere a un radical de alquilo, definido anteriormente, que se sustituye con uno o más radicales de halo, definido anteriormente, por ejemplo, trifluorometilo, difluorometilo, triclorometilo, 2,2,2-trifluorometilo, 1-fluorometil-2-fluorometilo, 3-bromo-2-fluoropropilo, 1-bromometil-2-bromoetilo, y similares.

"Haloalquenilo" se refiere a un radical de alquenilo, definido anteriormente, que se sustituye con uno o más radicales de

468
470

halo, definido anteriormente, por ejemplo, 2-bromoetenilo, 3-bromoprop-1-enilo y similares.

El término "haloarilo" como se usa aquí, significa un grupo arilo, definido anteriormente, sustituido con uno o más grupos halo. Ejemplos de grupos haloarilo incluyen, en forma no taxativa, bromofenilo, fluorofenilo, pentafluorofenilo, cloronaftilo, cloro-yodofenilo y similares.

"Heterociclilo" se refiere a un radical de anillo no aromático de 3 a 18 miembros que comprende átomos de carbono y de uno a cinco heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre. A los fines de esta invención, el radical de heterociclilo puede ser un sistema de anillo monocíclico, bicíclico, tricíclico, o tetracíclico, que puede incluir sistems de anillo fusionado o en puente; y los átomos de nitrógeno, carbono o azufre del radical de heterociclilo optativamente se oxidan; el átomo de nitrógeno optativamente se cuaterniza; y el radical de heterociclilo puede estar total o parcialmente saturado. Ejemplos de dichos radicales de heterociclilo incluyen, en forma no taxativa, dioxolanilo, decahidroisoquinolilo, imidazolinilo, imidazolidinilo, isotiazolidinilo, isoxazolidinilo, morfolinilo, octahidroindolilo, octahidroisoindolilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, oxazolidinilo,

471
469

piperidinilo, piperazinilo, 4-piperidonilo, pirrolidinilo, tiazolidinilo, tetrahidrofuranilo, tritianilo, tetrahidropiranilo, tiomorfolinilo, tiamorfolinilo, 1-oxo-tiomorfolinilo, y 1,1-dioxo-tiomorfolinilo. A menos que se diga de otro modo específicamente en la memoria descriptiva, el término "heterociclilo" incluye radicales de heterociclilo definido anteriormente que optativamente se sustituyen con uno o más sustituyentes seleccionados del grupo formado por alquilo, alquenilo, halo, haloalquilo, haloalquenilo, nitro, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroarilalquilo, $-OR^{11}$, $-N(R^{11})_2-$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2OR^{11}$, $-SO_2R^{11}$, y $-SO_2N(R^{11})_2$, donde cada R^{10} y R^{11} son lo definido anteriormente en el primer aspecto de la invención.

"Heterociclilalquilo" se refiere a un radical de la fórmula -RaRc en donde Ra es un radical de alquilo definido anteriormente y Rc es un radical de heterociclilo definido anteriormente, y si el heterociclilo es un heterociclilo que contiene nitrógeno, el heterociclilo puede estar unido al radical de alquilo en el átomo de nitrógeno. El radical de heterociclilo y el radical de alquilo optativamente se sustitueyen como se definió anteriormente.

El término "heterocicliloxi" como se usa aquí, significa un grupo heterociclilo, definido anteriormente, unido a una molécula madre a través de un átomo de oxígeno. Ejemplos de grupos "heterocicliloxi" incluyen, en forma no taxativa, piperidiniloxi, tetrahidrofuraniloxi, tetrahidrotieniloxi, tetrahidropiraniloxi, dihidropiraniloxi, pirrolidiniloxi, oxetaniloxi y oxiraniloxi.

"Heteroarilo" se refiere a un anillo de 3 a 10 miembros que comprende átomos de carbono y de uno a cicno heteroátomos seleccionados del grupo formado por nitrógeno, oxígeno y azufre. A los fines de la invención, el radical de heteroarilo puede ser un sistema de anillo monocíclico, bicíclico, tricíclico o tetracíclico, que puede incluir sistemas de anillos fusionados o de puente; y los átomos de nitrógeno, carbono o azufre del radical de heteroarilo están optativamente oxidados; el átomo de nitrógeno está optativamente cuaternizado. Ejemplos incluyen, en forma no taxativa, azepinilo, acridinilo, bencimidazolilo, benztiazolilo, bencindolilo, benzotiadiazolilo, benzonaftofuranilo, benzodioxolilo, benzodioxinilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzofuranonilo, benzotienilo (benzotiofenilo), benzotiazolilo, benzo[4,6]imidazo[1,2-a]piridinilo, carbazolilo, cinolilo, dibenzofuranilo, furanilo, furanonilo,

isotiazolilo, imidazolilo, indolilo, indazolilo, isoindolilo, indolinilo, isoindolinilo, indolizinilo, isoxazolilo, naftiridinilo, oxadiazolilo, 2-oxazepinilo, oxazolilo, oxiranilo, fenazinilo, fenotiazinilo, fenoxazinilo, ftalazinilo, ftalimidilo, pteridinilo, purinilo, pirrolilo, pirazolilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, quinazolinilo, quinoxalinilo, quinolinilo, quinuclidinilo, isoquinolinilo, tiazolilo, tiadiazolilo, tiazolilo, tetrazolilo, triazinilo y tiofenilo. A menos que se diga de otro modo específicamente en la memoria descriptiva, el término "heteroarilo" incluye radicales de heteroarilo definido anteriormente que optativamente se sustituyen con uno o más sustituyentes seleccionados del grupo formado por alquilo, alquenilo, halo, haloalquilo, haloalquenilo, nitro, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heterociclilo, heterociclilalquilo, heteroarilo, heteroarilalquilo, $-OR^{11}$, $-N(R^{11})_2-$, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-N(R^{11})COOR^{10}$, $-N(R^{11})COR^{11}$, $-NSO_2R^{11}$, $-N(R^{11})SO_2R^{11}$, $-SO_2R^{11}$ y $-SO_2N(R^{11})_2$, donde cada R^{10} y R^{11} son lo definido anteriormente en el primer aspecto de la invención. A los fines de la invención, el término "N-heteroarilo" se refiere a radicales de heteroarilo definidos anteriormente que contienen por lo menos un átomo de nitrógeno en el anillo.

El término "heteroariloxi" como se usa aquí, significa un grupo heteroarilo, definido anteriormente, unido a una molécula madre a través de un átomo de oxígeno. Ejemplos de grupos "heteroariloxi" incluyen, en forma no taxativa, piridiloxi, indoliloxi y quinoliloxi.

"Heteroarilalquilo" se refiere a un radical de la fórmula $-R_aR_f$ en donde R_a es un radical de alquilo definido anteriormente y R_f es un radical de heteroarilo definido anteriormente, y si el heteroarilo es un heteroarilo que contiene nitrógeno, el heteroarilo puede unirse al radical de alquilo en el átomo de nitrógeno. El radical de heteroarilo y el radical de alquilo optativamente se sustituyen como se definió anteriormente.

El término "grupo ligador" o "ligadura" significa un grupo orgánico que une dos partes de un compuesto. Las ligaduras generalmente están compuestas de un átomo tal como oxígeno o azufre, una unidad tal como -NH-, $-CH_2-$, -CO-, -CONH-, o una cadena de átomos, tal como una cadena de alidilo. La masa molecular de una ligadura generalmente está en la gama de 14 a 200, preferentemente en la gama de 14 a 96, con una longitud de hasta seis átomos. Ejemplos de ligaduras incluyen una cadena de alidilo de C_{1-6} saturada o insaturada que optativamente se sustituye, y en donde uno o más átomos saturados de la cadena optativamente se reemplazan por -CO-, -

COCO-, -CONH-, CONHNH-, $-CO_2-$, $-NHCO_2-$, -O-, NHCONH-, -OCONH-, -NHNH-, -NHCO-, -S-, -SO-, $-SO_2-$, -NH-, $-SO_2NH-$, o $-NHSO_2-$.

El término "alidilo" o "cadena de alidilo" se refiere a una cadena de carbono recta o ramificada, optativamente sustituida, que puede estar totalmente saturada o tener una o más unidades de insaturación. Los sustituyentes opcionales son los descritos anteriormente para un grupo alifático. La cadena de alidilo usada puede incluir cadenas de alidilo que contienen 0-4 sustituyentes de flúor. Un "agonista para un receptor nuclear" es un agente que, cuando se une al receptor nuclear, activa la actividad del receptor nuclear para activar o reprimir la función del gen. En algunos casos, los receptores nucleares pueden actuar a través de las vías de señalización del segundo mensajero, y la invención s aplicaría también a estas acciones. La activación puede tener un nivel similar a aquel provisto por una hormona natural para el receptor, o puede ser más fuerte (optativamente denominado "agonista fuerte") o puede ser más débil (optativamente denominado "agonista débil" o "agonista parcial"). Un ejemplo de una hormona para un receptor nuclear es la hormona tiroides, que es una hormona natural para el receptor de tiroides. Un "agonista putativo" es un agente que se debe ensayar por la actividad agonista.

Los agonistas parciales o los antagonistas parciales se unen a los receptores y dan una respuesta menor que aquella de un agonista total a las concentraciones de ligando de saturación. Un agonista parcial bloquea la unión de un agonista total y elimina la actividad del receptor al nivel inducido por el agonista parcial solo. Por ejemplo, los agonistas parciales se unen a los receptores e inducen solamente una parte de los cambios en los receptores que están inducidos por los agonistas. Las diferencias pueden ser cualitativas o cuantitativas. Por lo tanto, un agonista parcial puede inducir algunos de los cambios de conformación inducidos por los agonistas, por no otros, o puede incluir solamente ciertos cambios a una magnitud limitada. Algunos de estos compuestos se producen naturalmente. Por ejemplo, muchoos estrógenos vegetales (fitoestrógenos), tales como genisteína, pueden compoartarse como agonistas de receptores de estrógenos parciales.

Un "antagonista para un receptor nuclear" es un agente que reduce o bloquea la actividad mediada por el receptor en respuesta a un agonista del receptor. La actividad del antagonista se puede mediar, por ejemplo, uniendo el agonista al receptor, o alterando la configuración y/o actividad del receptor. Un "antagonista putativo" es un agente que se debe ensayar por su actividad antagonista.

Un "receptor nuclear" es un receptor que activa o reprime la transcripción de uno o más genes en el núcleo (pero también puede tener acciones de señalización de segundo mensajero), generalmente en conjunto con otros factores de transcripción. El receptor nuclear es activado por el ligando natural para el receptor. Los receptores nucleares normalmente se encuentran en el citoplama o el núcleo, en lugar de estar unidos a la membrana. El receptor nuclear es un miembro de una superfamilia de proteínas reguladoras que son receptores, por ejemplo, para esteroides, retinoides, vitamina D y hormonas tiroides. Estas proteínas se unen a los elementos que actúan cis en los promotores de sus genes objetivo y modulan la expresión de genes en respuesta a un ligando para ellas. Los receptores nucleares se pueden clasificar basado en sus propiedades de unión al ADN. Por ejemplo, los receptores de glucocorticoides, estrógeno, andrógeno, progestina y corticoide mineral se unen como homodímeros a los elementos de respuesta a la hormona (HRE) organizados como repeticiones invertidas. Otro ejemplo son los receptores, que incluyen aquellos activados por el ácido retinoico, la hormona tiroides, la vitamina D_3, la proliferación de ácidos grasos/peroxisoma, y ecdisona, que se unen a HRE como heterodímeros con un compañero común, el receptor X retinoide (RXR). Entre los últimos receptores está LXR.

Como se usa en la presente, un receptor nuclear huérfano es un receptor nuclear para el cual el ligando natural es desconocido.

Como se usa aquí, el receptor X de hígado o LXR se refiere a un receptor nuclear implicado en la biosíntesis del colesterol. Como se usa aquí, el término LXR se refiere tanto a LXRα como a LXRβ, dos formas de la proteían halladas en los mamíferos. El receptor X de hígado α o LXRα se refiere al receptor descrito en las Patentes Estadounidenses N° 5.571.696, 5.696.233 y 5.710.004 y Willy et al (1995) Gene Dev. 9(9):103-1045. El receptor X de hígado β o LXRβ se refiere al receptor descrito en Peet et al (1998) Curr. Opin. Genet. Dev. 8(5):571-575; Song et al (1995) Ann. N.Y. Sci. 761:38-49; Alberti et al (2000) Gene 243(1-2):93-103; y referencias citadas en ellas, y en las Patentes Estadounidenses N° 5.571.696, 5.696.233 y 5.710.004.

Como se usa aquí, los compuestos que están "disponibles comercialmente" pueden obtenerse de fuentes comerciales convencionales que incluyen Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, que incluye Sigma Chemical y Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, UK), BDH Inc. (Toronto, Canadá), Bionet

(Cornwell, UK), Chemservice, Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan UT), ICN Biomedicals Inc. (Costa Mesa CA), Key Organics (Cornwall UK), Lancaster Synthesis (Windham NH), Maybridge Chemical Co. Ltd. (Cornwall UK), Parish Chemical Co. (Orem UT), Pfalz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Riedel de Haen AG (Hannover, Alemania), Spectrum Quality Product Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD) y Wako Chemicals USA Inc. (Richmond VA).

Como se usa aquí, "condiciones adecuadas" para realizar un paso sintético se dan explícitamente aquí o se pueden discernir mediante la referencia a publicaciones referidas a métodos usados en la química orgánica sintética. La bibliografía de referencia expuesta anteriormente que detalla la síntesis de reactivos útiles en la preparación de compuestos de la presente invención, también proporcionan condiciones para realizar un paso de síntesis de acuerdo con la presente invención.

Como se usa aquí, "métodos conocidos para un experto en el arte" pueden identificarse a través de la bibliografía de referencia y las bases de datos. La bibliografía de referencia adecauda que detalla la síntesis de los reactivos útiles en la preparación de compuestos de la presente invención, o proporciona referencias a artículos que describen la preparación, incluyen, por ejemplo, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S.R. Sandler et al "Organic Functional Group Preparations" 2nd Ed., Academic Press, New York, 1983; H.O. House, "Modern Synthetic Reactions" 3rd Ed., W.A. Benjamin, Inc. Menlo Park, Calif. 1972; T.L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. También se pueden didentificar reactivos específicos y análogos a través de los índices de compuestos químicos conocidos preparados por el Servicio de Resúmenes de Química de la Sociedad Química de Estados Unidos, que están disponibles en la mayor parte de las bibliotecas públicas y universitarias, así como a través de bases de datos en línea (puede comunicarse con la American Chemical Society, Washington, DC para más detalles). Los compuestos químicos que son conocidos pero no están disponibles comercialmente se pueden preparar en comercios de síntesis químicas personalizados, donde muchos de los

proveedores de compuestos químicos comunes (por ejemplo, aquellos enumerados anteriormente) prestan servicios de síntesis personalizados.

"Profármacos" indica un compuesto que se puede convertir en condiciones fisiológicas o mediante solvólisis en un compuesto activo biológicamente de la invención. Por lo tanto, el término "profármaco" se refiere a un precursor metabólico de un compuesto de la invención que es farmacéuticamente aceptable. Un profármaco puede ser inactivo cuando se administra a un sujeto que lo necesita, pero se convierte in vivo en un compuesto activo de la invención. Los profármacos generalmente se transforman rápidamente in vivo para dar el compuesto madre de la invención, por ejemplo, mediante hidrólisis en la sangre. El compuesto profármaco suele ofrecer ventajas de solubilidad, compatibilidad con el tejido o liberación retardada en un organismo de mamífero (véase, Bundgard, H., Design of Prodrug (1985), pp. 7-9, 21-24 (Elsvier, Amsterdam). Una discusión de profármacos se da en Higuchi, T. et al, "Pro-drugs as Novel Delivery Systems", A.C.S. Symposium Series, Vol. 14, y en Bioreversible Carriers ikn Drug Design, ed. Edward B. Roche, American Pharmaceutical Associeation y Pergamon Press, 1987, ambos incorporados en su totalidad como referencia en la presente. El término "profármaco" también incluye cualquier portador unido

covalentemente que libera el compuesto activo de la invención in vivo cuando dicho profármaco se administra a un sujeto mamífero. Los profármacos de un compuesto de la invención se pueden preparar modificando grupos funcionales que están presentes en el compuesto de la invención de manera tal que las modificaciones se rompan, en la manipulación habitual o in vivo, hacia el compuesto padre de la invención. En virtud del conocimiento de los procesos farmacodinámicos y el metabolismo de los fármacos in vivo, los expertos en el arte, una vez que se conoce un compuesto farmacéuticamente activo, pueden diseñar profármacos del compuesto (véase, por ejemplo, Nogrady (1985) Medicinal Chemistry A Biohemical Approach, Oxford University Press, New York, páginas 388-392). Los profármacos incluyen compuestos de la invención en donde un grupo hidroxi, amino o mercapto se une a cualquier grupo que, cuando el profármaco del compuesto de la invención se administra a un sujeto mamífero, se rompen para formar un grupo hidroxi libre, amino libre o mercapto libre, respectivamente. Ejemplos de profármacos incluyen, en forma no taxativa, derivados formato y benzoato de grupos funcionales alcohol y amina en los compuestos de la invención y similares.

"Polimorfo" se refiere a las diferentes formas cristalinas de un compuesto, que derivan de la posibilidad de por lo menos dos disposiciones diferentes de las moléculas del compuesto en

el estado sólido. Los polimorfos de un compuesto dado son diferentes en la estructura cristalina pero idénticos en los estados líquido y de vapor. Diferentes formas polimórficas de una sustancia dada pueden diferir de una a otra con respecto a una o más propiedades físicas, tales como solubilidad y disociación, densidad verdadera, forma del cristal, comportamiento con la compactación, propiedades de flujo y/o estabilidad del estado sólido.

"Compuesto estable" y "estructura estable" indican un compuesto que es suficientemente robusto para sobrevivir el aislamiento a un nivel de pureza útil desde una mezcla de la reacción, y la formulación en un agente terapéutico eficaz.

"Mamífero" incluye humanos y animales domésticos, tales como gatos, perros, cerdos, ganado vacuno, ovejas, cabras, caballos, conejos y similares.

"Optativo" u "optativamente" significa que el evento o circunstancia descritos en secuencia puede ocurrir o no, y que la desripción incluye instancias en las cuales dicho evento o circunstancia ocurre e instancias en las cuales no ocurre. Por ejemplo, "arilo optativamente sustituido" significa que el radical de arilo puede o no ser sustituido y que la descripción incluye tanto radicales de arilo sustituidos

definidos aquí como radicales de arilo que no tienen ninguna sustitución.

"Portador, diluyente o excipiente farmacéuticamente aceptable" incluye en forma no taxativa, todos los diluyentes, portadores, excipientes, agentes edulcorantes, diluyentes, conservantes, colorantes, mejoradores del sabor, surfactantes, agentes de humedecimiento, agentes dispersantes, agentes de suspensión, estabilizadores, agentes isotónicos, solventes o emulsionadores que están aprobados por la Administración de Alimentos y Medicamentos de Estados Unidos ya que son aceptables para su uso en humanos o animales domésticos.

"Sal farmacéuticamente aceptable" incluye tanto sales de adición ácidas como básicas.

"Sal de adición ácida farmacéuticamente aceptable" se refiere a aquellas sales que retienen la eficacia biológica y las propiedades de las bases libres, que no son biológicamente o de otro modo indeseables, y que se forman con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, y ácidos orgánicos tales como ácido acético, ácido trifluoroacético, ácido propiónico, ácido glicólico, ácido pirúvico, ácdo oxálico, ácido maleico, ácido malónico, ácido

succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido cinámico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido p-toluenosulfónico, ácido salicílico y similares.

"Sal de adición básica farmacéuticamente aceptable" se refiere a aquellas sales que retienen la eficacia biológica y las propiedades de los ácidos libres, que no son biológicamente o de otro modo indeseables. Estas sales se preparan a partir del agregado de una base inorgánica o una base orgánica al ácido libre. Las sales derivadas de bases inorgánicas incluyen, en forma no taxativa, las sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Las sales inorgánicas preferidas son las sales de amonio, sodio, potasio, calcio y magnesio. Las sales derivadas de bases orgánicas incluyen, en forma no taxativa, sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen ainas sustituidas naturales, aminas cíclicas y resinas de intercambio iónico, tales como isopropilamina, trimetilamina, dietilamina, trietilamina, tripropilamina, etanolamina, 2-dimetilaminoetanol, 2-dietilaminoetanol, diciclohexilamina, lisina, arginina, histidina, cafeína, procaína, hidrabamina, colina, betaína, etilendiamina, glucosamina, metilglucosamina, teobromina, purinas, piperazina, piperidina, N-etilpiperidina, resinas de poliamina

y similares. Las bases orgánicas particularmente preferidas son isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, colina y cafeína.

"Derivado farmacéuticamente aceptable" se refiere a sales farmacéuticamente aceptable definidas aquí y también incluye ésteres, profármacos, solvatos y polimorfos de los compuestos de la invención.

"Cantidad terapéuticamente eficaz" se refiere a aquella cantidad de un compuesto de la invención que, cuando se administra a un mamífero, preferentemente un humano, es suficiente para efectuar el tratamiento, definido a continuación, para un estado de enfermedad asociado con la actividad de los receptores nucleares. La cantidad de un compuesto de la invención que constituye una "cantidad terapéuticamente eficaz" varía según el compuesto, las condiciones y su severidad, y la edad del mamífero a quien se debe tratar, pero la puede determinar habitualmente un experto en el arte que tiene en cuenta su propio conocimiento y esta invención.

"Modulando" o "modular" se refiere al tratamiento, prevención, supresión, mejoramiento o inducción de una función o condición. Por ejemplo, los compuestos de la presente

invención pueden modular la hiperlipidemia reduciendo el colesterol en un humano, suprimiendo así la hiperlipidemia.

"Tratar" o "tratamiento" como se usa aquí cubre el tratamiento de una enfermedad o condición asociada con la actividad de los receptores nucleares, en un mamífero, preferentemente un humano e incluye:

i. Prevenir que una enfermedad o condición asociada con la actividad de los receptores nucleares ocurra en un mamífero, en particular, cuando dicho mamífero tiene predisposición a la enfermedad o condición pero aún no se ha diagnosticado que la tenga;

ii. Inhibir una enfermedad o condición asociada con la actividad de los receptores nucleares, decir detener el desarrollo; o

iii. Aliviar una enfermedad o condición asociada con la actividad de los receptores nucleares, es decir producir la regresión de la condición.

Los compuestos de las fórmulas IIaa, IIbb, IIcc, o IIdd o sus sales farmacéuticamente aceptables pueden contener uno o más centros asimétricos y por lo tanto pueden dar origen a enantiómeros, diastereómeros, y otras formas estereoisoméricas que pueden definirse, en términos de estereoquímica absoluta,

como (R)- o (S)- o como (D)- o (L)- para aminoácidos. Se entiende que la presente invención incluyen todos aquellos isómeros posbles, así como, sus formas racémicas y ópticamente puras. Los isómeros ópticamente activos (+) y (-), (R) y (S) o (D) y (L) se pueden preparar usando síntomas quirales o reactivos quirales, o resolverse usando técnicas convencionales, tales como HPLC de fase invertida. Cuando los compuestos descritos en la presente contienen enlaces dobles olefínicos u otros centros de asimetría geométrica, y a menos que se especifique de otro modo, se desea que los compuestos incluyan los isómeros geométricos E y Z. Será evidente para los expertos en el arte que ciertos compuestos de esta invención pueden existir en formas tautoméricas, todas aquellas formas tautoméricas de los compuestos están dentro del alcance de la invención. A menos que se diga de otro modo, las estrucutras ilustradas en la presente también incluyen todas las formas estereoquímicas de la estructura, es decir, las configuraciones R y S para cada centro asimétrico. En consecuencia, los isómeros estereoquímicos simples así como las mezclas enatioméricas y diastereoméricas de los presentes compuestos están dentro del alcance de la invención. A menos que se diga de otro modo, las estructuras ilustradas aquí también incluyen compuestos que difieren solamente en la presencia de uno o más átomos enriquecidos isotópicamente. Por ejemplo, los compuestos que tienen las presentes estructuras

excepto por el reemplazo de un átomo de hidrógeno por un deuterio o tritio, o el reemplazo de un carbono por un carbono enriquecido con 13C o 14C están dentro del alcance de esta invención.

El protocolo de los nombres químicos y los diagramas de estructuras usados aquí emplean y se basan en las características de nombres químicos utilizadas por el programa ChemDraw (disponible en Cambridgesoft Corp., Cambridge, MA). En particular, los nombres de los compuestos se obtuvieron de las estructuras usando el programa Autonom utilizado por Chemdraw Ultra o la base ISIS (MDL Corp.).

El término "aterosclerosis" se refiere al proceso mediante el cual se forman placas ateroscleróticas dentro del revestimiento interior de la pared arterial que derivan en enfermedades cardiovasculares ateroscleróticas. Las enfermedades cardiovasculares ateroscleróticas pueden ser reconocidas y entendidas por los médicos que practican en los campos relevantes de la medicina, e incluyen en forma no taxativa, restenosis, enfermedad cardiaca coronaria (también denominada enfermedad cardiaca de las arterias coronarias o enfermedad cardiaca isquémica), enfermedad cerebrovascular que incluye ataque isquémico, demencia por infartos múltiples,

enfermedad de los vasos periféricos, que incluye claudicación intermitente, y disfunción eréctil.

El término "dislipidemia" se refiere a niveles anormales de lipoproteinas en el plasma sanguíneo que incluyen niveles deprimidos y/o elevados de lipoproteínas (por ejemplo, niveles elevados de Lipoproteína de Baja Densidad (LDL), Lipoproteína de Densidad Muy baja (VLDL) y niveles deprimidos de Lipoproteína de Alta Densidad (HDL) (menos de 40 mg/dL)).

Como se usa aquí, "EC50" se refiere a una dosificación, concentración o cantidad de un compuesto de ensayo particular que produce una respuesta que depende de la dosis al 50% de la expresión máxima de una respuesta particular que se induce, provoca o potencia con el compeusto de ensayo particular.

El término "colesterol" se refiere a un alcohol esteroide que es un componente esencial de las membranas celulares y fundas de mielina y, como se usa aquí, incorpora su uso común. El colesterol también sirve como un precursor para las hormonas esteroides y los ácidos biliares.

El término "triglicérido(s)" ("TG") como se usa aquí incorpora su uso común. Los TG comprenden tres moléculas de ácido graso esterificadas hacia una molécula de glicerol y sirven para

almacenar ácidos grasos usados por las células musculares para la producción de energía o se absorben y almacenan en el tejido adiposo.

El término "hiperlipidemia" se refiere a la presencia de un nivel anormalmente elevado de lípidos en la sangre. La hiperlipidemia puede aparecer en por lo menos tres formas (ES): (1) hipercolesterolemia, es decir un nivel de colesterol LDL elevado (120 mg/dL y más); (2) hipertrigliceridemia, es decir un nivel de triglicéridos elevado (150 mg/dL y más), y (3) hiperlipidemia combinada, es decir una combinación de hipercolesterolemia e hipertrigliceridemia.

Ejemplos de hiperlipidemia primaria incluyen, en forma no taxativa, los siguientes:

(1) Hiperquilomicronemia Familiar, un tratorno genético raro que produce una deficiencia en una enzima, LP lipasa, que rmpe las moléculas de grasa. La deficiencia de LP lipasa puede producir la acumulación de grandes cantidades de grasa o lipoproteínas en la sangres.

(2) Hipercolesterolemia Familiar, un tratorno genético relativamente común provocado cuando el defecto subyacente es una serie de mutaciones en el gen del receptor de LDL que derivan en el mal funcionamiento de los receptores de LDL y/ la ausencia de los receptores de LDL. Esto produce el

aclaramiento ineficaz de LDL por los receptores de LDL que deriva en niveles de LDL y colesterol total elevados en el plasma;

(3) Hiperlipidemia Combinada Familiar, también denominada hiperlipidemia de tipo de lipoproteínas múltiples, un trastorno hereditario donde los pacientes y sus parientes de primer grado afectados pueden manifestar varias veces colesterol alto y triglicéridos altos. Los niveles de coleterol HDL frecuentemente se reducen moderadamente;

(4) Apolipoproteína Defectuosa Familiar B-100 es una anormalidad genética dominante autosomal relativamente común. El defecto está causado por una mutación de un solo nucleótido que produce una sustitución de glutamina por arginina que puede producir afinidad reducida de las partículas de LDL para el receptor de LDL. En consecuencia, esto puede producir niveles de LDL y coleterol total en plasa altos;

Disbetalipoproteinemia Familiar, también denominada Hiperlipoproteinemia de Tipo III, es un trastorno heredado no común que deriva en elevaciones moderadas a severas de los niveles de triglicéridos (TG) y colesterol del suero con función anormal de la apolipoproteína E. Los niveles de HDL son generalmente normales; y

Hipertrigliceridemia Familiar, es un trastorno heredado común en el cual la concentración de la VLDL en el plasma es elevada. Esto puede producir niveles de triglicéridos

moderados a moderadamente elevados (generalmente no niveles de colesterol) y suele estar asociado con bajos niveles de HDL en plasma.

Los factores de riesgo en la Hiperlipidemia Secundaria incluyen, en forma no taxativa, los siguientes: (1) factores de riesgo de enfermedad, tales como antecedentes de diabetes de tipo 1, diabetes tipo 2, síndrome de Cushings, hipotiroidismo y ciertos tipos de insuficiencia renal; (2) factores de riesgo de fármacos, que incluyen, en forma no taxativa, pastillas para control de natalidad, hormonas, tales como estrógeno, y corticosteroides; ciertos diuréticos, y diferentes beta bloqueantes; (3) factores de riesgo dietarios incluyen la ingesta de grasas dietarias por calorías totales superior al 40%; ingesta de grasas saturadas por caloría total superior al 10%; ingesta de colesterol superior a 300 mg por día; consumo de alcohol habitual y excesivo; y obesidad; y (4) dislipidemia no genética.

Los métodos de la presente invención se pueden usar eficazmente en combinación con uno o más agentes activos de diabetes adicionales según la terapia deseada (véase, por ejemplo, Turner, N. et al, Prog. Drug Res. (1998) 51:33-94; Haffner, S. Diabetes Care (1998) 21: 160178, y DeFronzo, R. et al (eds), Diabetes Review (1997) Vol. 5 N°4). Numerosos

estudios han investigado los beneficios de las terapias de combinación con agentes orales (véase, por ejemplo, Mahler, R., J. Clin. Endocrinol. Metab. (1999)84:1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998)21:87-92; Bardin, C.W. (eds), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby-Year Book, Inc., St. Louis, MO, 1997); Chiasson, J. et al, Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. et al, Clin. Ther. (1997) 19:16-28; Coniff, R. et al, Am. J. Med. (1995) 98:443-45; y Iwamoto, Y. et al, Diabet. Med. (1996) 13:365-370; Kowiterovich, P., Am. J. Cardiol (1998) 82(12A):3U-17U). Estos estudios indican que la diabetes y la modulación de la hiperlipidemia se pueden mejorar adicionalmente agregando un segundo agente al régimen terapéutico. Como se usa aquí, "IC50" se refiere a una cantidad, concentración o dosificación de un compuesto de ensayo particular que alcanza un 50% de inhibición de una respuesta máxima, tal como la modulación del receptor nuclear, que incluye la actividad de LXRα o LXRβ en un ensayo que mide dicha respuesta.

Como se usa aquí, "LXRα" (LXR alfa) se refiere a todas las formas de maíferos de dicho receptor que incluyen, por ejemplo, isoformas de empalme alternativas e isoformas naturales. Las especies de LXRα representativas incluyen, en

forma no taxativa, las formas de rata (Genbank Accession NM_031627), ratón (Genbank Accession BC012646) y humana (GenBank Accession N° U22662) del receptor.

Como se usa aquí, "LXRβ" (LXR beta) se refiere a todas las formas de mamíferos de dicho receptor que incluyen, en forma no taxativa, las isoformas de empalme alternativas y las isoformas naturales. Las especies de LXRβ representativas incluyen, en forma no taxativa, las formas de rata (GenBank Accession NM_031628), ratón (Genbank Accession BC009473) y humana (GenBank Accession N° U07132) del receptor.

Como se usa aquí, "LXR" o "LXRs" se refiere a LXRα y LXRβ.

Los términos "obeso" y "obesidad" se refieren a un Índice de Masa Corporal (BMI) superior a 27,8 kg/m^2 para hombres y 27,3 kg/m^2 para mujeres (BMI equivale a peso(kg)/(altura)^2(m^2).

Uso de los compuestos de la invención

Los compuestos de la invención presentan propiedades farmacológicas valiosas en los mamíferos, y son particularmente útiles como agonistas de LXR selectivos, agonitas invertidos, agonistas parciales y antagonistas, para

el tratamiento, o la prevención de enfermedades asociadas con, o síntomas que surgen de las complicaciones, transporte de colesterol alterado, transporte invertido de colesterol, metabolismo de ácidos grasos, absorción de colesterol, reabsorción de colesterol, secresión de colesterol, excreción de colesterol o metabolismo de colesterol.

Estas enfermedades incluyen, por ejemplo, hiperlipidemia, dislipidemia, hipercolesterolemia, aterosclerosis, enfermedades cardiovasculares ateroscleróticas, hiperlipoproteinemia (véase, por ejemplo, Publicación de Solicitud de Patente N° WO 00/57915 y WO 00/37077), hiperglucemia, resistencia a la insulina, diabetes, lipodistrofia, obseidad, síndrome X (Solicitud de Patente Estadounidense N° 20030073614, Publicación de Solicitud de Patente Internacional N° WO 01/82917), deposición excesiva de lípidos en tejidos periféricos tales como la piel (xantomas) (véase por ejemplo, Patentes Estadounidenses N° 6.184.215 y 6.187.814), ataque, enfermedad oclusiva periférica, pédida de memoria (Brain Research (1997), Vol. 752, pp. 189-196), patologías del nervio óptico y retinales (es decir, degeneración macular, retinitis pigmentosa), reparación de lesión traumática al sistema nervioso central o periférico (Trends in Neurosciences (1994), Vol. 17, pp. 525-530), prevención del proceso degenerativo debido al envejecimiento

(American Journal of Pathology (1997), Vol. 151, pp. 1371-1377), enfermedad de Parkinson o enfermedad de Alzheimer (véase, por ejemplo, la Publicación de Solicitud de Patente Internacional N° WO 00/17334; Trends in Neurosciences (1994), Vol. 17, pp. 525-530), prevención de neuropatías degenerativas que ocurren en enfermedades tales como neuropatías diabéticas (véase, por ejemplo, la Publicación de Solicitud de patente Internacional N° WO 01/82917), esclerosis múltipl (Annals of Clinical Biochem. (1996), Vol. 33, N° 2, pp. 148-150), y enfermedades autoinmunes (J. Lipid Res. (1998), Vol. 39, pp. 1740-1743).

También se proporcionan métodos para aumentar la expresión del Cassette de Unión a ATP (BCA1) (véase, por ejemplo, Publicación de Solicitud de Patente Internacional N° WO 00/78972) aumentando así el transporte de colesterol invertido en células de memíferos usando los compuestos y composiciones reivindicados.

Por consiguiente, en otro aspecto, la invención también incluye métodos para remover el colesterol de los depósitos de tejidos tales como placas ateroscleróticas o xantomas en un paciente con aterosclerosis o enfermedad cardiovascular ateroscleróticа manifestda por signos clínicos de dicha enfermedad, en donde los métodos comprenden administrar al

paciente una cantidad terapéuticamente eficaz de un compuesto o composición de la presente invención. Por consiguiente, la presente invención también proporciona un método para prevenir o reducir el riesgo de una primera ocurrencia u ocurrencia posterior de un evento de enfermedad cardiovascular aterosclerótica que incluye enfermedad cardiaca isquémica, ataque isquémico, demencia por infartos múltiples, y claudicación intermitente, que comprende administrar una cantidad profilácticamente eficaz de un compuesto o composición de la presente invención a un paciente en riesgo de dicho evento. El paciente puede ya tener la enfermedad cardiovascular aterosclerótica en el mismo momento de la administración, o puede estar en riesgo de desarrollarla. Los factores de riesgo para desarrollar eventos de enfermedad cardiovascular aterosclerótica, incluyen edad avanzada (65 años y más), sexo masculino, antecedentes familiares de eventos de enfermedad cardiovascular aterosclerótica, alto colesterol en sangre (especialmente LDL o colesterol "malo" superior a 100 mg/dL), fumar y exposición al humo del tabaco, alta presión sanguínea, diabetes, obesidad e inactividad física.

También está contemplado aquí el uso de un compuesto de la invención, o un derivado farmacéuticamente aceptable de é, en combinación con uno o más de los siguientes agentes

terapéuticos en el tratamiento de la aterosclerosis: agentes antihiperlipidémicos, agentes de aumento de LDL en el plasma, agentes antihipercolesterolémicos, inhibidores de la biosíntesis del colesterol (tales como inbibidores de HMG CoA reductasa, tales como lovastatina, simvastatina, pravastatina, fluvastatina, atorvastatina y rivastatina), inhibidores de acil-coenzima A:colesterol aciltransferasa (ACAT), probucol, raloxifeno, ácido nicotínico, niacinamida, inhibidores de la absorción del colesterol, secuestrantes de ácido biliar (tales como resinas de intercambio de aniones, o aminas cuaternarias (por ejemplo, colestiramina o colestipol), inductores de receptor de lipoproteína de baja densidad, clofibrato, fenofibrato, benzofibrato, cipofibrato, gemfibrizol, vitamina B_6, vitamina B_{12}, vitaminas antioxidantes, beta-bloqueantes, agentes antidiabetes, antagonistas de angiotensina II, inhibidores de enzima convertidora de angiotensina, inhibidores de agregación de plaquetas, antagonistas de receptor de fibrinógeno, aspirina o derivados de ácido fíbrico.

En una realización los compuestos de la invención se usan en combinación con un inhibidor de la biosíntesis del colesterol, particularmente un inhibidor de HMG-CoA reductasa. El término inhibidor de HMG-CoA reductasa incluye todas las formas de sal, éster, ácido libre y lactona farmacéuticamente aceptables

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de los compuestos que tienen actividad inhibidora de HMG-CoA reductasa y, en consecuencia, el uso de dichas formas de sal, éster, ácido libre y lactona están incluidas dentro del alcance de esta invención. Los compuestos que tienen actividad inhibidora para HMG-CoA reductasa se pueden identificar fácilmente usando ensayos conocidos en el arte. Por ejmplo, los ensayos adecuados se describen o revelan en la Patente Estadounidense N° 4.231.938 y en WO 94/02131. Ejemplos de inhibidores de HMG-CoA reductasa adecuados incluyen, en forma no taxativa, lovastatina (MEVACOR®; véase la Patente Estadounidense N° 4.231.938); simvastatina (ZOCOR®; véase, la Patente Estadounidense N° 4.444.784); sodio de pravastatina (PRAVACHOL®; véase, la Patente Estadounidense N° 4.346.227); sodio de fluvastatina (LESCOL®; véase la Patente Estadounidense N° 5.354.772); calcio de atorvastatina (LIPITOR®; véase la Patente Estadounidense N° 5.273.995) y rivastatina (también denominada cerivastatina; véase la Patente Estadounidense N° 5.177.080). Las fórmulas estructurales de éstos y otros inhibidores de HMG-CoA reductasa que se pueden usar combinados con los compuestos de la invención se describen en la página 87 de M. Yalpani, "Cholesterol Lowering Drugs", Chemistry & Industry, pp. 85-89 (5 de febrero de 1996). En las realizaciones preferidas

actualmente, el inhibidor de HMG-CoA reductasa se selecciona de lovastatina y simvastatina.

Los compuestos de la presente invención también se pueden usar en métodos para reducir la hiperglucemia y la resistencia a la insulina, es decir, en métodos para tratar diabetes (Publicación de Solicitud de Patente Internacional N° WO 01/82917) y en métodos de tratamiento, prevención, o mejoramiento de trastornos relacionados o surgidos como complicaciones de la diabetes, hiperglucemia o resistencia a la insulina que incluyen el grupo de estados de enfermedad, condiciones o tratornos que constituyen el "Síndrome X" (Véase la Solicitud de Patente Estadounidense 20030073614) que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de la presente invención a un paciente que necesita dicho tratamiento. Además, la presente invención proporciona un método para prevenir o reducir el riesgo de desarrollar la hiperglucemia, resistencia a la insulina, diabetes o síndrome X en un paciente, que comprende la administración de una cantidad profilácticamente eficaz de un compuesto o composición de la presente invención a un paciente en riesgo de dicho evento.

La diabetes mellitus, comúnmente denominada diabetes, se refiere a un proceso de enfermedad derivado de varios factores

causales y caracterizados por niveles elevados de glucosa en plasma, denominados hiperglucemia. Véase, por ejemplo, LeRoith, D. et al, (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Ph. USA, 1996). Según la Asociación de Diabetes Estadounidense, se estima que la diabetes mellitus afecta a aproximadamente un 69% de la población mundial. La hiperglucemia no controlada está asociada con la mortalidad aumentada y prematura debido a un riesgo aumentado de enfermedades macrovasculares, que incluyen nefropatía, neuropatía, retinopatia, hipertensión, enfermedad cerebrovascular y enfermedad cardiaca coronaria. En consecuencia, el control de la homeostasis de glucosa es un enfoque criticamente importante para el tratamiento de la diabetes.

Existen dos formas principales de la diabetes: diabetes tipo 1 (anteriormente denominada diabetes insulino-dependiente o IDEM); y diabetes tipo 2 (anteriormente denominada diabetes no insulino dependiente o NIDDM).

La diabetes tipo 2 es una enfermedad caracterizada por la resistencia a la insulina acompañada por la deficiencia de insulina relativa, no absoluta. La diabetes tipo 2 puede estar en la gama de resitencia a la insulina predominante con deficiencia de insulina relativa a predominante con alguna

resistencia a la insulina. La resistencia a la insulina es la capacidad disminuida de insulina para ejercer su acción biológica a través de una amplia gama de concentraciones. En individuos resistentes a la insulina, el cuerpo segrega anormalmente elevadas cantidades de insulina para compensar por este defecto. Cuando están presentes cantidades insuficientes de insulina para compensar la resistencia a la insulina y el control adecuado de la glucosa, se desarrolla un estado de tolerancia a la glucosa deteriorado. En una cantidad significativa de individuos, la secreción de insulina se reduce adicionalmente y el nivel de glucosa en plasma aumenta, y deriva en el estado clínico de la diabetes. La diabetes tipo 2 se puede deber a una resistencia profunida a la insulina que estimula efectos reguladores sobre el metabolismo de la glucosa y los lípidos en tejidos sensibles a la insulina: tejido muscular, hepático y adiposo. Esta sensibilidad a la resistencia a la insulina deriva en una activación de la insulina insuficiente de la absorción de de glucosa, oxidación y almacenamiento en los músculos y la represión de la insulina insuficiente de la lipólisis en el tejido adiposo y de la producción y secreción de glucosa en el hígado. En la diabetes tipo 2, los niveles de ácido graso libre suelen ser elevados en pacientes obesos y algunos no obesos y se incrementa la oxidación de los lípidos.

El desarrollo prematuro de aterosclerosis y el índice aumentado de enfermedades cardiovasculares y vasculares periféricas son características de los pacientes con diabetes. La hiperlipidemia es un importante factor de precipitación para estas enfermedades. La hiperlipidemia es una condición generalmente caracterizada por un aumento anormal en los lípidos en el suero, por ejemplo colesterol y triglicéridos, en el torrente sanguíneo y es un importante factor de riesgo en el desarrollo de aterosclerosis y la enfermedad cardiaca. Para la revisión de trastornos del metabolismo de los lípidos, véase, por ejemplo, Wilson, J. et al (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W.B. Sanders Company, Philadelphia, Pa. USA, 1998). La hiperlipidemia generalmente se clasifica como hiperlipidemia primaria o secundaria. La hiperlipidemia primaria generalmente está causada por defectos genéticos, mientras que la hiperlipidemia secundaria generalmente está causada por otros factores, tales como diferentes estados de enfermedad, fármacos y factores dietarios. Alternativamente, la hiperlipidemia puede derivar de la combinación de causas primarias y secundarias de la hiperlipidemia. Los niveles elevados de colesterol están asociados con numerosos estados de enfermedad, que incluyen enfermedad de arterias coronarias, angina de pecho, enfermedad de arteria carótida, ataque, arteriosclerosis cerebral y xantoma.

La dislipidemia, o los niveles anormales de liproteínas en el plasma sanguíneo, es una ocurrencia frecuente entre los diabéticos, y se ha demostrado que uno de los que más contribuyen a la incidencia aumentada de eventos coronarios y muertes entre los sujetos diabéticos (véase, por ejemplo, Joslin, E., Ann. Chim. Med. (1927), Vol. 5, pp. 1061-1079). Los estudios epidemiológicos desde entonces han confirmado la asociación y se ha demostrado que aumentan varias veces en las muertes coronarias entre los sujetos diabéticos cuando se comparan con sujetos no diabéticos (véase, por ejemplo, Garcia, M.J. et al, Diabetes (1974), Vol. 23, pp. 105-11 (1974); y Laakso, M. y Lehto, S., Diabetes Reviews (1997), Vol. 5, N° 4, pp. 294-315). Se han descrito varias anormalidades de las lipoproteínas entre los sujetos diabéticos (Howard E. et al, Arteriosclerosis (1978), Vol. 30, pp. 153-162).

Los compuestos de la invención también pueden usarse eficazmente en combinación con uno o más agentes diabéticos activos según la terapia deseada (véase, por ejemplo, Turner, N. et al, Prog. Drug. Res. (1998), Vol. 51, pp. 33-94; Huffner, S., Diabetes Care (1998), Vol. 21, pp. 160-178; y DeFronzo, R. et al (eds.), Diabetes Reviews (1997), Vol. 5, N° 4). Numerosos estudios han investigado los beneficios de las terapias de combinación con agentes orales (véase, por

ejemplo, Mahler, R.J. Clin. Endocrinol. Metab. (1999), Vol. 84, pp. 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998), Vol. 21, pp. 87-92; Bardin, C. W. (ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th edition (Mosby-Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al, Ann. Intern. Med. (1994), Vol. 121, pp. 928-935; Coniff, R. et al, Clin. Ther. (1997), Vol. 19, pp. 16-26; Coniff, R. et al, Ann. J. Med. (1995), Vol. 98, pp. 443-451, Ivamoto, Y. et al, Diabet. Med. (1996), Vol. 13, pp. 365-370; Kwiterovich, P., Ann. J. Cardiol. (1998), Vol. 82 (12A), pp. 3U-17U). Estos estudios indican que la modulación de diabetes e hiperlipidemia también se puede mejorar agregando un segundo agente al régimen terapéutico.

Por consiguiente, los compuestos de la invención se pueden usar en combinación con uno o más de los siguientes agentes terapéuticos en el tratamiento de la diabetes: sulfonilureas (tales como cloropropamida, tributamida, acetohexamida, tolazamida, gliburida, gliclazida, glinasa, glimepirida, y glipizida), biguanidas (tales como metformina), tiazolidindionas (tales como ciglitazona, pioglitazona, troglitazona, y rosiglitazona) y sensibilizadores de la insulina relacionados, tales como activadores selectivos y no selectivos de PPARα, PPARβ y PPARγ; deshidroepiandrosterona (también denominada DHEA o su éster de sulfato conjugado,

DHEA-SO4); ntiglucocorticoides; inhibidores de TNFα; inhibidores de α-glucosidasa (tales como acarbosa, miglitol, y voglibosa), pramlintide (un análogo sintético de la anilina de hormona humana), otros secretogogos de insulina (tales como repaglinida, gliquidona, y nateglinida), insulina, así como los agentes terapéuticos discutidos anteriormente para tratar la aterosclerosis.

La invención también proporciona métodos para usar los compuestos de la invención para tratar la obesidad, así como las complicaciones de la obesidad. La obesidad está vinculada con una variedad de condiciones médicas que incluyen diabetes e hiperlipidemia. La obesidad también es un factor de riesgo conocido para el desarrollo de diabetes tipo 2 (Véase, por ejemplo, Barett-Conner, E, Epidemiol. Rev. (1989), Vol. 11, pp. 172-181; y Knowler, et al, Am. J. Clin. Nutr. (1991), Vol. 53, pp. 1543-1551).

Además, los compuestos de la invención se pueden usar en combinación con agentes usados en la obesidad tratada o trastornos relacionados con la obesidad. Dichos agentes incluyen, en forma no taxativa, fenilpropanolamina, fentermina, dietilpropion, mazindol, fenfluramina, dexfenfluramina, fentiramina, agentes de agonistas de β_3

adrenoreceptor; sibutramina, inhibidores de lipasa gastrointestinal (tales como orlistat), y leptinas. Otros agentes usados en el tratamiento de la obesidad o los trastornos relacionados con la obesidad incluyen el neuropéptido Y, enterostatina, colecitocinina, bombesina, amilina, receptores de histamina H_3, moduladores de receptor de dopamina D_3, hormona estimuladora de melanocito, factor liberador de corticotrofina, galantina y ácido gamma amino butírico (GABA).

Evaluación del Uso de los Compuestos de la Invención

Los procedimientos fisiológicos, farmacológicos y bioquímicos estándar están disponibles para ensayar los compuestos para identificar aquellos que poseen actividades biológicas que modulan la actividad de receptores nucleares, que incluyen los LXR (LXRα y LXRβ). Esos ensayos incluyen, por ejemplo, ensayos bioquímicos tales como ensayos de unión, ensayos de polarización de fluorescencia, ensayos de reclutamiento de coactivador basado en FRET (véase en general Glickman *et al.*, *J. Biomolecular Screening*, 7 No. 1, pp. 3-10 (2002)), así como ensayos basados en células que incluyen el ensayo de co-transfección, el uso de quimeras de LBD-Gal 4 y ensayos de interacción de proteína-proteína (véase Lehmann. *et al.*, *J. Biol Chem.* (1997), Vol. 272, N°6, pp. 3137-3140.

Están comercialmente disponibles sistemas de detección de alto rendimiento (véase, por ejemplo, Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) que permiten que se realicen estos ensayos en un modo de alto rendimiento. Estos sistemas generalmente automatizan procedimientos completos, que incluyen pasar por una pipeta todas las muestras y reactivos, incubaciones temporizadas de vertido de líquido, y lecturas finales de la microplaca en el detector(es) apropiado para el ensayo. Estos sistemas configurables proporcionan alto rendimiento e inicio rápido así como un alto nivel de flexibilidad y personalización. Los fabricantes de esos sistemas proporcionan protocolos detallados para diferentes sistemas de alto rendimiento. Por lo tanto, por ejemplo, Zymark Corp. proporciona boletines técnicos que describen sistemas de detección para detectar la modulación de la transcripción de genes, la unión de ligandos, y similares.

Los ensayos que no requieren pasos de lavado o separación de líquidos son preferidos para esos sistemas de detección de alto rendimiento e incluyen ensayos bioquímicos tales como ensayos de polarización de fluorescencia (véase, por ejemplo, Owicki, J., Biomol Screen (octubre de 2000), Vol. 5, No.5, pp. 297), ensayos de proximidad de centelleo (SPA) (véase, por

ejemplo, Carpenter et *al.*, Methods Mol Biol (2002), Vol. 190, pp. 31-49) y transferencia de energía de resonancia de fluorescencia (FRET) o ensayos de reclutamiento de coactivadores basados en FRET resueltos en el tiempo (Mukherjee *et al.*, *J Steroid Biochem Mol Biol* (julio de 2002), Vol. 81, No. 3, pp. 217-25; (Zhou *et al.*, *Mol Endocrinol.* (octubre de 1998), Vol. 12, N° 10, pp. 1594-604). Generalmente, esos ensayos pueden realizarse utilizando el receptor de longitud completa, o el dominio de unión al ligando aislado (LBD). En el caso del LXRα, el LBD comprende los aminoácidos 188-447, para el LXRβ el LBD comprende los aminoácidos 198-461, y para FXR, el LBD comprende los aminoácidos 244 a 472 de la secuencia de longitud completa.

Si el ligando rotulado en forma fluorescente está disponible, los ensayos de polarización de fluorescencia proporcionan una manera de detectar la unión de los compuestos al receptor nuclear de interés midiendo cambios en la polarización de fluorescencia que ocurren como resultado del desplazamiento de una cantidad de trazos del ligando del rótulo por el compuesto. Además este enfoque también puede utilizarse para monitorear la asociación que depende del ligando de un péptido coactivador rotulado en forma fluorescente al receptor nuclear

de interés para detectar el ligando que se une al receptor nuclear de interés.

La capacidad de un compuesto de unirse a un receptor, o complejo de heterodímeros con RXR, también puede medirse en un formato de ensayo homogéneo evaluando el nivel al cual el compuesto puede competir con un ligando radiorotulado con una afinidad conocida con el receptor utilizando un ensayo de proximidad de centelleo (SPA). En este enfoque, la radioactividad emitida por un compuesto radiorotulado (por ejemplo, [^{3}H] 24,25 Epoxicolesterol) genera una señal óptica cuando se lo acerca estrechamente a un aparato de centelleo por ejemplo una cuenta que contiene Ysi-cobre, al cual está unido el receptor nuclear. Si el compuesto radiorotulado es desplazado desde el receptor nuclear la cantidad de luz emitida desde el receptor nuclear unido al aparato de centelleo disminuye, y esto puede detectarse rápidamente utilizando lectores de placas de centelleo de líquido de microplacas estándar tales como, por ejemplo, un lector Wallac MicroBeta.

La heterodimerización del LXR con RXRα también puede medirse mediante transferencia de energía de resonancia de fluorescencia (FRET) o FRET resuelta en el tiempo, para monitorear la capacidad de los compuestos provistos aquí de

unirse al LXR o a otros receptores nucleares. Ambos enfoques dependen del hecho de que la transferencia de energía desde una molécula de donador a una molécula de receptor ocurre solamente cuando el donador y el receptor están estrechamente próximos. Generalmente el LBD purificado del receptor nuclear de interés se rotula con biotina y luego se mezcla con cantidades estequiométricas de estreptavidina rotulada con europio (Wallac Inc.) y el LBD purificado de RXRα se rotula con un fluoróforo adecuado tal como CY5®. Se mezclan juntas cantidades equimolares de cada LBD modificado y se las deja equilibrar durante al menos 1 hora antes de agregar concentraciones variables o constantes de la muestra para la cual se debe determinar la afinidad. Después del equilibrio, la señal fluorescente resuelta con el tiempo se cuantifiacca usndo un lector de placas fluorescente. La afinidad del compuesto puede entonces estimarse a partir de un gráfico de fluorescencia contra concentración del compuesto agregado.

Este enfoque también puede explotarse para medir la interacción que depende del ligando de un péptido coactivador con un receptro nuclear para caracterizar la actividad del agonista o antagonista de los compuestos revelados aquí. Generllmente, el ensayo en este caso consiste en utilizar una proteína de fusión de dominio de unión (LBD) de ligando de receptor nuclear de Glutationa-S-transferasa (GST) y una

secuencia de péptido biotinilado sintético derivado del dominio de interacción del receptor de un péptido coactivador tal como el coactivador de receptor esteroide 1 (SRC-1). Generalmente el GST-LBD se rotula con un quelato de europio (donador) a través de un anticuerpo anti-GST marcado con europio, y el péptido coactivador se rotula con aloficocianina a través de una ligadura de estreptavidina-biotina.

En la presencia de un antagonista para el receptor nuclear, se recluta el péptido para el GST-LBD que acerca estrechamente el europio y la aloficocianina para permitir la transferencia de energía desde el quelato de europio a la aloficocianina. Al excitar el complejo con luz a 340 nm de excitación la energía absorbida por el quelato de europio se transmite al grupo aloficocianina que deriva en la emisión a 665 nm. Si no se acerca estrechamente el quelato de europio al grupo aloficocianina hay escasa o ninguna transferencia de energía y la excitación del quelato de europio deriva en la emisión a 615 nm. Por lo tanto la intensidad de la luz emitida a 665 nm da una indicación de la resistencia de la interacción de proteína-proteína. La actividad de un antagonista de receptor nuclear se puede medir determinando la capacidad de un compuesto para inhibir en forma competitiva (es decir, IC_{50}) la actividad de un agonista para el receptor nuclear.

Además se puede utilizar exitosamente una variedad de metodologías de ensayo basadas en células en ensayos de detección para identificar y determinar el perfil de la especificidad de compuestos de la presente invención. Estos enfoques incluyen el ensayo de co-transfección, ensayos de translocación, ensayos de complementación y el uso de tecnologías de activación de genes para sobreexpresar receptores nucleares endógenos.

Existen tres variantes básicas de la estrategia de ensayo de co-transfección, ensayos de cotransfección que utilizan el receptor nuclear de longitud completa, ensayos cotransfección que utilizan receptores nucleares que comprenden el dominio de unión al ligando del receptor nuclear de interés fusionado a un dominio de unión al ADN heterólogo, y ensayos basados en el uso del sistema de ensayo de dos híbridos de mamífero.

El ensayo de cotransfección básica está basado en la cotransfección en la célula de un plásmido de expresión para expresar el receptor nuclear de interés en la célula con un plásmido indicador que comprende un gen indicador cuya expresión está bajo el control de la secuencia de ADN que es capaz de interactuar con ese receptor nuclear. (Véase por ejemplo las Patentes Estadounidenses N° 5.071.773, 5.298.429 y 6.416.957). El tratamiento de las células transfectadas con un

agonista para el receptor nuclear aumenta la actividad de transcripción de ese receptor reflejada por un aumento en la expresión del gen indicador, que puede medirse mediante una variedad de procedimientos estándar.

Para estos receptores que funcionan como heterodímeros con RXR, tales como el LXRα, el ensayo de cotransfección generalmente incluye el uso de plásmidos de expresión para el receptor nuclear de interés y para RXR. Los ensayos de cotransfección típicos requieren el acceso al receptor nuclear de longitud completa y elementos de respuesta adecuados que proveen sensibilidad y especificidad de detección suficiente al receptor nuclear de interés.

Generalmente, el plásmido de expresión comprende: (1) un promotor, tal como el promotor de primera región SV40, el prmotor de tk HSV o el promotor de fosfoglicerato cinasa (ppk), el promotor CMV, el promotor Srα u otros elementos adecuados conocidos en el arte ,(2) una secuencia de polinucleótido clonado, tal como un cADN que codific un receptor, co-factor, o un fragmento de ellos, ligado al promotor en la oritenación de sentido de manera tal que la transcripción desde el promotor produzca un ADN que cofiica una proteína funcional, y (3) una secuencia de

poliadenilación. A modo de ejemplo y no de limitación, un cassette de expresión de la invención puede comprender los vectores de clonación de expresión de cADN, u otros vectores de expresión preferidos conocidos y comercialmente disponibles desde los vendedores tales como Invitrogen, (CA), Stratagene, (CA) o Clontech (CA). Alternativamente, también se pueden usar vectores de expresión desarrollados por grupos académicos tales como los vectores pCMX desarrollados originalmente en Evans lab (Willey et al, Genes & Development 9 1033-1045 (1995).

Las secuencias reguladoras de transcripción en un cassette de expresión son seleccionadas por el practicante basado en la aplicación deseada; según el uso específico, la regulación de la transcripción puede emplear un tipo inducible, reprimible, constitutivo, específico del tipo de célula, específico de la etapa de desarrollo, específico del sexo, u otro tipo deseado de promotor o secuencia de control.

Alternativamente, el plásmido de expresión puede comprender una secuencia de activación para activar o aumentar la expresión de una secuencia de cromosoma endógena. Dichas secuencias de activación incluyen por ejemplo, un motivo de indicador de zinc sintético (por ejemplo, véanse las Patentes Estadounidenses 6.534.261 y 6.503.7171) o una secuencia de

promotor o mejorador resistente con una secuencia deseada para permitir la recombinación homóloga o no homóloga de la corriente ascendente de la secuencia de activación del gen deseado.

Los genes que codifican las siguientes proteínas de longitud completa decritas previamente, que son adecuados para su uso en los estudios de cotransfección y en el perfil de los compuestos descritos aquí, incluyen el LXRα humano (acceso U22662), LXRβ humano (acceso U07132), FXR de rata (acceso U18374), RXRα humano (acceso NM_002957), RXR β humano (acceso. XM_042579), RXRγ humano (acceso XM_053680), PPARα humano (acceso NM_005036) y PPARδ humano (acceso NM_006238). Todos los números de acceso de esta solicitud de patente se refieren a números de acceso de GenBank.

Los plásmidos indicadores pueden construirse utilizando técnicas biológicas moleculares estándar colocando el cADN que codifica el gen indicador corriente abajo desde un promotor mínimo adecuado. Por ejemplo, los plásmidos indicadores de luciferasa pueden construirse colocando el cADN que codifica luciferasa (generalmente con intron t pequeño de SV40 y cola poli-A (de Wet et al (1987) Mol. Cell. Biol. 7 725-735) corriente abajo desde el promotor de timidina cinasa del virus

del herpes (ubicado en los residuos de nucleótidos -105 a +51 de la secuencia de nucleótidos de timidina cinasa, obtenida por ejemplo, del plásmido pBLCAT2 (Luckow & Schutz (1987) Nucl. Acid Res. 15:5490-5494)) que está unido a su vez al elemento de respuesta apropiado (RE).

La elección del elemento de respuesta depende del tipo de ensayo que se debe usar. En el caso del uso del LXRα o LXRβ de longitud completa, generalmente se usaría un plásmido indicador que comprende un LXR RE conocido, por ejemplo en un plásmido indicador tal como una LXREx1-tk-luciferasa (véase la patente estadounidense N° 5.747.661, que se incorpora por la presente como referencia). En el caso de un LXRα o una fusión de LXRβ-LBD-Gal4, se usarían las Secuencias de Activación Corriente Arriba GAL4 (UAS). Generalmente las UAS de GAL4 comprenden la secuencia: 5'CGGRNNRCYNYNCNCCG-3', donde Y= C o T, R= A o G, y N = A, C, T o G; y estaría presente como una repetición de tandem de 4 copias.

Numerosos métodos de cotransfección de los plásmidos de expresión e indicador son conocidos para los expertos en el arte y pueden utilizarse pára el ensayo de cotransfección para introducir los plámidos en un tipo celular adecuado. Generalmente, esa célula no expresa en forma endógena los

receptores nucleares que interactúan con los elementos de respuesta utilizados en el plásmido indicador.

Numerosos sistemas de genes indicadores son conocidos en el arte e incluyen, por ejemplo, fosfatasa alcalina Berger, J., *et al.* Gene (1988), Vol. 66, pp. 1-10; y Kain, S.R. Methods. Mol. Biol. (1997), Vol. 63, pp. 49-60), β-galactosidasa (Véase la Patente Estadounidense N° 5.070.012, concedida el 3 de diciembre de 1991 de Nolan *et al.*, y Bronstein, I., *et al.*, J. Chemilum. Biolum. (1989), Vol. 4, pp. 99-111), cloranfenicol acetiltransferasa (Véase Gorman *et al.*, Mol Cell Biol. (1982), Vol. 2, pp. 1044-51), β-glucuronidasa, peroxidasa, β-lactamasa (Patentes Estadounidenses Nos. 5.741.657 y 5.955.604), anticuerpos catalíticos, luciferasas (Patentes Estadounidenses N° 5.221.623; 5.683.888; 5.674.713; 5.650.289; y 5.843.746) y proteínas naturalmente fluorescentes (Tsien, R.Y. Annu. Rev. Biochem. (1998), Vol 67, pp. 509-44).

El uso de quimeras que comprenden el dominio de unión del ligando (LBD) del receptor nuclear de interés a un dominio de unión de ADN heterólogo (DBD) expande la versatilidad de los ensayos basados en células dirigiendo la activación del receptor nuclear en cuestión a elementos de unión del ADN definidos reconocidos por el dominio de unión del ADN definido

(véase WO 95/18380). Este ensayo expande la capacidad de los ensayos de cotranfección basados en células en casos en los cuales la respuesta biológica o la ventana de detección que utiliza el dominio de unión de ADN nativo no es satisfactoria.

En general la metodología es similar a aquella utilizada con el ensayo de cotrasnfección básica, excepto que se utiliza una construcción quimérica en lugar del receptor nuclear de longitud completa. Como con el receptor nuclear de longitud completa, el tratamiento de las células transfectadas con un agonista para el LBD de receptor nuclear aumenta la actividad de transcripción del dominio de unión de ADN heterólogo que se refleja por un aumento en la expresión del gen indicador descrito anteriormente. Generalmente para esas construcciones quiméricas, se utilizan dominios de unión de ADN de receptores nucleares definidos, o de levadura o reguladores de transcripción obtenidos bacterialmente tales como miembros de las superfamilias de GAL-4 y Lex A/Umud.

Un tercer ensayo basado en células de utilidad para detectar compuestos de la presente invención es un ensayo de dos hibridos de mamifero que mide la capacidad del recepetor nuclear de hormona de interactuar con un cofactor en la presencia de un ligando (Véase, por ejemplo, las Patentes Estadounidenses N° 5.667.973, 5.283.173 y 5.468.614). El

521
519

enfoque básico es crear tres construcciones de plasmidos que permiten la interacción del receptor nuclear con el proteína interactuante que se debe acoplar a la lectura de transcripción dentro de una célula viva. La primera construcción es un plásmido de expresión para expresar una proteína de fusión que comprende la proteína interactuante, o una parte de la proteína que contiene el dominio de interacción, fusionado a un dominio de unión de ADN de GAL4. El segundo plásmido de expresión comprende el ADN que codifica el receptor nuclear de interés fusionado a un dominio de activación de transcripción resistente tal como VP16, y la tercera construcción comprende el plásmido indicador que comprende un gen indicador con un promotor mínimo y secuencias de activación corriente arriba de GAL4.

Una vez que se introducen los tres plásmidos en una célula, el dominio de unión de ADN de GAL4 codificado en la primera construcción permite la unión específica de la proteína de fusión a sitios de GAL4 corriente arriba de un promotor mínimo. Sin embargo como el dominio de unión de ADN de GAL4 generalmente no tiene ninguna propiedad de activación de transcripción resistente aislada, la expresión del gen indicador ocurre solamente a un bajo nivel. En la presencia de un ligando, la proteína de fusión VP16 del receptor nuclear puede unirse a la proteína de fusión de proteína que

interactúa con GAL4 que acerca VP16 de activador de transcripción resistente a los sitios de unión de GAL4 y la región de promotor mínimo del gen indicador. La interacción mejora significativamente la transcripción del gen indicador, que puede medirse para diferentes genes indicadores como se describió anteriormente. La transcripción del gen indicador por lo tanto se ve activada por la interacción de la proteína interactuante y el receptor nuclear de interés en la fusión que depende del ligando.

Cualquier compuesto que sea un candidato para la activación del LXRα o LXRβ se puede ensayar mediante estos métodos. Generalmente, los compuestos se ensayan a diferente concentraciones para optimizar las oportunidades de que la activación del receptor sea detectada y reconocida si está presente. Generalmente, se realizan ensayos por triplicado y varían dentro del error experimental en menos del 15%. Cada experimento generalmente se repite tres o más veces con resultados similares.

La actividad del gen indicador se puede normalizar convenientemente al control interno y los datos se pueden graficar como activación de pliegues en relación con las células no tratadas. Un compuesto control positivo (agonista) puede incluirse junto con DMSO como controles alto y bajo para

la normalización de los datos del ensayo. En forma similar, la actividad del antagonista se puede medir detrminando la capacidad de un compuesto de inhibir en forma competitiva la actividad de un agonista.

Además los compuestos y las composiciones pueden evaluarse por su capacidad de aumentar o disminuir la expresión de genes que se sabe que es modulada por el LXRα o LXRβ y otros receptores nucleares in vivo, utilizando el análisis Northern blot, RT PCR o análisis de microgrupos de oligonucleótidos para analizar los niveles de ARN. El análisis Western blot se puede utilizar para medir la expresión de las proteínas codificadas por los genes blanco de LXR. Los genes que se sabe que son regulados por los LXR incluyen los transportadores de cassette de unión a ATP ABCA1, ABCG1, ABCG5, ABCG8, el gen de proteína de unión al elemento de respuesta de esterol 1c (SREBP1c), estearil CoA desaturasa 1 (SCD-1) y el gen de apolipoproteína apoE (ApoE).

Existen modelos animales establecidos para numerosas enfermedades de relevancia directa para los compuestos reivindicados y éstos pueden utilizarse para describir el perfil y caracterizar adicionalmente los compuestos reivindicados. Estos sistemas de modelos incluyen dislipidemia diabética utilizando ratas (fa/fa) o ratones (db/db) Zucker,

hiperlipidemia espontánea utilizando ratones con insuficiencia de apolipoproteína E (ApoE$^{-/-}$), hiperlipidemia inducida por la dieta, utilizando ratones con insuficiencia de receptor de lipoproteína de baja densidad (LDR$^{-/-}$) y aterosclerosis utlizando ratones con Apo E($^{-/-}$) y LDL($^{-/-}$) alimentados con una dieta occidental (21% grasa, 0,05% colesterol). Además se pueden utilizar modelos animales de LXR o FXR (por ejemplo, ratones knockout) para evaluar adicionalmente los presentes compuestos y composiciones in vivo (véase, por ejemplo, Peet, *et al., Cell* (1998), Vol. 93, pp. 693-704 y Sinal et al, Cell (2000), Vol. 102, pp. 731-744).

Administración de los Compuestos de la Invención

La administración de los compuestos de la invención, o sus sales farmacéuticamente aceptables, en forma pura o en una composición farmacéutica apropiada, se puede realizar a través de cualquiera de las modalidades aceptadas de adinistración de agentes para tener utilidades similares. Las composiciones farmacéuticas de la invención se pueden preparar combinando un compuesto de la invención con un portador, diluyente o excipiente farmacéuticamente aceptable, y se pueden formular en la preparación en formas sólidas, semisólidas, líquidas o gasesosas, tales como tabletas, cápsulas, polvos, gránulos, ungüentos, soluciones, supositorios, inyecciones, inhaladores,

geles, microesferas, y aerosoles. Las vías de administración típicas de tales composiciones farmacéuticas incluyen, en forma no taxativa, oral, tópica, transdérmica, inhalación, parenteral, sublingual, rectal, vaginal e intranasal. El término parenteral como se usa aquí incluye inyecciones subcutáneas, intravenosas, intramusculares, intraesternales, o técnicas de infusión. Las composiciones farmacéuticas de la invención se formulan como para permitir que el ingrediente activo contenido dentro de ellas esté biodisponible al administrar la composición a un paciente. Las composiciones que se administran a un sujeto o paciente toman la forma de una o más unidades de dosificación, donde por ejemplo, una tableta puede ser una sola unidad de dosificción, y un envase de un compuesto de la invención en forma de aerosol puede contener una pluralidad de unidades de dosificación. Los étodos reales de preparación de tales formas de dosificación son conocidos, o serán evidentes para los expertos en el arte; por ejemplo, véase Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). La composición que se debe administrar, en cualquier caso, contienen una cantidad terapéuticamente eficaz de un compuesto de la invención, o una sal farmacéuticamente aceptable de él, para el tratamiento de un estado de enfermedad asociado con l actividad de un receptor nuclear con las enseñanzas de esta invención.

Una composición farmacéutica de la invención puede estar en la forma de un sólido o líquido. En un aspecto, el portador(es) es particulado, de manera tal que las composiciones estén por ejemplo, en forma de tableta o polvo. El portador puede ser líquido, donde la composición es, por ejemplo, un jarabe oral, líquido inyectable o un aerosol, que es útil, por ejemplo, en la administración inhalatoria.

Cuando se desea para la administración oral, la composición farmacéutica preferentemente está en forma sólida o líquida, donde las formas de suspensión y gel semisólido, semilíquido están incluidas dentro de las formas consideradas en la presente como sólida o líquida.

Como una composición sólida para la administración oral, la composición farmacéutica se puede formular en un polvo, gránulo, tableta comprimida, pastilla, cápsula, chicle, oblea o una forma similar. Dicha composición sólida generalmente comprende uno o más diluyentes inertes o portadores comestibles. Además, uno o más de los siguientes pueden ser ligantes presentes tales como carboximetilcelulosa, etil celulosa, celulosa microcristalina, goma de tragacanto, o gelatina; excipientes tales como almidón, lactosa o dextrina, agentes de desintegración tales como ácido algínico, alginato de sodio, Primogel, almidón de maíz y similares; lubricantes

tales como estearato de magnesio o Stezotex; deslizantes tales como dióxido de silicio coloidal; agentes edulcorantes tales como sucrosa o sacarina; un agente saborizante tal como menta, salicilato de metilo o saborizante de naranja; y un agente colorante.

Cuando la composición farmacéutica está en la forma de una cápsula, por ejemplo, una cápsula de gelatina, puede contener además de los materiales del tipo precedente, un portador líquido tal como polietilenglicol o aceite.

La composición farmacéutica puede estar en la forma de un líquido, por ejemplo, un elixir, jarabe, solución, emulsión o suspensión. El líquido puede ser para administración oral o para administración mediante inyección, como dos ejemplos. Cuando se desea para la administración oral, la composición preferida contiene, además de los presentes compuestos, uno más de un agente edulcorante, conservante, colorante, y mejorador del sabor. En una composición que se desea que se administre por inyección, se puede incluir uno o más de los surfactantes, conservantes, agente de humedecimiento, agente de dispersión, agente de suspensión, tampón, estabilizador y agente isotónico.

Las composiciones farmacéuticas líquidas de la invención, ya sean solución, suspensión u otra forma similar, pueden incluir uno o más de los siguientes coadyuvantes: diluyentes estériles tales como agua para inyección, solución salina, preferentemente, solución salina fisiológica, solución de Ringer, cloruro de sodio isotónico, aceites fusionados tales como mono o diglicéridos sintéticos que pueden servir como el solvente o medio de suspensión, polietilenglicoles, glicerina, propilenglicol u otros solventes; agentes antibacterianostales como alcohol bencílico o metil parabeno; antioxidantes tales como ácido ascórbico o bisulfito de sodio; agentes quelantes tales como ácido etilendiaminotetraacético, tampones tales como acetatos, citratos o fosfatos y agentes para el ajuste de la tonicidad tales como cloruro de sodio o dextrosa. La preparación parenteral se puede encerrar en ampollas, jeringas descartables o frascos de varias dosis hechos de vidrio o plástico. La solución salina fisiológica es un coadyuvante preferido. Una composición farmacéutica inyectable es preferentemente estéril.

Una composición líquida de la invención destinada para la administración parenteral u oral debe contener una cantidad de la invención tal que se obtenga una dosificación adecuada. Generalmente, esta cantidad es por lo menos un 0,01% de un compuesto de la invención en la composición. Cunado se desea

para la administración oral, esta cantidad se puede variar y puede ser entre el 0,1 y el 70% del peso de la composición. Las composiciones farmacéuticas orales preferidas contienen entre el 4% y el 50% del compuesto de la invención. Las composiciones y preparaciones farmacéuticas preferidas de acuerdo con la presente invención se preparan de manera tal que una unidad de dosificación unitaria contenga entre el 0,01 y el 1% en peso del compuesto de la invención.

La composición farmacéutica de la invención puede estar destinada para la administración tópica, en cuyo caso el portador puede comprender adecuadamente una solución, emulsión, ungüento o base de gel. La base, por ejemplo, puede comprender uno o más de los siguientes: petrolato, lanolina, polietilenglicoles, cera de abejas, aceite mineral, diluyentes tales como agua y alcohol, y emulsionadores y estabilizadores. Pueden estar presentes agentes espesantes en la composición farmacéutica para la administración tópica. Si se desea para la administración transdérmica, la composición puede incluir un parche transdérmico o un dispositivo de iontoforesis. Las formulaciones tópicas pueden contener una concentración del compuesto de la invención del 0,1 al 10% p/v (peso por unidad de volumen).

La composición farmacéutica de la invención puede desearse para la administración rectal, en la forma,por ejemplo, de un supositorio, que se funde en el recto y libera el fármaco. Las composiciones para la administración rectal pueden contener una base oleaginosa como un excipiente no irritante adecuado, dicha base incluye, en forma no taxativa, lanolina, manteca de cacao y polietilenglicol.

La composición farmacéutica de la invención puede incluir diferentes materiales, que modifican la forma física de una unidad de dosificación sólida o líquida. Por ejemplo, la composición puede incluir materiales que forman una cápsula de recubrimiento alrededor de los ingredientes activos. Los materiales que forman la cápsula de recubrimiento son generalmente inertes, y se pueden seleccionar, por ejemplo, de azúcar, laca, y otros agentes de recubrimiento entéricos. Alternativamente, los ingredientes activos se pueden encerrar en una cápsula de gelatina.

La composición farmacéutica de la invención en forma sólida o líquida pueden incluir un agente que une al compuesto de la invención y así contribuye a la administración del compuesto. Los agentes adecuados que pueden actuar en este carácter incluyen un anticuerpo monoclonal o policlonal, una proteína o un liposoma.

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529

Las composiciones farmacétuicas de la invención pueden comprender unidades de dosificación que pueden administrarse como un aerosol. El término aerosol se usa para indicar una variedad de sistemas desde aquellos de carácter coloidal hasta sistemas que comprenden envases presurizados. La administración puede ser mediante un gas licuado o comprimido o mediante un sistema de bomba adecuado que distribuye los ingredientes activos. Los aerosoles de compuestos de la invención se pueden administrar en sistemas de una fase, bifásicos o trifásicos para administrar el ingrediente(s) activo. La administración del aerosol incluye el envase, los activadores las válvulas, los subenvases necesarios y similares, que juntos pueden formar un estuche. Un experto en el arte puede, sin experimentación indebida, determinar los aerosoles preferidos.

Las composiciones farmacéuticas de la invención se pueden preparar mediante la metodología conocida en el arte farmacéutica. Por ejemplo, una composición farmacéutica destinada para ser administrada mediante inyección puede prepararse combinando un compuesto de la invención con agua estéril, destilada de manera que forme una solución. Se puede agregar un surfactante para facilitar la formación de una solución o suspensión homogénea. Los surfactantes son compuestos que interactúan en forma no covalente con el

compuesto de la invención de manera tal que facilite la disolución o la suspensión homogénea del compuesto en el sistema de administración acuosa.

Los compuestos de la invención o sus dales farmacéuticamente aceptables, se administran en una cantidad farmacéuticamente eficaz, que varían según una variedad de factores que incluyen la actividad del compuesto específico empleada; la estabilidad metabólica y la duración de la acción del compuesto; la edad, el peso corporal, la salud general, el sexo y la dieta del paciente; la forma y la hora de administración; el uso de la excreción; la combinación de fármacos; la severidad del trastorno o la condición particular; y la terapia a la que se está sometiendo el paciente. Generalmente, una dosis diaria terapéuticamente eficaz es de 0,1 mg a 20 mg/kg de peso corporal por día de un compuesto de la invención, o una sal farmacéuticamente aceptable de él; preferentemente, de 0,1 mg a 10 mg/kg de peso corporal por día; y más preferentemente de 0,1 mg a 7,5 mg/kg de peso corporal por día.

Los compuestos de la invención, o los derivados farmacéuticamente aceptables de ellos, se pueden administrar simultáneamente, antes o después de la administración de uno o más agentes terapéuticos descritos anteriormente en la Utilidad de los Compuestos de la Invención. Dicha terapia de

combinación incluye la administración de una formulación de dosificación farmacéutica simple que contiene un compuesto de la invención y uno o más agentes activos adicionales, así como la administración del compuesto de la invención y cada agente activo en su propia formulación de dosificación farmacéutica por separado. Por ejemplo, un compuesto de la invención y un inhibidor de HMG-CoA reductasa se puede administrar al paciente juntos en una composición de dosificación oral simple tal como una tableta o cápsula, o cada agente se administra en formulaciones de dosificación orales por separado. Cuando se usan formulaciones de dosificación por separado, los compuestos de la invención y uno o más ingredientes activos adicionales se pueden administrar esencialmente al mismo tiempo, es decir en forma concurrente, o en horarios escalonados por separado, es decir secuencialmente; se entiende que la terapia de combinación incluye todos estos regímenes.

La información de la dosificación para los inhibidores de HMG-CoA reductasa es conocida en el arte, ya que varios inhibidores de HMG-CoA reductasa se comercializan en Estados Unidos. En particular, las cantidades de dosificación diarias del inhibidor de HMG-CoA reductasa pueden ser iguales o simialres a aquellas cantidades que se emplean para el tratamiento anti-hipercolesterolémico y que se describen en la

Physicians' Desk Reference (PDR). Por ejemplo, véase la 50th Ed. de la PDR, 1996 (Medical Economics Co); en particular, véase en la página 216 el título "Hypolipidemics", subtítulo "HMG-CoA Reductase Inhibitors", y las páginas de referencia citadas allí. Preferentemente, la cantidad de dosificación oral del inhibidor de HMG-CoA reductasa es de 1 a 200 mg/día y, más preferentemente de 5 a 160 mg/día. Sin embargo, las cantidades de dosificación varían según la potencia del inhibidor de HMG-CoA reductasa específico usado así como otros factores indicados anteriormente. Un inhibidor de HMG-CoA reductasa que tiene una potencia suficientemente mayor se puede administrar en dosificaciones diarias inferiores a 1 miligramo.

Como ejemplos, la cantidad de dosificación diaria para simvastatina se puede seleccionar de 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, y 160 mg; para luvastatina, 10 mg, 20 mg, 40 mg, y 80 mg; para sodio de fluvastatina, 20 mg, 40 mg y 80 mg; y para sodio de pravastatina, 10 mg, 20 mg y 40 mg. La cantidad de dosificación diaria para calcio de atorvastatina puede estar en la gama de 1 mg a 160 mg y más preferentemente de 5 mg a 80 mg. La administración oral puede ser en una sola dosis o en dosis divididas de dos, tres, o cuatro veces por día, aunque se prefiere una sola dosis diaria del inhibidor de HMG-CoA reductasa.

Preparación de los Compuestos de la invención

Se entiende que en la siguiente descripción, las combinaciones de sustituyentes y/o variables de las fórmulas ilustradas son adminisibles solamente si dichos aportes derivan en compuestos estables.

También apreciarán los expertos en el arte que en los procesos descritos a continuación los grupos funcionales de los compuestos intermedios pueden necesitar ser protegidos por grupos protectores adecuados. Dichos grupos funcionales incluyen hidroxi, amino, mercapto y ácido carboxílico. Los grupos protectores adecuados para hidroxi incluyen trialquilsililo o diarilalquilsililo (por ejemplo, t-butildimetilsililo, t-butildifenilsililo o trimetilsililo), tetrahidropiranilo, bencilo, y similares. Los grupos protectores adecuados para 1,2-dihidroxis incluyen grupos que forman cetales y acetales. Los grupos protectores adecuados para amino, amidino y guanidino incluyen t-butoxicarbonilo, benciloxicarbonilo y similares. Los grupos protectores adecuados para mercapto incluyen -C(O)-R (cuando R es alquilo, arilo o aralquilo), p-metoxibencilo, tritilo y similares. Los grupos protectores adecuados para el ácido carboxílico incluyen alquilo, arilo, o ésteres de aralquilo.

Los grupos protectores se pueden agregar o remover de acuerdo con técnicas comunes, que son conocidas para los expertos en el arte y descritos en la presente. El uso de grupos protectores se describe detalladamente en Green, T.W. y P.G.M. Wutz, Protective Groups in Organic Synthesis (1991), 2nd Ed., Wiley-Interscience. El grupo protector también puede ser una resina también puede ser una resina polimérica tal como una resina de Wang o una resina de cloruro de 2-clorotritilo.

También apreciarán los expertos en el arte que, aunque dichos derivados protegidos de compuestos de la invención, descritos anteriormente en el primer aspecto de la invención pueden no poseer actividad farmacéutica como tales, se pueden administrar a un mamífero que tiene una enfermedad asociada con defectos en el trasporte del colesterol, el metabolismo de la glucosa, el metabolismo de los ácidos grasos y el metabolismo del colesterol, y luego metabolizarse en el cuerpo para formar compuestos de la invención que son farmacológicamente activos. Dichos derivados pueden en consecuencia describirse coo "profármacos". Todos los profármacos de los compuestos de esta invención están incluidos dentro del alcance de la invención.

Se entiende que un experto en el arte podría elaborar los compuestos de la invención preparados en forma no específica

en la presente a la luz de la siguiente invención, que incluye las Preparaciones y Ejemplos, e información conocida para los expertos en el arte del campo de la síntesis química.

Los materiales iniciales en los ejemplos de síntesis dados en la presnte están disponibles de fuentes comerciales o a través de procedimientos de la bibliografía o mediante los métodos revelados en la presente. Todos los compuestos comercialmente disponibles se usaron sin nueva purificación a menos que se indique de otro modo. Los solventes deuterados tales como DMSO o $CDCl_3$ (99,8% D, Cambridge Isotope Laboratories) se usaron en todos los experimentos indicados. Los espectros de ^1H NMR se registraron en un espectrómetro de NMR de 400 Hz Bruker Avance. Los pios importantes se tabulan y generalmente incluyen el número de protones, la multiplicidad (s, singulete, d, doblete, t, triplete, q cuarteto, m, multiplete, brs singulete ancho) y la constante(s) de acoplamiento en Hertz. Los desplazamientos químicos se informan como partes por millón (δ) en relación con tetrametilsilano. Los espectros de masa se registraron en un instrumento de HPLC/MS SCIEX Perkin-Elmer usando condiciones de fase invertida (acetonitrilo/agua, 0,05% ácido trifluoroacético) y ionización de electrospray (ES). Las abreviaturas usadas en los siguientes ejemplos tienen sus definiciones aceptadas en la bibliografía química. Por ejemplo, CH_2Cl_2 (diclorometano), C_6H_6

(benceno), TFA (ácido trifluoroacético), EtOAc (Acetato de etilo), Et_2O (éter dietílico), DMAP (4-dimetilaminopiridina), DMF (N,N-dimetilformamida), y THF (tetrahidrofurano). Se realizó la cromatografía rápida usando Merck Silica Gel 60 (230-400 mesh).

Con fines ilustrativos exclusivamente, la mayor parte de los siguientes Esquemas de Reacción se refieren a realizaciones específicas de los compuestos de la invención. Sin embargo, un experto en el arte, en vista de las enseñanzas de esta memoria descriptiva se esperaría razonablemente que pueda preparar todos los compuestos de la invención en el primer aspecto de la invención utilizando los materiales iniciales y métodos sustituidos apropiadamente conocidos para los expertos en el arte.

En las descripciones generales que siguen a cada Esquema de Reacción, la frase "procedimientos de aislamiento comunes" incluye una o más de las siguientes técnicas familiares para un experto en el arte de la química orgánica: extracción orgánica, lavado de soluciones orgánicas con ácido o base acuosa diluida, uso de agentes de secado, filtración, concentración en vacío, seguida por la purificación usando destilación, cristalización, o cromatografía de fase sólida-líquida. La frase "temperatura elevada" se refiere a una

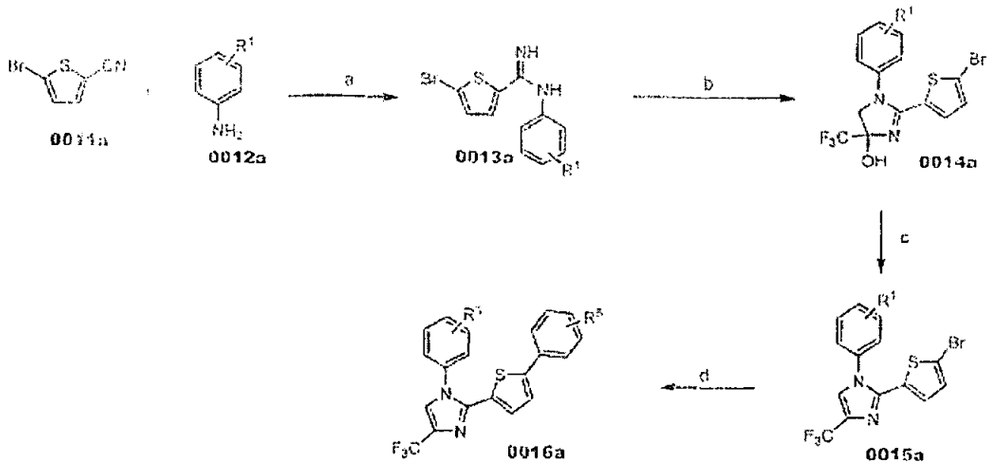
temperatura superior a la temperatura ambiente y la frase "temperatura reducida" se refiere a una temperatura inferior a la temperatura ambiente.

Las siguientes Preparaciones específicas (para intermedios) y Ejemplos (para compuestos, composiciones farmacéuticas y métodos de uso de la invención) se dan como una guía para contribuir a la práctica de la invención, y no limitan el alcnce de la invención. Sin hacer otra descripción, se cree qeu un experto en el arte, usando la descripción precedente y los siguientes ejemplos ilustrativos, podrá elaborar y utilizar los compuestos de la presente invención y practicar los métodos reivindicados. Se debe entender que el análisis precedente y los ejemplos solamente presentan una descripción detallada de ciertas realizaciones preferidas. Será evidente para un experto en el arte que se pueden hacer diferentes modificaciones y equivalentes sin apartarse del espíritu y alcance de la invención.

A menos que se indique de otro modo, todos los compuestos asociados con datos de espectros de NMR y/o de masa se prepararon y los espectros de NMR y de masa se midieron.

540
538

Esquema 1



Reacción y Condiciones: (a) NaHMDS, THF, 0°C-temperatura ambiente; (b) 3-bromo-1,1,1-trifluoroacetona, $NaHCO_3$, 2-PrOH, 80°C; (c) TSA, tolueno, reflujo; (d) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

En general, los compuestos de la fórmula (0016a) se preparan primero haciendo reaccionar una anilina de la fórmula (0012a) con aril nitrilos (0011a), tales como 5-bromo-tiofeno-2-carbonitrilo, en la presencia de una base para dar compuestos de la fórmula (0013a) después de procedimientos de aislamiento comunes. En un paso posterior, la exposición de la amidina (0013a) a una halocetona, tal como 1-bromo-3,3,3-trifluoroacetona, en condiciones básicas a temperatura elevada proporciona 1H-imidazol-4-ol de la fórmula (0014a) después de procedimientos de aislamiento comunes. La conversión de

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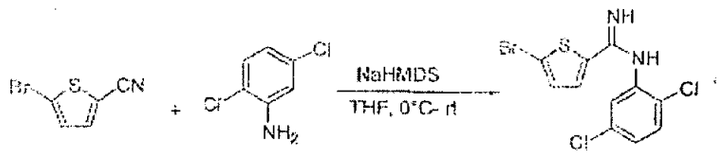
compuetos de la fórmula (0014a) en compuestos de la fórmula (0015a) luego se realiza tratando los compuestos de la fórmula (0014a) con un catalizador ácido tal como ácido p-toluenosulfónico a reflujo. En una reacción de acoplamiento mediada por paladio, por ejemplo, una reacción de Suzuki, los compuestos de la fórmula (0015a) luego reaccionan con un reactivo de boronato o ácido borónico y dan compuestos de la fórmula (0016a) después de procedimientos de aislamiento comunes).

Ejemplo 1

1-(2,5-dicloro-fenil)-2-[5-(3-metanosulfonil-fenil)-tiofen-2-il]-4-trifluorometil-1H-imidazol

Ejemplo 1a

Preparación de 5-Bromo-N-(2,5-dicloro-fenil)-tiofeno-2-carboxamidina



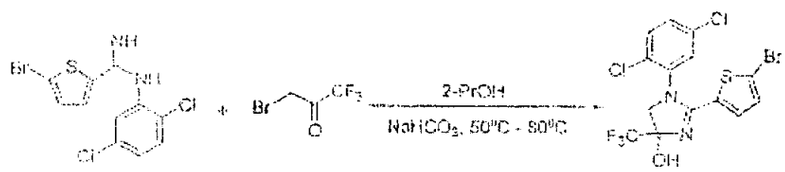
Bajo una atmósfera de N_2, en una solución de 2,5-dicloroanilina (341 mg, 2,1 mmol) en 2 ml de THF seco se agregó bis(trimetilsilil)amida de sodio (2,1 ml, 1M solución en THF 2,1 mmol). Después de agitar la mezcla a temperatura ambiente durante 40 minutos, una solución de 5-bromo-tiofeno-2-

542

carbonitrilo (376 mg, 2 mmol) en 2 ml de THF seco se agregó gota a gota. La mezcla de la reacción se agitó toda la noche, y luego se vertió en 100 ml de agua helada. El precipitado naranja se recogió mediante filtración, se lavó con una solución de éter y hexano (3/7, v/v), y se secó con aire y dio un sólido naranja claro (653 mg, 94% de rendimiento). ^{1}H-NMR (400 MHz, MeOH-d_4): δ 6,94 (d, 1H), 6,99 (dd, 1H), 7,06 (d, 1H), 7,32 (d, 1H), 7,37 (d, 1H).

Ejemplo 1b

Preparación de 2-(5-bromo-tiofen-2-il)-1-(2,5-dicloro-fenil)-4-trifluorometil-4,5-dihidro-1H-imidazol-4-ol



A una suspensión de 5-bromo-N-(2,5-dicloro-fenil)-tiofeno-2-carboxaidina (634 mg, 1,8 mmol) y bicarbonato de sodio (227 g, 2,7 mmol) en 8 ml de 2-propanol se agregó 3-bromo-1,1,1-trifluoroacetona (520 mg, 2,7 mmol). La mezcla de la reacción se calentó a 50°C durante 1,5 horas, luego a 80°C durante 4 horas. Después de enfriar a temperatura ambiente, el residuo se filtró y se lavó con diclorometano. El filtrado y los lavados se combinaron juntos y se concentraron bajo vacío para dar un sólido rosa claro que se usó directamente en el paso

siguiente (820 mg, 99% de rendimiento). ^{1}H-NMR (400 MHz, DMSO-d_4): δ 3,09 (d, 1H), 3,95 (dd, 1H), 6,31 (d, 1H), 6,91 (d, 1H), 7,15 (m, 1H), 7,33 (dd, 1H), 7,44 (m, 2H).

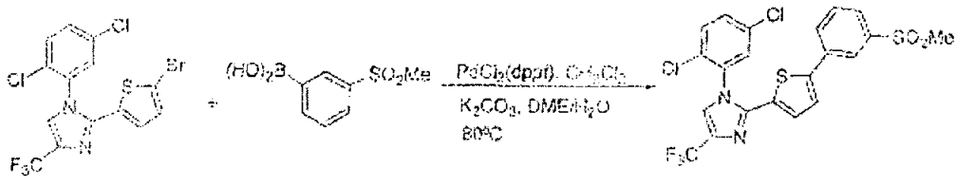
Ejemplo 1c

Preparación de 2-(5-bromo-tiofen-2-il)-1-(2,5-dicloro-fenil)-4-trifluorometil-1H-imidazol

La mezcla de 2-(5-bromo-tiofen-2-il)-1-(2,5-dicloro-fenil)-4-trifluorometil-4,5-dihidro-1H-imidazol-4-ol (822 mg, 1,8 mmol) y ácido p-toluenosulfónico monohidratado (172 mg, 0,9 mmol) en 10 ml de tolueno se calentó a 120°C durante 6 horas. El solvente se removió, y el residuo se redisolvió en diclorometano, luego se lavó con $NaHCO_3$ saturado y solución salina, se secó sobre Na_2SO_4 y se concentró en vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice (hexano/EtOAc 85/15) y dio un sólido blancuzco (512 mg, 64% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6,68 (d, 1H), 6,89 (d, 1H), 7,31 (dd, 1H), 7,47 (dd, 1H), 7,55 (d, 1H), 7,56 (s, 1H).

Ejemplo 1d

Preparación de 1-(2,5-Dicloro-fenil)-2-[5-(3-metanosulfonil-fenil)-tiofen-2-il]-4-trifluorometil-1H-imidazol



2-(5-Bromo-tiofen-2-il)-1-(2,5-dicloro-fenil)-4-trifluorometil-1H-imidazol (90 mg, 0,2 mmol), ácido 3-metilsulfonil)fenilborónico (60 mg, 0,3 mmol), carbonato de potasio (110 mg, 0,8 mmol) y $PdCl_2(dppf).CH_2Cl_2$ (16 mg, 0,02 mmol) se mezclaron con 2 ml de 9:1 DME/H_2O (v/v), luego se calentaron a 80°C toda la noche. Todo el solvente se removió en vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc, 6/4) y dio un sólido blanco (76 mg, 74% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3,08 (s, 3H), 6,79 (d, 1H), 7,22 (d, 1H), 7,36 (d, 1H), 7,52 (d, 1H), 7,58 (m, 3H), 7,78 (m, 1H), 7,86 (m, 1H), 8,00 (d, 1H).

Todos los siguientes compuestos se prepararon en forma similar a la descrita en el Esquema 1 y se midieron los espectros de NMR y de masa. Los reactivos de ácido borónico o boronato par el acoplamiento de Suzuki, si no están comercialmente disponibles, se prepararon usando técnicas comunes que son fácilmente evidentes para un experto en el arte.

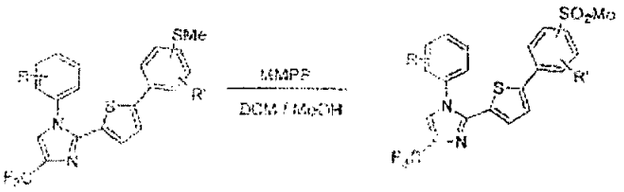
543

- 1-(2,5-diclorofenil)-2-{5-[3-(metilsulfonil)fenil]-2-tienil}-4-(trifluorometil)-1H-imidazol; MS (ES): 517,3 $[M+H]^+$;
- 5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-3-metil-2-(metiltio)piridina; MS (ES): 500,4 $[M+H]^+$;
- 5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-2-(etiltio)-3-metilpiridina; MS (ES): 514,2 $[M+H]^+$;
- 4-(5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-piridin-2-il)morfolina; MS (ES): 525,4; 527,3 $[M+H]^+$;
- 1,1-dimetiletil 4-(5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}pirdin-2-il)piperazin-1-carboxilato; MS (ES): 624,5; 626,3 $[M+H]^+$;
- 1-(2-clorofenil)-2-{5-[3-(metilsulfonil)fenil]-2-tienil}-4-(trifluorometil)-1H-imidazol; MS (ES): 483,2 $[M+H]^+$;

548

- 5-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-3-metil-2-(metiltio)pirdina; MS (ES): 466,2 $[M+H]^+$;
- 5-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-2-(etiltio)-3-metilpiridina; MS (ES): 514,2 $[M+H]^+$;
- Metil (4-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-3-metilfenil)acetato; MS (ES): 491,2 $[M+H]^+$;
- 3-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}bencensulfonamida; MS (ES): 484,0 $[M+H]^+$;
- 4-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}bencensulfonamida; MS (ES): 484,1 $[M+H]^+$;

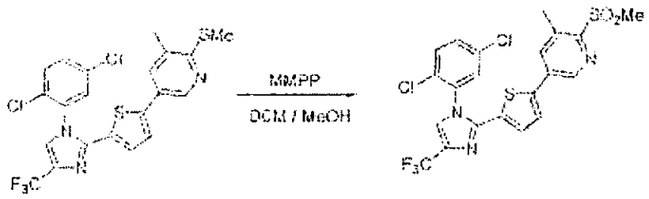
Esquema 2



Los materiales iniciales se prepararon en forma similar al Esquema 1, seguido por nuevas transformaciones para elaborar los productos finales descritos en el Esquema 2.

Ejemplo 2

Preparación de 5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-2-(metilsulfonil)-3-metilpiridina



5-{5-[1-(2,5-dicloro-fenil)-4-trifluorometil-1H-imidazol-2-il}-3-metil-2-metilsulfanil-piridina (80 mg, 0,16 mmol) se disolvió en 8 ml de mezcla de diclorometano y metanol (5:1, V/V). Luego se agregó MMPP (monoperoxiftalato de magnesio hexahidratado, 200 mg, 0,35 mmol, 80% tec.). La mezcla se agitó a temperatura ambiente durante 2 horas, luego se diluyó con diclorometano y se filtró. El filtrado se lavó con $NaHCO_3$ saturado y solución salina, se secó sobre Na_2SO_4 y se concentró en vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (15→60% EtOAc/Hexano) para dar un sólido blanco (52 mg, 61% de redndimiento). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2,61 (s, 3H), 3,37 (s, 3H), 6,58 (d,J= 4,0, 1H), 7,63 (d, J=4,0, 1H), 7,86-7,79 (m, 2H), 8,20-8,17 (m, 2H), 8,31-8,30 (m, 1H), 8,80 (m, 1H). MS (ES): 532,2, 536,2 $[M+H]^+$.

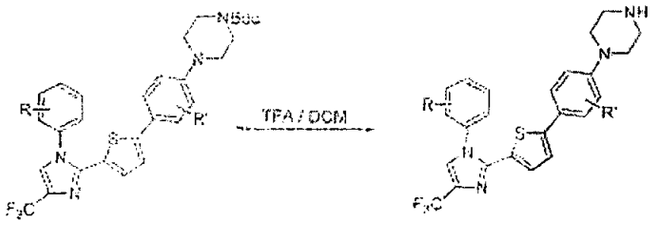
Los compuestos se prepararon en forma similar mediante oxidación de sulfuros apropiados.

- 5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il)-2-tienil}-

2-(etilsulfonil)-3-metilpiridina; MS (ES): 546,2 $[M+H]^+$;

- 5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-3-metil-2-(metilsulfonil)piridina; MS (ES): 532,2 $[M+H]^+$;
- 5-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-3-metil-2-(metilsulfonil)piridina; MS (ES): 498,4 $[M+H]^+$;
- 5-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-2-(etilsulfonil)-3-metilpiridina; MS (ES): 512,2 $[M+H]^+$;

Esquema 3

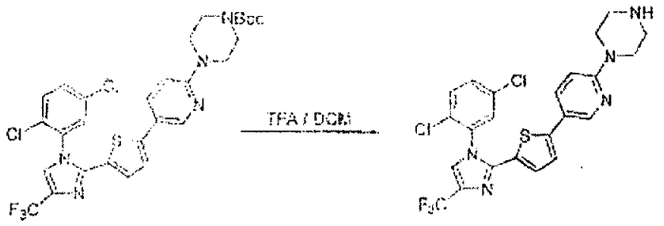


Los materiales iniciales se prepararon en forma similar al Esquema 1, seguido por otras transformaciones para preparar los productos finales descritos en el Esquema 3.

549

Ejemplo 3

1-(5-{5-[5-1-(2,5-dicloro-fenil)-4-trifluorometil-1H-imidazol-2-il]-tiofen-2-il)-piridin-2-il)-piperazina



El éster de terc-butilo del ácido 4-(5-{5-[1-(2,5-dicloro-fenil)-4-trifluorometil-1H-imidazol-2-il]-tiofen-2-il}-piridin-2-il)-piperazina-1-carboxílico (104 mg, 0,17 mmol) se mezcló con 4 ml de 50% de ácido trifluorometilacético en diclorometano, y se agitó a temperatura ambiente durante 2 horas. Todo el solvente se removió; el residuo se redisolvió en diclorometano y se neutralizó a pH 7 con $NaHCO_3$. La capa orgánica se lavó con solución salina, se secó sobre Na_2SO_4 y se concentró en vacío. El residuo se precipitó desde una mezcla de diclorometano/Hexano, luego se filtró y se lavó varias veces con diclorometano y dio un sólido amarillo (50 mg, 57% de rendimiento). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3,30-2,97 (m, 4H), 3,57-3,45 (m, 4H), 6,63 (d, J= 8,7, 1H), 6,78 (d, J=4,0, 1H), 7,31 (s, 1H), 7,60-7,50 (m, 4H), 8,37 (m, 1H). MS (ES): 524,3, 526,5 $[M+H]^+$.

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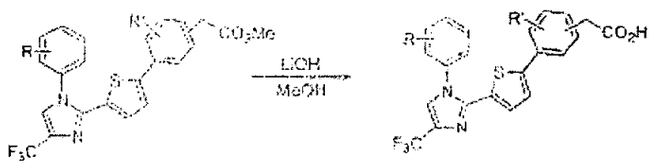
548

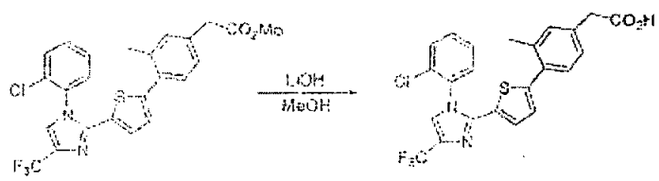
Esquema 4



Los materiales iniciales se prepararon en forma similar al Esquema 1, seguido por otras transformaciones para preparar los productos finales descritos en el Esquema 4.

Ejemplo 4

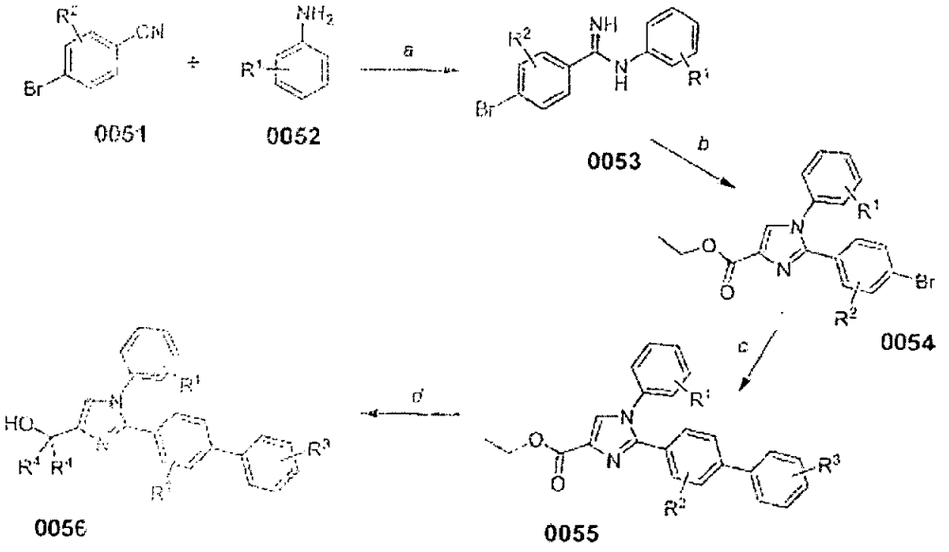
Ácido (4-{5-[5-(2-Cloro-fenil)-4-trifluorometil-1H-imidazol-2-il]-tiofen-2-il}-3-metil-fenil)-acético



Éster de metilo del ácido (4-{5-[5-(2-Cloro-fenil)-4-trifluorometil-1H-imidazol-2-il]-tiofen-2-il}-3-metil-fenil)-acético (123 mg, 0,25 mmol) se disolvió en 6 ml de una mezcla de THF y agua (3:1 V/V). Luego se agregó hidróxido de litio monohidratado (2,3 mg, 0,55 mmol). La mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla se neutralizó a pH 7 con 1N HCl y luego se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron en vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel

de sílice (0→5% MeOH/DCM) y dio un sólido blanco (47 mg, 39% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2,35 (s, 3H), 3,64 (s, 2H), 6,83 (s, 2H), 7,13-7,10 (m, 1H), 7,16 (m, 1H), 7,29-7,27 (m, 1H), 7,35 (m, 1H), 7,47-7,46 (m, 2H), 7,57-7,52 (m, 1H), 7,64-7,62 (m, 1H). MS (ES): 477,1 $[M+H]^+$.

Esquema 5



(a) Me_3Al, PhMe, 9°C; (b) etil bromopiruvato, $NaHCO_3$, 2-PrOH, 95°C; (c) $ArB(OH)_2$, $Cl_2Pd(dppf)$, K_2CO_3, H_2O/DME, 80°C; (d) R^4MgBr, THF, 0°C.

En general, los compuestos de la fórmula (0056) se pueden preparar como se ilustra en el Esquema 5. Un arilnitrilo (0051) y una arilamina (0052) pueden reaccionar en la

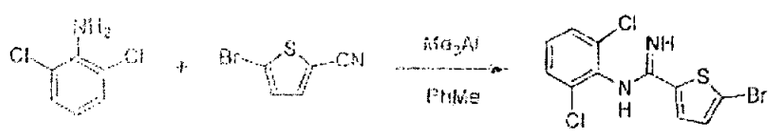
presencia de un ácido de Lewis, tal como trimetilamonio, para dar la amidina correspondiente (0053). También se pueden utilizar heteroarilnitrilos 0051 y/o heteroarilaminas 0052 para la síntesis de sus amidinas respectivas 0053. El intermedio 0053 luego puede reaccionar con etil bromopiruvato en la presencia de una base débil, tal como bicarbonato de sodio, seguido por la deshidratación a temperatura elevada para dar el imidazol correspondiente (0054). Este intermedio 0054 puede pasar por reacciones de acoplamiento cruzado, por ejemplo con un ácido arilborónico en condiciones de Suzuki típicas, para dar el 2-biaril-imidazol correspondiente (0055). El compuesto 0055 reacciona con un reactivo de Grignard, tal como un bromuro de alquilmagnesio para dar el producto 0056 deseado.

Ejemplo 5

2-{1-(2,6-diclorofenil)-2-[5-(3-metanosulfonil)-tiofen-2-il]-1H-imidazol-4-il}-propan-2-ol

Ejemplo 5a

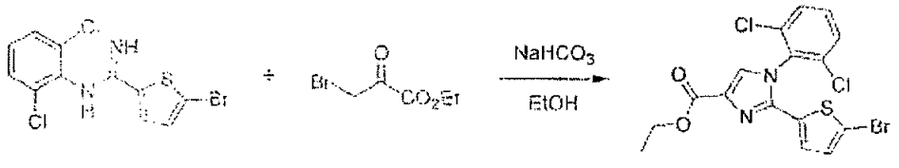
Preparación de 5-bromo-N-(2,6-diclorofenil)-tiofeno-2-carboxamidina



A una solución agitada de 2,6-dicloroanilina (1,75 g, 10,8 mmol) en tolueno (25 ml, anhidro) se agregó gota a gota una solución 2,0 M de trimetilaluminio en tolueno (8,0 mL, 16 mmol). Después de 90 minutos la mezcla de la reacción se cargó con una solución de 5-bromotiofeno-2-carbonitrilo (3,00 g, 16 mmol) en tolueno (20 ml, anhidro) y luego se calentó a 90°C. Después de 5 horas la mezcla de la reacción se dejó enfriar a temperatura ambiente y se enfrió agregando un suspensión agitada de sílice (25 g) en 3:1 $CHCl_3$/MeOH (100 ml). Después de 30 minutos la mezcla resultante se filtró y los sólidos se enjuagaron con MeOH y DCM. Los filtrados combinados se concentraron y dieron el compuesto del título (3,9 g, cuantitativo) como un sólido amarillo pálido, que se usó en el paso siguiente sin purificación. GC-MS(EI): 348, 350, 352.

Ejemplo 5b

Preparación de éster de etilo del ácido 2-(5-bromotiofen-2-il)-1-(2,6-diclorofenil)-1H-imidazol-4-carboxílico

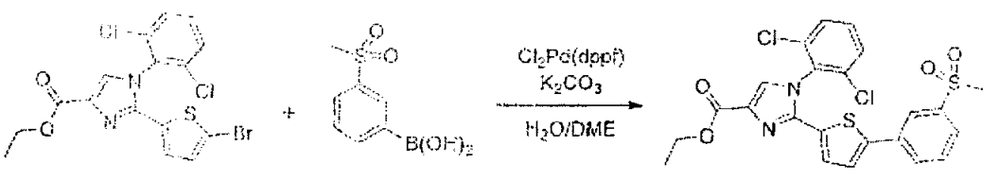


Una mezcla agitada de 5-bromo-N-(2,6-diclorofenil)-tiofeno-3-carboxamidina (3,9 g, 11 mmol) y bicarbonato de sodio (1,85 g, 22 mmol) en isopropanol (55 ml) se cargó con bromopiruvato de

etilo (2,5 ml, 20 mmol) y luego se calentó a 55°C. Después de 17 horas la mezcla de la reacción se dejó enfriar a temperatura ambiente, se filtró y los sólidos se enjuagaron con EtOAc. Los filtrados combinados se concentraron bajo presión reducida y se purificaron mediante cromatografía (sílice, EtOAc/Hexanos, 15:85 a 65:35) y dio el compuesto del título (3,3 g, 67%) como un sólido amarillo pegajoso, que se usó en el paso siguiente sin nueva purificación. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,60 (s, 1H), 7,49-7,59 (m, 3H), 6,89 (d, 1H), 6,56 (d, 1H), 4,37 (q, 2H), 1,38 (t, 3H).

Ejemplo 5c

Preparación de Éster de etilo del ácido 1-(2,6-diclorofenil)-2-[5-(3-metanosulfonil-fenil)-tiofen-2-il]-1H-imidazol-4-carboxílico



Una mezcla de éster de etilo del ácido 2-(5-bromotiofen-2-il)-1-(2,6-diclorofenil)-1H-imidazol-4-carboxílico (335 mg, 0,75 mmol), ácido 3-metanosulfonil-fenilborónico ((180 mg, 0,90 mmol), K_2CO_3 (0,32 g, 2,3 mmol), $Cl_2Pd(dppf)\cdot DCM$ (30 mg, 5% en moles) y H_2O (0,4 ml) en DME (4 ml) se roció con Argón durante 5 minutos y luego se calentó a 80°C cmo un matraz sellado.

Después de 2 horsa la mezcla de la reacción se dejó enfriar a temperatura ambiente, se filtró (Celite®) y el agente de filtro se enjuagó con EtOAc. Los filtrados combinados se concentraron bajo presión reducida y se purificaron mediante cromatografía (silice, EtOAc/Hexano, 30:70 a 80:20) y dio el compuesto del título (313 mg, 80%) como un sólido amarillo pálido, que se usó en el paso siguiente sin nueva purificación. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,08 (m, 1H), 7,82 (m, 2H), 7,64 (s, 1H), 7,51-7,62 (m, 4H), 7,24 (d, 1H), 6,72 (d, 1H), 4,38 (q, 2H), 3,05 (s, 3H), 1,40 (t, 3H).

Ejemplo 5d

Preparación de 2-{1-(2,6-diclorofenil)-2-[5-(3-metanosulfonil-fenil)-tiofen-2-il]-1H-imidazol-4-il}-propan-2-ol

A una solución agitada de éster de etilo del ácido 1-(2,6-diclorofenil)-2-[5-(3-metanosulfonil-fenil)-tiofen-2-il]-1H-imidazol-4-carboxílico (300 mg, 0,58 mmol) en THF (3 ml) a 0°C se agregó una solución 3,0M de bromuro de metilmagnesio en Et_2O (0,80 ml, 2,4 mmol). Después de que terminó el agregado el matraz se retiró del baño de agua helada y se dejó enfriar a temperatura ambiente. A los 40 minutos la mezcla de la

reacción se enfrió agregando NH_4Cl saturado, se extrajo con EtOAc, se secó (Na_2SO_4), se concentró y se purificó mediante cromatografía (silice, EtOAc/Hexano, 40:60 a 90:10 y dio el compuesto del título (0,17 g, 59%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,07 (m, 1H), 7,81 (m, 2H), 7,46-7,60 (m, 4H), 7,21 (d, 1H), 6,85 (s, 1H), 6,62 (d, 1H), 3,05 (s, 3H), 2,68 (br s, 1H), 1,61 (s, 6H); MS(ES): 507, 509 $[M+H]^+$.

En forma similar, los siguientes imidazoles se prepararon a partir de reactivos apropiados. Optativamente el orden del acoplamiento cruzado de Suzuki y el agregado del reactivo de Grignard se cambia.

- 2-{1-(2,6-diclorofenil)-2-(5-(3-(etilsulfonil)fenil)tiofen-2-il)-1H-imidazol-4-il}-propan-2-ol; MS(ES): 521, 523 $[M+H]^+$
- 2-{1-(2,6-diclorofenil)-2-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$
- 2-{1-(2,6-diclorofenil)-2-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529, 531 $[M+H]^+$

557
558

- 2-(1-(2-isopropil-6metilfenil)-2-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 503 $[M+H]^+$
- 2-(2-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1-(2-isopropil-6-metilfenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 517 $[M+H]^+$
- 2-(1-(2-isopropilfenil)-2-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 489 $[M+H]^+$
- 2-(2-(3'-(etilsulfonil)bifenil-4-il)-1-(2-isopropilfenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 503 $[M+H]^+$
- 2-(1-(2,6-diclorofenil)-2-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 501, 503 $[M+H]^+$
- 2-(1-(2,6-diclorofenil)-2-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$
- 2-(2-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-1-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 535, 537 $[M+H]^+$
- 2-(2-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-1-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 551 $[M+H]^+$

Ejemplo 6

2-[5-Cloro-2-(3-cloro-3'-metanosulfonil-bifenil-4-il)-1-(2,6-diclorofenil)-1H-imidazol-4-il]-propan-2-ol

Ejemplo 6a

Preparación de 2-[2-(4-bromo-2-clorofenil)-1-(2,6-diclorofenil)-1H-imidazol-4-il]-propan-2-ol

A una solución 3,0M de MeMgBr en Et_2O (7,0 ml, 21,0 mmol) a 0°C se agregó lentamente una solución de éster de etilo del ácido 2-(4-bromo-2-clorofenil)-1-(2,6-diclorofenil)-1H-imidazol-4-carboxílico (2,80 g, 5,90 mmol) en THF (30 ml, anhidro). Después de que terminó el agregado el matraz se retiró del baño de agua helada y se dejó calentar a temperatura ambiente. A los 50 minutos la mezcla de la reacción se enfrió agregando NH_4Cl saturado, se extrajo con EtOAc, se secó (Na_2SO_4), se concentró y se purificó mediante cromatografía (sílice, EtOAc/Hexanos, 15:85 a 55:45) y dio el compuesto del título (21, g, 77%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,58 (d, 1H), 7,37-7.41 (m, 3H), 7,26-7,32 (m, 2H), 7,11 (d, 1H), 6,93 (s, 1H), 2,73 (br s, 1H), 1,61 (s, 6H).

559

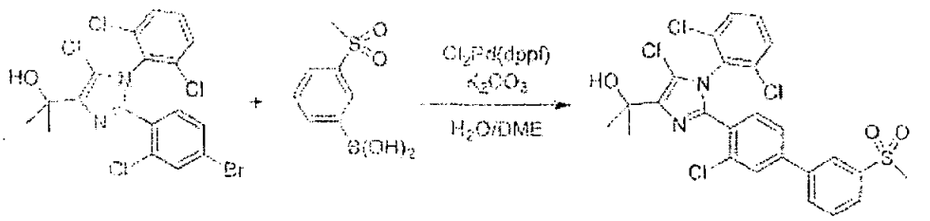
Ejemplo 6b

Preparación de 2-[2-(4-bromo-2-clorofenil)-5-cloro-1-(2,6-diclorofenil)-1H-imidazol-4-il]-propan-2-ol

Una suspensión de 2-[2-(4-bromo-2-clorofenil)-1-(2,6-diclorofenil)-1H-imidazol-4-il]-propan-2-ol (230 mg, 0,50 mmol) en MeCN (4 ml, anhidro) se cargó con N-clorosuccinimida (70 mg, 0,52 mg) y luego se calentó a 70°C. Después de 22 horas la mezcla de la reacción se cargó con N-clorosuccinimida (67 mg, 0,50 mmol) y se calentó a 85°C. Después de 40 horas (tiempo total de la reacción) la mezcla de la reacción se dejó enfriar a temperatura ambiente, se concentró y se purificó mediante cromatografía (sílice, EtOAc/Hexano, 0:100 a 30:70) y dio el compuesto del título (0,19 g, 77%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,61 (d, 1H), 7,42-7,45 (m, 2H), 7,36 (m, 1H), 7,27 (dd, 1H), 7,00 (s, 1H), 3,33 (s, 1H), 1,65 (s, 6H).

Ejemplo 6c

Preparación de 2-[5-cloro-2-(3-cloro-3'-metanosulfonil-bifenil-4-il)-1-(2,6-diclorofenil)-1H-imidazol-4-il]-propan-2-ol



Una mezcla de 2-[2-(4-bromo-2-clorofenil)-5-cloro-1-(2,6-diclorofenil)-1H-imidazol-4-il]-propan-2-ol (184 mg, 0,37 mmol), ácido 3-metanosulfonil-fenilborónico (90 mg, 0,45 mmol), K_2CO_3 (0,15 g, 1,1 mmol), $Cl_2Pd(dppf)\cdot DCM$ (15 mg, 5% en moles) y H_2O (0,2 ml) en DME (2 ml) se roció con Argón durante 5 minutos y luego se calentó a 60°C como un matraz sellado. Después de 70 minutos, la mezcla de la reacción se dejó enfriar a temperatura ambiente, se filtró (Celite®) y el agente de filtro se enjuagó con EtOAc. Los filtrados combinados se concentraron bajo presión reducida y se purificó mediante cromatografía (sílica, EtOAc/Hexanos, 20:80 a 60:40) y dio el compuesto del título (165 mg, 78%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,08 (m, 1H), 7,93 (m, 1H), 7,84 (m, 1H), 7,73 (d, 1H), 7,67 (m, 1H), 7,33-7,47 (m, 5H), 3,42 (br s, 1H), 3,06 (s, 3H), 1,68 (s, 6H); MS(ES): 591, 593, 595 $[M+Na]^+$.

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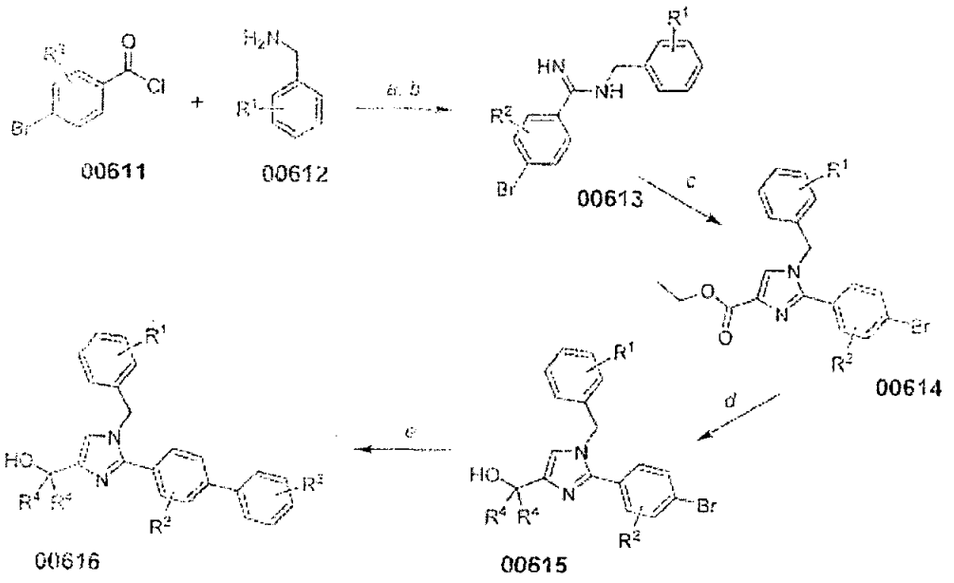
Esquema 6



(a) Et_3N, THF; (b) $SOCl_3$, 90°C; concentrar y agregar a $NF_3/MeOH$, (c) etil bromopiruvato, $NaHCO_3$, EtOH, μW 175°C, (d) R^4MgBr, THF, 0°C-temperatura ambiente; (e) $ArB(OH)_2$, $Cl_2Pd(dppf)$, K_2CO_3, H_2O/DME, μW, 120°C.

En general, los compuestos de la fórmula 00616 se pueden preparar como se muestra en el Esquema 6. En primer lugar, una amida se puede generar a partir de la reacción de un cloruro de benzoilo (00611) y una bencilamina (00612) en condiciones básicas. La amida resultante se puede tratar con cloruro de tionilo a temperatura elevada y da un cloruro de imidoilo, que se puede convertir directamente en su amidina correspondiente (00613) al agregarla a una solución de amoníaco. La amidina

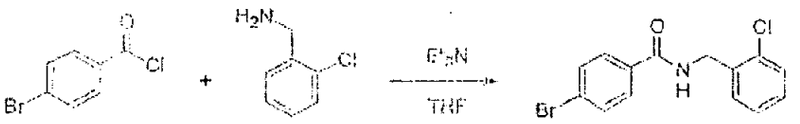
00613 y el etil bromopiruvato pueden reaccionar en condiciones básicas y a temperatura elevada y dan el imidazol correspondiente (00614). Este intermedio éster 00614 puede reaccionar con un reactivo de Grignard, tal coo un bromuro de alquilmagnesio, para dar el carbinol respectivo (00615). El último intermedio 00615 puede pasar por reacciones de acoplamiento cruzado, tales como una reacción de Suzuki-Miyaura con ácidos borónicos (ésteres), para dar el imidazol deseado 00616.

Ejemplo 7

2-[1-(2-clorobencil)-2-(3'metanosulfonil-bifenil-4-il)-1H-imidazol-4-il)-propan-4-ol

Ejemplo 7a

Preparación de 4-bromo-N-(2-clorobencil)-benzamida



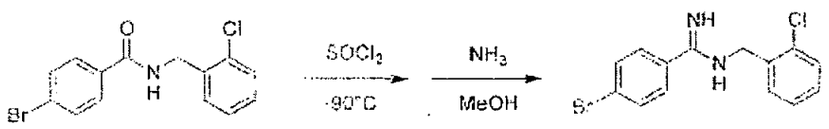
A una solución agitada de 2-clorobencilamina (2,42 ml, 20 mmol) en THF (80 ml, anhidro) a 0°C se agregó una solución de cloruro de 4-bromobenzoilo (4,39 g, 20 mmol) en THF (20 ml, anhidro) y luego trietilamina (2,93 ml, 21 mmol). Después de 12 horas la mezcla resultante se filtró y los sólidos se enjuagaron con EtOAc. Los filtrados combinados se diluyeron

563

con EtOAc (100 ml), se lavaron con 1N HCl y $NaHCO_3$ y solución salina, luego se secaron (Na_2SO_4 anhidro) y se concentraron para dar el compuesto del título (6,36 g, 98%) como un sólido blanco, que se usó en el paso siguiente sin purificación. GC-MS(EI): 322, 324.

Ejemplo 7b

Preparación de 4-bromo-N-(2-clorobencil)-benzamidina

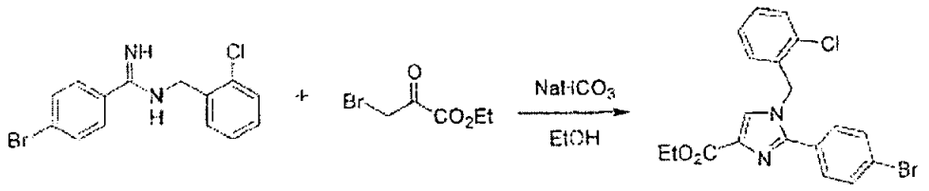


Una mezcla de 6-bromo-N-(2-clorobencil)-benzamida (1,62 g, 5,0 mmol) y cloruro de tionilo (0,73 ml, 10 mmol) se calentó a 90°C. Después de 150 minutos la mezcla de la reacción se enfrió y se concentró bajo presión reducida. El residuo se diluyó con tolueno (10 ml, anhidro) y se concentró para dar el cloruro de imidoílo correspondiente [conversión confirmada mediante NMR] como un sólido amarillo pálido. A una solución 2M agitada de NH_3 en MeOH (8 ml, 16 mmol) se agregó este intermedio en partes pequeñas. Después de 12 horas la mezcla de la reacción se agregó $NaHCO_3$ saturado y se extrajo con EtOAc (2 x 50 ml). Los extractos combinados se lavaron con solución salina, se secaron (Na_2SO_4) y se concentraron bajo presión reducida para dar el compuesto del título (1,5 g, 93%) que se

usó en el paso siguiente sin purificación. GC-MS(EI): 321, 323.

Ejemplo 7c

Preparación de éster de etilo del ácido 2-(4-bromofenil)-1-(2-clorobencil)-1H-imidazol-4-carboxílico

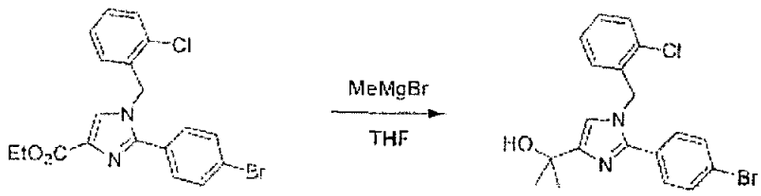


Una mezcla de 4-bromo-N-(2-clorobencil)-benzamidina (1,4 g, 4,3 mmol), bicarbonato de sodio (0,72 g, 8,6 mmol) y etil bromopiruvato (0,98 ml, 7,8 mmol) en EtOH (14 ml) se calentó en una unidad de microondas (Biotage Initiator®) a 175°C durante 12 minutos. La mezcla resultante se decantó y los sólidos se enjuagaron con EtOAc. Los filtrados combindos se concentraron y se purificaron mediante cromatografía (sílice, EtOAc/Hexano, 0:100 a 40:60) para dar el compuesto del título (0,24 g, 13%) como un residuo marrón pálido. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,58-7,62 (m, 3H), 7,43-49 (m, 3H), 7,34 (m, 1H), 7,28 (m, 1H), 6,96 (d, 1H), 5,30 (s, 2H), 4,32 (q, 2H), 1,35 (t, 3H); MS(ES): 419, 421 $[M+H]^+$.

Ejemplo 7d

563

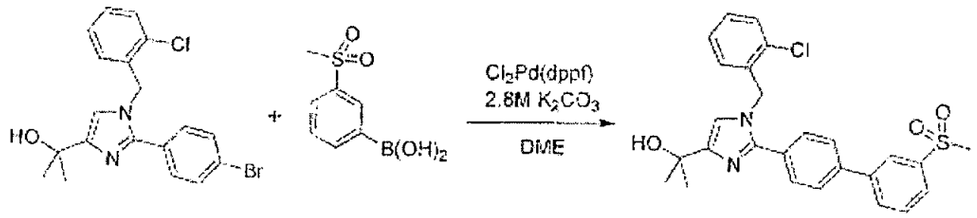
Preparación de 2-[2-(4-bromofenil)-1-(2-clorobencil)-1H-imidazol-4-il]-propan-2-ol



A un solución 3,0 M de MeMgBr en Et_2O (1,0 ml, 3,0 mmol) a 0°C se agregó lentamente una solución de éster del ácido 2-(4-bromofenil)-1-(2-clorobencil)-1H-imidazol-4-carboxílico (235 mg, 0,56 mmol) en THF (3 ml, anhidro). Después de que se terminó el agregado se retiró el matraz del baño de agua helada para calentarlo a temperatura ambiente. A los 40 minutos la mezcla de la reacción se enfrió agregando NH_4Cl saturado con EtOAc, se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía (sílice, EtOAc/Hexano, 2=:80 a 60:40) para dar el compuesto del título (135 mg, 59%) como un sólido color ámbar pálido. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,54 (d, 2H), 7,38-7,45 (m, 3H), 7,24-7,30 (m, 2H), 6,89 (d, 1H), 6,82 (s, 1H), 5,25 (s, 2H), 2,86 (br s, 1H), 1,54 (s, 6H); MS(ES): 405, 407 $[M+H]^+$.

Ejemplo 7e

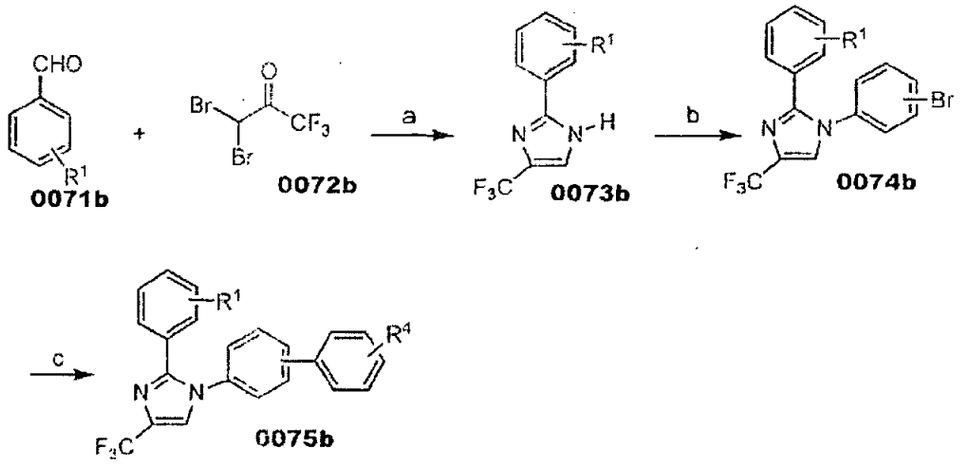
Preparación de 2-[1-(2-clorobencil)-2-(5'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-propan-2-ol



Una mezcla de 2-[2-(4-bromofenil)-1-(2-clorobencil)-1H-imidazol-4-il]-propan-2-ol (130 mg, 0,32 mmol), ácido 3-metanosulfonil-fenilborónico (80 mg, 0,40 mmol), $Cl_2Pd(dppf)\cdot DCM$ (13 mg, 5% en moles) y una solución acuosa 2,8 M de K_2CO_3 (0,35 ml, 0,98 mmol) en DME (2 ml) se calentó en una unidad de microondas (Biotage Initiator®) a 120°C durante 4 minutos. La mezcla de la reacción se concentró y se purificó mediante cromatografía (sílice, EtOAc/Hexano, 45:55 a 90:10) para dar el compuesto del título (118 mg, 77%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,08 (m, 1H), 7,84 (dd, 2H), 7,55-7,64 (m, 5H), 7,38 (m, 1H), 7,17-7,26 (m, 2H), 6,85 (d, 1H), 6,77 (s, 1H), 5,24 (s, 2H), 3,00 (s, 3H), 2,86 (br s, 1H), 1,49 (s, 6H); MS(ES): 481 $[M+H]^+$.

En forma similar, se preparó 2-[1-(2,3-diclorobencil)-2-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-propan-2-ol, reemplazando 2-clorobencilamina con 2,3-diclorobencilamina. MS(ES): 515, 517 $[M+H]^+$.

Esquema 7



Reacción y condiciones: (a) NaOAc, NH_4OH, MeOH; (b) $ArB(OH)_2$, $[Cu(OH).TMDA]_2Cl_2$, DCM; (c) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

En general, los compuestos de la fórmula (0075b) se preparan primero haciendo reaccionar 3,3-dihalocetona tal como 3,3-dibromo-1,1,1-trifluorometilacetona con acetato de sodio acuoso para generar un glioxal que reacciona in situ con aldehído de la fórmula (0071b) y amoníaco para dar un imidazol de la fórmula (0073b). La conversión de los compuestos de la fórmula (0073b) en los compuestos de la fórmula (0074b) luego se realiza mediante N-arilación tal como una reacción de Buchwald o acoplamiento catalizado con Cu(II) con reactivos de ácido borónico. En una reacción de acoplamiento mediado con paladio, por ejemplo una reacción de Suzuki, los compuestos de la fórmula (0074b) luego reaccionan con un boronato o ácido

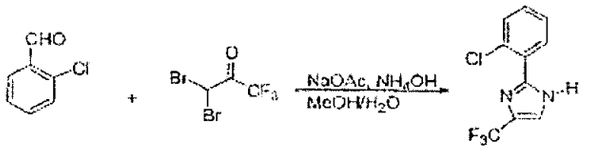
borónico para dar compuestos de la fórmula (0075b) después de procedimientos de aislamiento comunes.

Ejemplo 8

2-(2-Cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-4-trifluorometil-1H-imidazol

Ejemplo 8a

Preparación de 2-(2-Cloro-fenil)-4-trifluorofenil-1H-imidazol



3,3-Dibromo-1,1,1-trifluoroacetona (6,75 g, 25 mmol) se agregó a una solución de NaOAc (4,11 g, 50 mmol) en 15 ml de agua, y la mezcla se calentó a 100°C durante 60 minutos. Después de enfriar a temperatura ambiente, se agregó 2-clorobenzaldehído (2,8 g, 20 mmol) disuelto en MeOH (45 ml), seguido por NF_4OH concentrado (10 ml). La mezcla se agitó a temperatura ambiente toda la noche. Después de que se removió mediante evaporación, se agregó agua. El precipitado se recogió mediante filtración y se lavó con agua y se secó bajo vacío para dar un sólido amarillo claro (4,7 g, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7,37 (dd, 1H), 7,40 (dd 1H), 7,46 (dd, 1H), 7,50 (m, 1H), 8,33 (dd, 1H).

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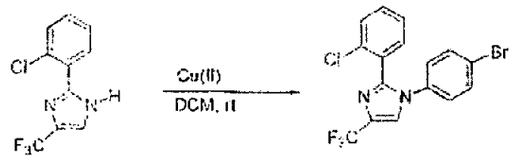
Ejemplo 8b

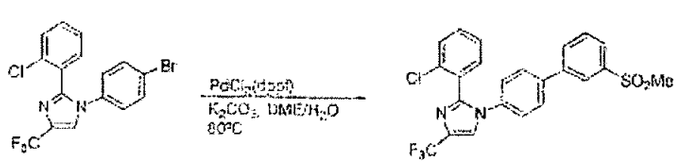
Preparación de 1-(4-bromo-fenil)-2-(2-cloro-fenil)-4-trifluorometil-1H-imidazol



2-(2-Cloro-fenil)-4-trifluorometil-1H-imidazol (370 mg, 1,5 mmol), ácido 4-bromo-fenilborónico (600 mg, 3 mmol) y $[Cu(OH)/TMEDA]_2Cl_2$ (140 mg, 0,3 mmol) se mezclaron con 6 ml de diclorometano seco, y se agitaron a temperatura ambiente bajo una atmósfera de dioxígeno durante 2 días. La mezcla de la reacción se diluyó con diclorometano y se filtró a través de celita. El filtrado se concentró bajo vacío, y el residuo se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc 8/2) para dar un sólido (151 mg, 25% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7,02 (d, 2H), 7,34 (m, 3H), 7,47 (d, 2H), 7,53 (dd, 1H), 7,56 (dd, 1H).

Ejemplo 8c

Preparación de 2-(2-Cloro-fenil)-1-(3'-metanosulfonil-4-il)-4-trifluorometil-1H-imidazol



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1-(4-bromo-fenil)-2-(2-cloro-fenil)-4-trifluorometil-1H-imidazol (100 mg, 0,25 mmol), ácido (3-metilsulfonil)fenilborónico (100 mg, 0,5 mmol), carbonato de potasio (155 mg, 1,13 mmol) y $PdCl_2(dppf)\cdot CH_2Cl_2$ (20 mg, 0,025 mmol) se mezclaron con 3 ml de 9:1 DME/H_2O (v/v), luego se calentaron a 80°C toda la noche. Todo el solvente se removió en vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc; 6/4), luego mediante HPLC de fase invertida (30% acetonitrilo en agua) para dar un sólido blanco (55 mg, 46% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3,00 (s, 3H), 7,26 (m, 2H), 7,37 (m, 3H), 7,62 (m, 5H), 7,84 (m, 1H), 7,94 (m, 1H), 8,12 (t, 1H).

En forma similar, todos los compuestos siguientes se prepararon usando reactivos aldehídos y ácidos borónicos.

- 2-(2-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-4-(trifluorometil)-1H-imidazol; MS(ES): 677,0 $[M+H]^+$
- 4'-[2-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-1-il]bifenil-3-sulfonamida; MS(ES): 478,0 $[M+H]^+$

- 1-(4-bromofenil)-4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol; MS(ES): 435,0 $[M+H]^+$
- 1-[3'-(metilsulfonil)bifenil-4-il]-4-(trifluorometil)-2-(trifluorometil)fenil]-1H-imidazol; MS(ES): 511,3 $[M+H]^+$
- 4'-{4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-sulfonamida; MS(ES): 512,3 $[M+H]^+$

Los siguientes compuestos se prepararon en forma similar a la descrita en el Esquema 7, excepto que la reacción de acoplamiento catalizada por Cu (II) para preparar compuestos de la fórmula (0047b) se reemplazó por una base, como hidruro de sodio, la reacción de reemplazo catalizada con bromuro de arilo que transporta grupos salientes apropiados, tales como 2,5-dibromopiridina.

- 5-[3-(metilsulfonil)fenil]-2-{4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}piridina; MS(ES): 512,3 $[M+H]^+$
- 2-[2-(clorofenil)-4-(trifluorometil)-1H-imidazol-1-il]-5-[3-

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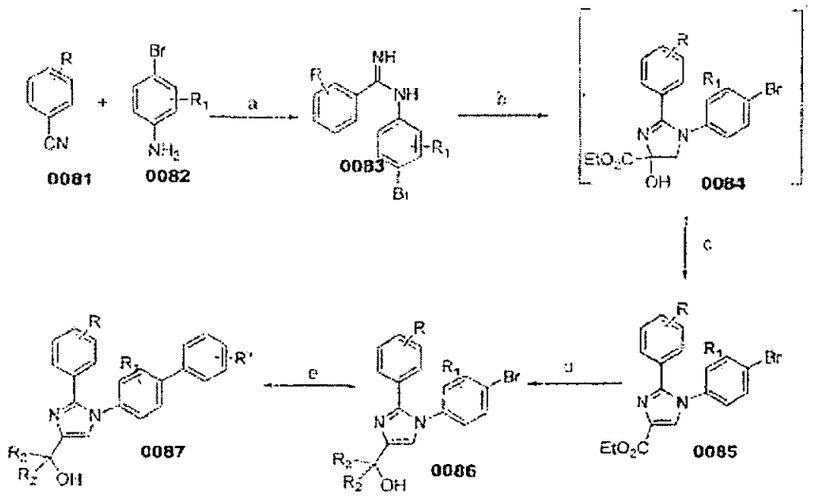
(metilsulfonil)fenil]piridina; MS(ES): 478,0 $[M+H]^+$

Esquema 8



(a) Método A: Me_3Al, Tolueno, 0°C-80°C; Método B: NaHMDS, 0°C-temperatura ambiente; (b) Etil bromopiruvato, $NaHCO_3$, 2-PrOH, 80°C; (c) $NaHCO_3$/2-PrOH o HOAc/2-PrOH, reflujo; (d) R_2MgBr, THF, 0°C-temperatura ambiente, (e) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C.

En general, los compuestos de la fórmula (0087) se preparan primero haciendo reaccionar anilina de la fórmula (0082) con aril nitrilos (0081), en la presencia de Ácido de Lewis (Método A) o base (Método B) para dar compuestos de la fórmula (0083) después de procedimientos de aislamiento comunes. En un paso posterior, la exposición de amidina (0083) a haloéster,

tal como Etil alfa-bromopiruvato, en condiciones básicas a temperatura elevada da el intermedio 1H-imidazol-4-ol de la fórmula (0084), que es puede convertir en compuestos de la fórmula (0085) in situ, o por medio de deshidratación catalizada con ácido. Los compuestos de la fórmula (0085) luego se someten a transformación de funcionalidad, tal como a partir de éster a carbinol. En una reacción de acoplamiento mediada por paladio, por ejemplo la reacción de Suzuki, los compuestos de la fórmula (0086) luego reaccionan con un reactivo diboronato o ácido borónico para dar compuestos de la fórmula (0087) después de procedimientos de aislamiento comunes.

Ejemplo 9

2-[2-(2,6-Difluoro-fenil)-1-(3'-metanosulfonil-bifenil)-1H-imidazol-4-il]-propan-2-ol

Ejemplo 9a

(Método A)

Preparación de N-(4-bromofenil)-2,6-difluorobencimidamida

N-(4-bromo-fenil)-2,6-difluoro-benzamidina:4-bromoanilina (1,72 g, 10 mmol) se colocó en un reactor de tres cuellos, y el reactor se inundó con argón durante 20 minutos. Se

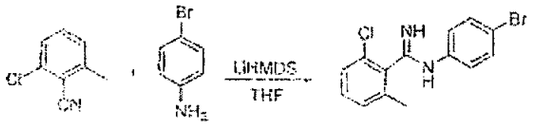
577

agregaron 50 ml de tolueno anhidro. Después de enfriar a 0°C, se agregó trimetilaluminio (7,5 ml, 2,0M solución en tolueno, 15 mmol) se agregó lentamente para mantener la temperatura interior debajo de 18°C. Después del agregado, la mezcla de la reacción se calentó a temperatura ambiente y luego se agitó durante otras 2 horas. Una solución 2,6-difluorobenzonitrilo (2,78 g, 20 mmol) en 50 ml, se agregó tolueno anhidro, y la mezcla de la reacción se calentó a 0°C. Después de 18 horas, la mezcla de la reacción se enfrió a temperatura ambiente y se vertió sobre una suspensión de gel de sílice en $CHCl_3$/MeOH (4/1, V/v). Después de agitar durante 20 minutos, la mezcla se filtró y el residuo se lavó con una mezcla de $CHCl_3$/MeOH (4/1, V/V). Los filtrados combinados se concentraron en vacío, y el sólido resultante se agitó con una solución de hexano/Éter (3/1, V/V). El intermedio se filtró y se lavó con hexano/éter adicional (3/1, V/V) para dar un sólido blanco (2,4 g, 79% de rendimiento), que se usó directamente para el paso siguiente sin nueva purificación.

Ejemplo 9aa

(Método B)

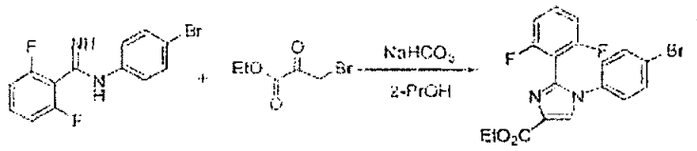
Preparación de N-(4-bromofenil)-2-cloro-6-metilbencimidamida



N-(4-bromo-fenil)-2-cloro-6-metil-benzamidina: Bajo una atmósfera de N_2 a temperatura ambiente a una solución de litio bis(trimetilsilil)amida (9,7 ml, 1,0M solución en THF, 9,7 mmol) se agregó una solución de 4-bromoanilina (1,67 g, 9,7 mmol) en 10 ml de THF anhidro. Después de que la mezcla se agitó a temperatura ambiente durante 40 minutos, se agregó una solución de 2-cloro-6-metilbenzonitrilo (1,55 mg, 10,2 mmol) en 10 ml de THF anhidro. La mezcla de la reacción se agitó a temperatura ambiente toda la noche, y luego se vertió en 380 ml de agua helada. El precipitado naranja se recogió mediante filtración, se lavó hexano y se secó para dar un sólido naranja (2,09 g, 66% de rendimiento), que se usó directamente para el paso siguiente sin nueva purificación.

Ejemplo 9b

Preparación de etil 1-(4-bromofenil)-2-(2,6-difluorofenil)-1H-imidazol-4-carboxilato

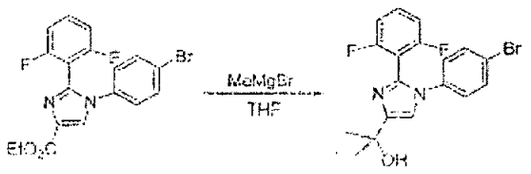


A una mezcla de N-(4-bromo-fenil)-2,6-difluorobenzamidina (2,4g, 7,7 mmol) y bicarbonato de sodio (1,3 g, 15,4 mmol) en 40 ml de 2-propanol se agregó etil alfa-bromopiruvato (3,34 g, 15,4 mmol, 90% tec). La mezcla se calentó a 80°C-85°C toda la noche. Después de enfriar a temperatura ambiente, el solvente

se removió y el residuo se redisolvió en diclorometano. El precipitado se filtró, y el filtrado se concentró. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (30→50% de EtOAc/hexano) para dar un sólido amarillo (1,82 g, 58% de rendimiento).

Ejemplo 9c

Preparación de 2-(1-(4-bromofenil)-2-(2,6-difluorofenil)-1H-imidazol-4-il)propan-2-ol



Bromuro de metilmagnesio (11,2 ml, 15,7 mmol, 1,4M en tolueno/THF 75:25) se colocó en un matraz de tres cuellos. Bajo nitrógeno a 0°C a ello se agregó una solución de éster de etilo del ácido 1-(4-bromo-fenil)-2-(2,6-difluoro-fenil)-1H-midazol-4-carboxílico en 15 ml de THF. Después del agregado, el baño de hielo se removió y la mezcla de la reacción se agitó a temperatura ambiente durante 2,5 horas. La reacción se enfrió con cloruro de amonio saturado. Se separaron dos capas, y la capa acuosa se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron en vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel

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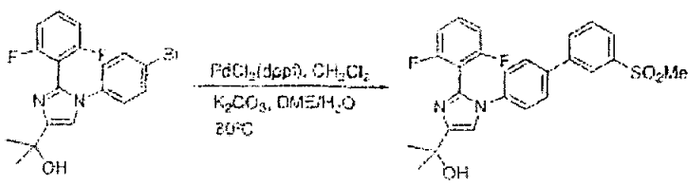
de sílice (30→50% de EtOAc/Hexano) para dar un sólido blancuzco (0,9 g, 51% de rendimiento).

Ejemplo 9d

Preparación de 2-(2-(2,6-difluorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-4-ol



2-[1-(4-Bromo-fenil)-2-(2,6-difluoro-fenil)-1H-imidazol-4-il]-propan-2-ol (250 mg, 0,64 mmol), ácido (3-metilsulfonilfenil)borónico (254 mg, 1,27 mmol) y carbonato de potasio (398 mg, 2,88 mmol) se colocaron en un matraz. Se agregaron 6 ml de una mezcla de DME (1,2-dimetoxietano) y agua (9:1, V/V). El matraz se inundó con argón durante 15 minutos y luego se agregó catalizador Pd (agregado Dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) diclorometano, 52 mg, 0,064 mmol). La mezcla se calentó a 80°C toda la noche. Después de enfriar a temperatura ambiente, todo el solvente se removió. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (43 → 99% EtOAc/Hexanos) para dar un sólido blancuzco (240 mg, 77% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1,70 (s, 6H), 2,71 (m, 1H), 3,09 (m, 3H), 6,92-6,88 (m, 2H), 7,21 (s, 1H), 7,39-7,28 (m, 3H), 7,59-7,57

(m, 2H), 7,66 (t, 1H, J=7,8), 7,86-7,83 (M, 1H), 7,95-7,92 (m, 1H, 8,12 (t, 1H, J=1,7). MS(ES) 491,4 $[M+Na]^+$.

En forma similar, la totalidad de los siguientes compuestos se prepararon usando el Método A (ejemplo 9a) o el Método B (Ejemplo 9aa) para preparar amidinas. El orden de los dos últimos pasos de la adición de Grignard y el acoplamiento de Suzuki se cambió en algunos casos. Los reactivos ácido borónico o boroanto para el acoplamiento de Suzuki, si no están comercialmente disponibles, se prepararon usando técnicas comunes que son fácilmente evidentes para un experto en el arte.

- etil 1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(2-(trifluorometil)fenil]-1H-imidazol-4-carboxilato; MS(ES): 515,3 $[M+H]^+$;
- 2-{1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-4-ol; MS(ES): 523,3 $[M+H]^+$;
- 5-{3-[(1-metiletil)sulfonil]bifenil}-2-{4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}piridina; MS(ES): 540,3 $[M+H]^+$;

- 1-{3'-[(1-metiletil)sulfonil]bifenil-4-il}-4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol; MS(ES): 593,3 $[M+H]^+$;
- N-(4'-{4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-il)metanosulfonamida; MS(ES): 526,5 $[M+H]^+$;
- Etil 1-[3'-(metilsulfonil)bifenil-4-il]-2-fenil-1H-imidazol-4-carboxilato; MS(ES): 447,3 $[M+H]^+$;
- 2-{1-[3'-(metilsulfonil)bifenil-4-il]-2-fenil-1H-imidazol-4-il}propan-2-ol;
- 2-[2-(2-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}-propan-2-ol; MS(ES): 467,4 $[M+H]^+$;
- 2-{2-(2-fluorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 451,1 $[M+H]^+$;
- 1-{2-(2-fluorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona; MS(ES): 457,1 $[M+H]^+$;
- 2-{2-(4-fluorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 451,3 $[M+H]^+$;

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- 2-{2-(2-cloro-6-metilfenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 481,1 $[M+H]^+$;
- 2-{1-[4'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometl)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501,5 $[M+H]^+$;
- 2-{1-[3'-(etilsulfonil)bifenil-4-il]-2-[2-(trifluometil)fenil}-1H-imidazol-4-il}propan-2-ol; MS(ES): 515,5 $[M+H]^+$;
- 2-{1-[3'-(metilsulfonil)bifenil-2-il]-2-[3-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501,4 $[M+H]^+$;
- 2-{1-[4'-(metilsulfonil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501,4 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491,4 $[M+Na]^+$;
- 2-{1-{3'-[(1-metiletil)sulfonil]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 529,3 $[M+H]^+$;
- 2-{1-{3'-[(1-metiletil)sulfonil]bifenil-3-il}-2-{2-(trifluorometil)fenil]-1H-imidazol-4-il)porpan-2-ol; MS(ES): 529,3 $[M+H]^+$;

581
579

- 2-{2-(2-clorofenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 481,3 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 485,3 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 483,4 $[M+H]^+$;
- 2-(1-{5-[3-(metilsulfonil)fenil]piridin-2-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 502,5 $[M+H]^+$;
- 2-{1-{6-[3-(metilsulfonil)fenil]piridin-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 502,3 $[M+H]^+$;
- 2-{2-(2,6-diclorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 523,3 $[M+Na]^+$;
- 2-{2-[2-fluoro-6-(trifluorometil)fenil]-1-{3'-(metilsulfonil)bifenil-4-il}-1H-imidazol-4-il}propan-2-ol, MS(ES): 541,3 $[M+H]^+$;
- 2-{2-(2-metilfenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 447,0 $[M+H]^+$;

- 2-{1-[3'-(metilsulfonil)bifenil-4-il]-2-{2-[(trifluorometil)oxi]fenil}-1H-imidazol-4-il}propan-2-ol; MS(ES): 539,3 $[M+Na]^+$;
- 2-{2-[2-(dimetilsulfonil)-6-fluorofenil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 516,3 $[M+Na]^+$;
- 2-{3-(2,6-diclorofenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515,2 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 499,5 $[M+H]^+$, 521,3 $[M+Na]^+$;
- 2-{2-(2,6-diclorofenil)-1-[4'-(dihidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 531,1, 533,3 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515,7, 517,3 $[M+H]^+$;
- 2-{2-(3-cloro-3'-(metilsulfonil)bifenil-2-il)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-

imidazol-4-il)propan-2-ol; MS(ES): 621,5 $[M+H]^+$;

- 2-{2-(2,3-diclorofenil)-1-[3'-(hidroximetil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{2-(2,3-diclorofenil)-1-[4'-(hidroximetil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{2-[3-metil-3'-(metilsulfonil)bifenil-4-il]-2-(2-tienil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-(2-cloro-6-fluorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-2-(2,6-diclorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 537 $[M+H]^+$;
- 2-{1-[3'-(etilsulfonil)-3-metilbifenil-4-il]-2-isoquinolin-5-il-1H-imidazol-4-il}propan-2-ol; MS(ES): 512 $[M+H]^+$;
- 2-{2-isoquinolin-5-il-1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 498 $[M+H]^+$;

- 2-{2-(1,5-dimetil-1H-pirrol-2-il)-1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 464 $[M+H]^+$;
- 2-{1-[3-metil-3-(metilsulfonil)bifenil-4-il]-2-(2-tienil-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-2-isoquinolin-1-il-1H-imidazol-4-il}propan-2-ol; MS(ES): 529 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-2-isoquinolin-1-il-1H-imidazol-4-il}propan-2-ol; MS(ES): 518 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[3'-(etilsulfonil)-3-fluorobifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 513 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 499 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[3'-(etilsulfonil)-3-metilbifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 509 $[M+H]^+$;

- 2-{2-(3-cloro-2-metilfenil)-1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 495 $[M+H]^+$;
- 2-{1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trimetilsulfonil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501 $[M+H]^+$;
- 2-{1-[3cloro-3'-(etilsulfonil)bifenil-4-il]-2-naftalen-1-il-1H-imidazol-4-il}propan-2-ol; MS(ES): 531 $[M+H]^+$;
- 2-{1-[3'-(etilsulonil)-3-metilbifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 529 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-(3-cloro-2-metilfenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 529 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[3-cloro-2'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;
- 2-{1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-2-naftalen-1-il-1H-imidazol-4-il}propan-2-ol; MS(ES): 517 $[M+H]^+$;

~~587~~
586

- 2-{1-[3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-(2-clorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 549 $[M+H]^+$;
- 2-{1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;
- 2-{1-[3'-(etilsulfonil)-2-fluorobifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 533 $[M+H]^+$;
- 2-{1-[2-fluoro-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 519 $[M+H]^+$;
- 2-{1-[3'-(etilsulfonil)-3-fluorobifenil-4-il]-2-[2-(trifluorometil]fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 533 $[M+H]^+$;
- 2-{1-[5-fluoro-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 519 $[M+H]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(3-fluoro-3-(mtilsulfonil)bifenil-4-il)-1H-imiazol-4-il)propan-2-ol; MS(ES): 499,3 $[M+H]^+$;

588
587

- 2-(2-(2-cloro-6-metilfenil)-1-(3'-etilsulfonil)-3-fluorobifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 513,3 $[M+H]^+$;
- 2-(2-(2,6-diclorofenil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 515,3, 517,3 $[M+H]^+$;
- 2-(2-(2,6-diclorofenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529,3, 513,3 $[M+H]^+$;
- 2-(1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)2-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 549,3, 551,3, 553,3 $[M+H]^+$;
- 2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 565,0, 567,0, 569,2 $[M+H]^+$;
- 2-(1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2-cloro-6-metilfenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 515,2, 517,3 $[M+H]^+$;
- 2-(2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-2-(2-cloro-6-

589
588

metil)fenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 542,3, 547,3 $[M+H]^+$;

- 2-(1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-2-(2-cloro-6-metilfenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529,2, 531,2 $[M+H]^+$;
- 2-(2-(2,6-diclorofenil)-1-(3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 549,3, 551,3 $[M+H]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(3'-(etilsulfonil)-3-metilfenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 509,3, 511,3 $[M+H]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 495,4, 497,4 $[M+H]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)prpopan-2-ol; MS(ES): 495,4 $[M+H]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 511,3 $[M+H]^+$;

598
589

- 2-(2-(2,6-diclorofenil)-1-(3-fluoro-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 519,3, 520,3 $[M+H]^+$;
- 2-(2-(2,6-diclorofenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529,3, 531,3 $[M+H]^+$, 551,3, 553,3 $[M+Na]^+$;
- 2-(1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 525,3, 537,3, 539,3 $[M+H]^+$;
- 2-(2-(2,6-diclorofenil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 537,0 $[M+Na]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(4-(hidroximetil)-3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 525,5 $[M+H]^+$;
- 2-(2-(2-cloro-6-metilfenil)-1-(3-fluoro-4'-(hidroximetil)-3-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529,3, 531,3 $[M+H]^+$;
- Etil 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-

carboxilato; MS(ES): 549,0, 551,0, 553,0 $[M+H]^+$;

- 2-{1-[2'(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-(2',3'-difluorofenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 459 $[M+H]^+$;
- 2-(1-{4'-[(1-metiletil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-{1-(4'-fluoro-3'-metilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 455 $[M+H]^+$;
- 2-{1-(3'-fluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 441 $[M+H]^+$;
- 2-{1-(2',4',5'-trifluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 477 $[M+H]^+$;
- 2-{1-[5'-fluoro-2'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 471 $[M+H]^+$;

592
591

- 2-{1-(4'-clorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 457 $[M+H]^+$;
- 2-{1-(4-pirimidin-5-ilfenil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 425 $[M+H]^+$;
- 2-{1-[4'(hidroximetil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{1-[4'(dimetilamino)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 466 $[M+H]^+$;
- 2-{1-[4'(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-[4'(1-metiletil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 465 $[M+H]^+$;
- 2-{1-(4'-cloro-2'-(trifluorometil)bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 525 $[M+H]^+$;
- 2-{1-(2',3',4'-tritluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 477 $[M+H]^+$;

593
592

- 2-{1-(3',4'-difluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 459 $[M+H]^+$;
- 2-{1-(2'-cloro-6'-fluoro-3'-metilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 489 $[M+H]^+$;
- 2-{1-[5'-cloro-2'-(metiloxibifenil)-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 487 $[M+H]^+$;
- 2-{1-[2'-fluoro-5'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 509 $[M+H]^+$;
- 2-{1-[2'-(metiltio)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 469 $[M+H]^+$;
- Ácido 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil-1H-imidazol-1-il}bifenil-4-carboxílico; MS(ES): 467 $[M+H]^+$;
- 2-{1-[4-(1,3-benzodioxol-5-ilfenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- 2-(1-{4-[6-(metiloxi)-3-il]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 454 $[M+H]^+$;

- 2-(1-{4-[(1E)-3,3-dimetilbut-1-en-1-il]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 429 $[M+H]^+$;
- 2-{1-(3'-clorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 457 $[M+H]^+$;
- 2-{1-(2'-fluoro-5'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 471 $[M+H]^+$;
- Etil 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-il}bifenil-4-carboxilato; MS(ES): 495 $[M+H]^+$;
- 2-{1-(4-{2-[(1-metiletil)oxi]piridin-3-il}fenil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 462 $[M+H]^+$;
- 2-{1-[3'-cloro-4'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 487 $[M+H]^+$;
- 2-{1-[2'-fluoro-3'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 471 $[M+H]^+$;

~~595~~
594

- 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}bifenil-3-carboxamida; MS(ES): 466 $[M+H]^+$;
- 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}carboxamida; MS(ES): 466 $[M+H]^+$;
- 2-(1-{4'-[(trifluorometil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 507 $[M+H]^+$;
- 2-{1-(4'-fluoro-3'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 509 $[M+H]^+$;
- 2-{1-(4'-propilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 465 $[M+H]^+$;
- 2-{1-(4'-(etiloxi)-3'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;
- 2-(1-{2'-[(1-metiletil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-(1-{3'-cloro-4'-[(1-metiletil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-

~~596~~
595

imidazol-4-il)propan-2-ol; MS(ES): 515 $[M+H]^+$;

- 2-{1-[4-(1H-indol-4-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 462 $[M+H]^+$;
- 2-{1-[4'-(metiltio)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 469 $[M+H]^+$;
- 2-{1-[3'-(hidroximetil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{1-[3'-(etiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- 2-{1-(4'-etilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 451 $[M+H]^+$;
- 2-{1-(2',4'-difluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 459 $[M+H]^+$;
- 2-{1-(3',4'-diclorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;

597
596

- 2-{1-[2'-cloro-4'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 525 $[M+H]^+$;
- 2-{1-(4-naftalen-2-ilfenil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 473 $[M+H]^+$;
- 2-{1-[3'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-ol; MS(ES): 439 $[M+H]^+$;
- 2-{1-(3',4',5'-trifluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 477 $[M+H]^+$;
- 1-[5-(4-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}fenil)-2-tienil]etanona; MS(ES): 471 $[M+H]^+$;
- 2-{1-(3',5'-difluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 459 $[M+H]^+$;

598
597

- 2-{1-(3'-cloro-4'-fluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 475 $[M+H]^+$;
- 2-{1-[5'-metil-2'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- 2-{1-(2',5'-difluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 459 $[M+H]^+$;
- 2-{1-[3'-(butiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 495 $[M+H]^+$;
- 2-{1-[5'-cloro-2'-(etiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501 $[M+H]^+$;
- 2-{1-{3'-[(trifluorometil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 507 $[M+H]^+$;
- 2-{1-(2',3',5'-trifluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 477 $[M+H]^+$;
- 2-{1-[3'-(etiltio)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 483 $[M+H]^+$;

599
T98

- 2-(1-{3'-[(1-metiletil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-{1-[4-(1-benzotien-3-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 479 $[M+H]^+$;
- 2-{1-[4-(4-metilnaftalen-1-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 487 $[M+H]^+$;
- 2-{1-(2',4'-diclorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-[3',4'-bis(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 483 $[M+H]^+$;
- 2-{1-[2-(trifluorometil)fenil]-1-(2',2',5'-trimetilbifenil-4-il)-1H-imidazol-4-il}propan-2-ol; MS(ES): 465 $[M+H]^+$;
- 4-fluoro-4'-(1-hidroxi-1-metiletil)-2-{2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-2-ol; MS(ES): 457 $[M+H]^+$;
- 2-{1-[2'-(hidroximetil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;

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- 2-{1-[3'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-(2'-cloro-6'-fluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 475 $[M+H]^+$;
- 2-{1-[3',5'-(difluoro-2'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 489 $[M+H]^+$;
- 2-(1-{4-[2-(metiletoxi)piridin-3-il]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 454 $[M+H]^+$;
- 2-{1-(2'-metil-5'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- 2-{1-(2'-etilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 451 $[M+H]^+$;
- 2-(1-{2'-metil-4-[(1-metiletil)oxi]bifenil-4-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 495 $[M+H]^+$;
- 2-{1-[4'-(etilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;

- 2-{1-(5'-fluoro-2'-metilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 455 $[M+H]^+$;
- 2-{1-[3'-cloro-4'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 525 $[M+H]^+$;
- 2-{1-(2',5'-dimetilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 451 $[M+H]^+$;
- 2-{1-[2'-(etiloxi)-5'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;
- 2-{1-(3'-fluoro-4'-metilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 455 $[M+H]^+$;
- Metil (2E)-3-(4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-il)prop-2-enoato; MS(ES): 507 $[M+H]^+$;
- N-etil-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida; MS(ES): 494 $[M+H]^+$;

602
601

- 2-{1-[4-(2,3-dihidro-1-benzofuran-5-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 465 $[M+H]^+$;
- N-butil-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-sulfonamida; MS(ES): 558 $[M+H]^+$;
- N-(1,1-dimetiletil)-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-6-metilbifenil-3-sulfonamida; MS(ES): 572 $[M+H]^+$;
- 4'{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-metilbifenil-3-sulfonamida MS(ES): 516 $[M+H]^+$;
- N-etil-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-sulfonamida MS(ES): 530 $[M+H]^+$;
- N-(1,1-dimetiletil)-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-sulfonamida MS(ES): 558 $[M+H]^+$;

605
602

- 2-{1-(1'-amino-5'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 506 $[M+H]^+$;
- 2-{1-[3'-fluoro-5'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 509 $[M+H]^+$;
- 2-{1-[4'-cloro-3'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 525 $[M+H]^+$;
- Ácido 3-cloro-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-carboxílico MS(ES): 501 $[M+H]^+$;
- 2-(2-[2-(trifluorometil)fenil]-1-{3'-[(trifluorometil)tio]bifenil-4-il}-1H-imidazol-4-il)propan-2-ol; MS(ES): 523 $[M+H]^+$;
- 2-{1-[3'-(morfolin-4-ilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 572 $[M+H]^+$;
- 2-(1-{4-[5-(hidroximetil)-1,3-tiazol-2-il]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 460 $[M+H]^+$;

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603

- 2-{1-(2'-metil-5'-piperidin-1-ilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 584 $[M+H]^+$;
- 1-[4-(4-{4-(1-hiroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}fenil)-2-tienil]etanona MS(ES): 471 $[M+H]^+$;
- 2-(1-{4-[5-(hidroximetil)-3-tienil]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 459 $[M+H]^+$;
- Ácido 2-cloro-4'-[2-(2,6-diclorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3'-metilbifenil-4-carboxílico; MS(ES): 515$[M+H]^+$;
- 2-(1-{3-[6-(metiloxi)piridin-3-il]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 454 $[M+H]^+$;
- 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-3-sulfonamida; MS(ES): 544 $[M+H]^+$;

605
604

- 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-carboxamida; MS(ES): 466 $[M+H]^+$;
- 2-(1-{3-[2-(ciclopentiloxi)piridin-3-il]fenil}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 508 $[M+H]^+$;
- 2-{1-(3'-clorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 457 $[M+H]^+$;
- 2-{1-[2'-fluoro-5'-(metiloxi)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 471 $[M+H]^+$;
- 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida; MS(ES): 466 $[M+H]^+$;
- 2-{1-(3',4'-bis(metiloxi)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 457 $[M+H]^+$;
- N-(3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-2-il)metanosulfonamida; MS (ES): 516 [M+H]+;

~~606~~
605

- 2-{1-[3'-(trifluorometil)bifenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- Ácido 3-fluoro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-carboxílico; MS(ES): 485 $[M+H]^+$;
- 4-cloro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida; MS(ES): 500 $[M+H]^+$;
- 2-{1-(3-{2-[(1-metiletil)oxi]piridin-3-il}fenil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 482 $[M+H]^+$;
- N-(3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-il)acetamida; MS(ES): 480 $[M+H]^+$;
- 2-{1-[2'-metil-5'-(metiloxi)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- N-(3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-il)acetamida; MS(ES): 480 $[M+H]^+$;

- 2-{1-(4'-clorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 457 $[M+H]^+$;
- 2-{1-[4'-(feniloxi)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;
- 2-{1-[5'-fluoro-2'-(metiloxi)bifenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 471 $[M+H]^+$;
- 2-{1-(2',3'-diclorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-(1-{3'[(trifluorometil)oxi]bifenil-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 507 $[M+H]^+$;
- 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}bifenil-3-sulfonamida; MS(ES): 502 $[M+H]^+$;
- 2-{1-(3',5'-bis(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 559 $[M+H]^+$;
- 2-{1-(3',5'-diclorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;

608
607

- 3-cloro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-4-carboxamida; MS(ES): 542 $[M+H]^+$;
- N,N-dietil-3'-{4-(1-hidroxi-1-metiletil)2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-1-carboxamida; MS(ES): 522 $[M+H]^+$;
- 4-cloro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-3-carboxamida; MS(ES): 542 $[M+H]^+$;
- 2-{1-[3'-(metiloxi)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- Ácido 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxílico; MS(ES): 467 $[M+H]^+$;
- N-etil-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida; MS(ES): 494 $[M+H]^+$;
- 4-cloro-N-etil-3'-{4-(1-hidroxi-1-metiletil)-2-{2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida; MS(ES): 528 $[M+H]^+$;

- 2-{1-(2',5'-difluorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 459 $[M+H]^+$;
- 2-(1-{3'-[(1-metiletil)oxi]bifenil-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-{1-[2'-fluoro-5'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 509 $[M+H]^+$;
- 2-{1-(3',4'-diclorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-[3'-(etiloxi)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- 2-(1-{2'-metil-4'-[(1-metiletil)oxi]bifenil-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol; MS(ES): 495 $[M+H]^+$;
- 2-{1-[3-(1-metil-1H-indol-5-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 476 $[M+H]^+$;
- 2-{1-[4'-(etiloxi)-3'-(trifluorometil)bifenil-3-il]-2-[2-

(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;

- 2-{1-[3'-(etilsulfonil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;
- 2-{1-[2'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-[3'-(hidroximetil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 453 $[M+H]^+$;
- 2-{1-[3-(1H-indol-4-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 462 $[M+H]^+$;
- 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-carboxílico; MS(ES): 467 $[M+H]^+$;
- 1-[5-(3-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}fenil)-2-tienil]etanona; MS(ES): 471 $[M+H]^+$;
- 2-{1-(5'-cloro-2'-metilbifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 471 $[M+H]^+$;

- 2-{1-{4'-[(trifluorometil)oxi]bifenil-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 507 $[M+H]^+$;
- 2-{1-[2'-cloro-4'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 525 $[M+H]^+$;
- 2-{1-(2',5'-diclorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-[2'-(etiloxi)-5'-(trifluorometil)bifenil-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;
- 3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-4-carboxamida; MS(ES): 508 $[M+H]^+$;
- 2-{1-(2',4'-diclorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 491 $[M+H]^+$;
- 2-{1-[4'-(etilsulfonil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 $[M+H]^+$;

612
611

- 2-{1-(4'-fluoro-3'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 509 $[M+H]^+$;
- 2-{1-(3'-fluoro-4'-metilbifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 455 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3'-(etilsulfonil)-3-fluorobifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 599 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 533 $[M+H]^+$;
- 2-{1-(2,6-difluorofenil)-1-[3-fluoro-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 487 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil)-1-[3'-(etilsulfonil)-3-fluorobifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501 $[M+H]^+$;
- 2-{2-(2,6-difloro)-1-[3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-

613
612

il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 517 $[M+H]^+$;

- 2-{2-(2-clloro-6-fluorofenil)-1-[3-fluoro-3'-(metilsulfonil)bifenil-3-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 503 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil)-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 499 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3-cloro-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 519 $[M+H]^+$;
- 2-{1-(3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-(2-cloro-6-fluorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 535 $[M+H]^+$;
- 2-{1-(3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-(2-cloro-6-fluorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 533 $[+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 549 $[M+H]^+$;

- 2-{2-(2-cloro-6-fluorofenil)-1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 499 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3'-(etilsulfonil)-3-metilbifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 513 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[4'-(hidroximetil)-3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 529 $[M+H]^+$;
- 2-{1-(3'-(metilsulfonil)bifenil-4-il]-2-[4-(trifluorometil)piridin-3-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 502 $[M+H]^+$;
- 2-{1-[3'-(etilsulfonil)bifenil-4-il]-2-[4-(trifluorometil)piridin-3-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 516 $[M+H]^+$;
- 2-{1-(4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-[4-(trifluorometil)piridin-3-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 532 $[M+H]^+$;
- 2-{1-(3'-(metilsulfonil)bifenil-3-il]-2-(2-morfolin-4-inil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 470 $[M+H]^+$;

- 2-{1-(3-cloro-3'-(metilsulfonil)bifenil-4-il]-2-(2,6-difluorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 503 $[M+H]^+$;
- 2-{1-(3-cloro-3'-(etilsulfonil)bifenil-4-il]-2-(2,6-difluorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 517 $[M+H]^+$;
- 2-{1-(3-cloro4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-difluorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 533 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil)-1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 483 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil)-1-[3'-(etilsulfonil)-3-metilbifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 497 $[M+H]^+$;
- 2-{2-(2,6-difluorofenil)-1-[4'-(dihidroximetil)-3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 513 $[M+H]^+$;
- 2-{2-(2,3-diclorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 503 $[M+H]^+$;

- 2-{2-(2-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 485 $[M+H]^+$;
- 2-{2-(2-clorofenil)-1-[3-fluoro-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 485 $[M+H]^+$;
- 2-{2-(2-clorofenil)-1-[2-fluoro-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 485 $[M+H]^+$;
- 2-{1-[3'-(metilsulfonil)bifenil-4-il]-2-[3-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501 $[M+H]^+$;
- 2-{2-(3-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 467 $[M+H]^+$;
- 2-{1-(3-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 501, 503 $[M+H]^+$;
- 2-{2-(2-clorofenil)-1-[3-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-{2-(2,3-diclorofenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515, 517 $[M+H]^+$;

- 2-{2-(2-clorofenil)-1-[3'-(etilsulfonil)-3-fluorobifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 499 $[M+H]^+$;
- 2-{2-(2-clorofenil)-1-[3'-(etilsulfonil)-2-fluorobifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 499 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-{2-(2-clorofenil)-1-[2-metil-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 481 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 495 $[M+H]^+$;
- 2-(2-(2-clorofenil)-1-(3-etil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 495 $[M+H]^+$;
- 2-(2-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,3-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 535, 537 $[M+H]^+$;
- 2-(1-(3-cloro-(3'-(etilsulfonil)bifenil-4-il)-2-(2,3-diclorofeni)-1H-imidazol-4-il)propan-2-ol; MS(ES): 549, 551 $[M+H]^+$;

- 2-(2-(2,3-diclorofenil)-1-(3-metil-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$;
- 2-(2-(2,3-diclorofenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529, 531 $[M+H]^+$;
- 2-(2-(2,3-diclorofenil)-1-(3-fluoro-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 519, 521 $[M+H]^+$;
- 2-(2-(2,3-diclorofenil)-1-(3'-(etilsulfonil)-3-fluorobifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 533, 535 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3-metil-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 499 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 513 $[M+H]^+$;
- 2-(2-(2,3-diclorofenil)-1-(4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 531, 533 $[M+H]^+$;
- 2-(2-(2,3-diclorofenil)-1-(3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-

619
618

il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 549, 551 $[M+H]^+$;

- 2-(2-(2-cloro-3-fluorofenil)-1-(4'-(hidroximetil)-3-metil-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 529 $[M+H]^+$;
- 2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-2-(2,3-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 565, 567 $[M+H]^+$;
- 2-(2-(2,3-diclorofenil)-1-(4'-(hidroximetil)-3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 545, 547 $[M+H]^+$;
- 2-(1-(3-cloro-5-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 537, 539 $[M+H]^+$;
- 2-(1-(3-cloro-3'-(etilsulfonil)-5-metilbifenil-4-il)-2-(2-clorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 551, 553 $[M+H]^+$;
- 2-(1-(3-clor-3'-(metilsulfonil)bifenil-4-il)-2-(2-cloro-3-fluorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 541, 543 $[M+H]^+$;

~~620~~
619

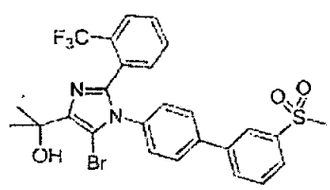
- 2-(1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-2-(2-cloro-3-fluorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 555, 557 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3-fluoro-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 525 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3'-(etilsulfonil)-3-fluorobifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 517 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 555 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 571, 573 $[M+H]^+$;
- 2-(2-(2-cloro-3-fluorofenil)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 499 $[M+H]^+$;

En forma similar, los siguientes compuestos se prepararon reemplazando el bromuro de metilmagnesio con bromuro de etilmagnesio.

- 3-(2-(2,3-diclorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)pentan-2-ol; MS(ES): 529,531 [M+H]+
- 3-(2-(2,3-diclorofenil)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)pentan-3-ol; MS(ES): 543, 545 [M+H]+
- 3-{2-(2,6-diclorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}pentan-3-ol; MS(ES): 529,3 [M+H]+

En forma similar el siguiente compuesto se preparó reemplazando etil bromopiruvato con etil 3-bromo-2-cetobutirato: 2-{5-metil-1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 515 [M+H]+.

Ejemplo 10



622
621

Preparación de 2-[5-bromo-1-(3'-metanosulfonil-bifenil-4-il)-2-(2-trifluorometil-fenil)-1H-imidazol-4-il]-propan-2-ol

A una solución de 2-[1-(3'-metanosulfonil-bifenil-4-il)-2-(2-trifluorometil-fenil)-1H-imidazol-4-il]-propan-2-ol (100 mg, 0,20 mmol) en MeCN (2 ml, anhidro) se agregó N-bromosuccinimida (45 mg, 0,25 mmol). Después de 2 horas, la mezcla de la reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado, agua (3x 10 ml) y solución salina, luego se secó (Na_2SO_4) y se concentró. El residuo se purificó mediante cromatografía (sílice) eluyendo con EtOAc/hexanos (65:40 a 95:5) para dar el compuesto del título (100 g, 86%) como un sólido blanco. En una forma similar, se preparó el siguiente compuesto reemplazando N-bromosuccinimida con N-clorosuccinimida. 2-{5-cloro-1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imiazol-4-il}propan-2-ol; MS (ES): 535 [m+H]+.

En forma similar, se preparó el siguiente compuesto tratando el éster de etilo del ácido imidazol-4-carboxílico apropiado con 1-clorometil-4-fluoro-1,4-diazoniabiciclo[2.2.2]octano bis(tetrafluoroborato) (Selectfluor®) seguido por la secuencia descrita previamente de acoplamiento cruzado de Suzuki y reacción con reactivos de Grignard: 2-{5-fluoro-1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS (ES): 519 [m+H]+.

623
622

Los siguientes compuestos se elaboraron en forma similar, excepto que los reactivos ácido borónico o boronato para el acoplamiento de Suzuki se prepararon como se describió en los Ejemplos 23-29:

- 6-{3-Cloro-4-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metil-etil)-imidazol-1-il]fenil}-1,1-diona-2,3-dihidro-1H-1λ*6*-benzo[b]tiofen-3-ol; MS (ES): 547 [m+H]+.
- 2-{2-(2,3-diclorofenil)-1-[4'-(metiloxi)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 531, 533 $[M+H]^+$;
- 2-{2-(2-cloro-6-fluorofenil)-1-[3-cloro-4'-(metiloxi)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 549, 551 $[M+H]^+$;
- Etil 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidoxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-carboxilato; MS(ES): 591, 593 $[M+H]^+$;
- 2-{2-(2,3-diclorofenil)-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 531, 533 $[M+H]^+$;
- 2-{4'-[2-(2,3-diclorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-

624
623

(metilsulfonil)bifenil-4-il}propan-2-ol; MS(ES): 559 $[M+H]^+$;

- 2-{3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-il}propan-2-ol; MS(ES): 577 $[M+H]^+$;
- 2-{1-[3-cloro-4'-(1-hidroxi-1-metiletil)-3'-(metilsulfonil)bifenil-4il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 593 $[M+H]^+$;
- 2-{3'-cloro-4'[2-(2-clorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-il}propan-2-ol; MS(ES): 559 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 511 $[M+H]^+$;
- 2-{1-[3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-(3-cloro-2-metilfenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 545 $[M+H]^+$;
- 2-{1-[3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-[2-

625
624

(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 549 $[M+H]^+$;

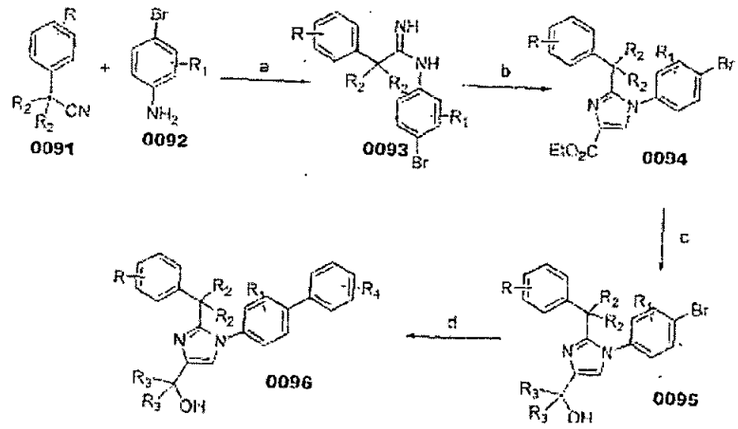
- 2-{2-(3-cloro-2-metilfenil)-1-[3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS(ES): 529 $[M+H]^+$;
- 2-{2-(3-cloro-2-metilfenil)-1-[4'-(hidroximetil)-3-metil-3'-(metilsulfonil)bifenil-4-il]-2-1H-imidazol-4-il}propan-2-ol; MS(ES): 523 $[M+H]^+$;
- 2-{1-[3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-naftalen-1-il-1H-imidazol-4-il}propan-2-ol; MS(ES): 547 $[M+H]^+$;
- 2-{1-[4'-(hidroximetil)-3-metil-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol; MS(ES): 545 $[M+H]^+$;
- 2-{1-[3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil-1H-imidazol-4-il}propan-2-ol; MS(ES): 565 $[M+H]^+$;
- 2-{1-[3-cloro-4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-(2-

clorofenil)-1H-imidazol-4-il}propan-2-ol; MS(ES): 531 $[M+H]^+$;

- Etil 4'-{4-(1-hidroxi-1-metil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-5-(metilsulfonil)bifenil-3-carboxilato; MS(ES): 573 $[M+H]^+$;
- 2-{1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil-1H-imidazol-4-il}propan-2-ol; MS(ES): 531 $[M+H]^+$;
- 2-{1-[4'-(metiloxi)-3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil-1H-imidazol-4-il}propan-2-ol; MS(ES): 531 $[M+H]^+$;
- 2-(2-(2,6-diclorofenil)-1-(3'-metil-5'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 515, 517 $[M+H]^+$;
- 2-(1-[2'-cloro-5'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol; MS(ES): 535, 537 $[M+H]^+$;
- 2-(1-[2',3-dicloro-5'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol; MS(ES): 591, 593, 595 $[M+Na]^+$;

627
626

Esquema 9



(a) Me_3AL, tolueno, 0°C-80°C; (b) etil bromopiruvato, $NaHCO_3$, EtOH, 80°C, (c) R_3MgBr, THF, 0°C-temperatura ambiente; (d) $ArB(OH)_2$, K_2CO_3, $PdCl_2(dppf)$, DME/H_2O, 80°C

En general, los compuestos de la fórmula (0096) se preparan primero haciendo reaccionar anilina dela fórmula (0092) con cianuro de bencilo (0091), tal como 2,3-diclorobencil cianuro en la presencia de una base para dar compuestos de la fórmula (0093) después de procedimientos de aislamiento comunes. En un paso posterior, la exposición de la amidina (0093) a haloéster, tal como etil alfa-bromopiruvato, en condiciones básicas a temperatura elevada da 1H-imidazol de la fórmula (0094), después de procedimientos de aislamiento comunes. Los compuestos de la fórmula (0094) luego se someten a transformación de funcionalidad, tal como de un éster a un carbinol. En una reacción de acoplamiento mediada por

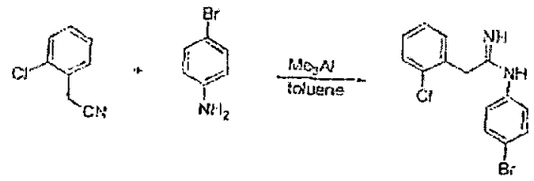
paladio, por ejemplo, la reacción de Suzuki, los compuestos de la fórmula (0095) reaccionan luego con un reactivo diboronato o ácido borónico y dan compuestos de la fórmula (0096) después de procedimientos de aislamiento comunes.

Ejemplo 11

Preparación de 2-{2-[(2-fluorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol

Ejemplo 11a

Preparación de N-(4-bromofenil)-2-(2-clorofenil)acetimidamida

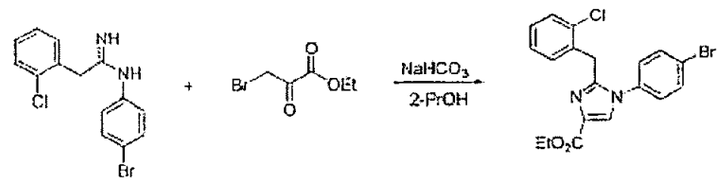


4-bromoanilina (6,4 g, 37 mmol) se colocó en un reactor de tres cuellos y el reactor se inundó con argón durante 20 minutos. Se agregaron 60 ml de trolueno anhidro. Después de enfriar a 0°C, se agregó lentamente trimetilaluminio (28 ml, 1,0M solución en tolueno, 56 mmol) para mantener la temperatura debajo de 20°C. Durante 0,5 hora, se terminó el agregado. Se retiró el baño de hilo y la mezcla de la reacción se calentó a temperatura ambiente y luego se agitó durante otras 2,5 horas. Una solución de cianuro de 2-clorobencilo (8,4 g, 55 mmol) en 35 ml, de de tolueno anhidro se agregó y la mezcla de la reacción se calentó a 0°C. Después de 10

horas, la mezcla de la reacción se enfrió a temperatura ambiente y se vertió sobre una suspensión de gel de sílice en $CHCl_3$/MeOH (4/1). Los filtrados combinados se concentraron en vacío, y el sólido resultante se lavó con hexano para dar un sólido rosa claro (5,78 g, 48% de rendimiento).

Ejemplo 11b

Preparación de etil 1-(4-bromofenil)-2-(2-clorobencil)-1H-imidazol-4-carboxilato



A una mezcla de N-(4-bromo-fenil)-2-(2-cloro-fenil)-acetamidina (5,78 g, 179 mmol, de la reacción precedente) y bicarbonato de sodio (3,0 g, 36 mmol) en 50 ml de 2-propanol se agregó etil bromopiruvato (7,8 g, 36 mmol, 90% tec). La mezcla se calentó a 80°C toda la noche y luego se enfrió a temperatura ambiente. El sobrenadante se decantó y se concentró en vacío. El residuo es redisolvió en diclorometano, y luego se fltró. El precipitado se lavó varias veces con diclorometano. Los filtrados combinados se concentraron. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (30→50% EtOAc/hexano) para dar un sólido conocido (0,75 g, 23% de rendimiento).

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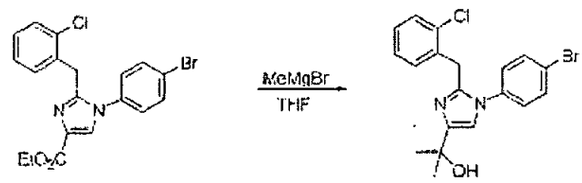
Ejemplo 11c

Preparación de 2-(1-(4-bromofenil)-2-(2-clorofenil)-1H-imidazol-4-il)propan-2-ol

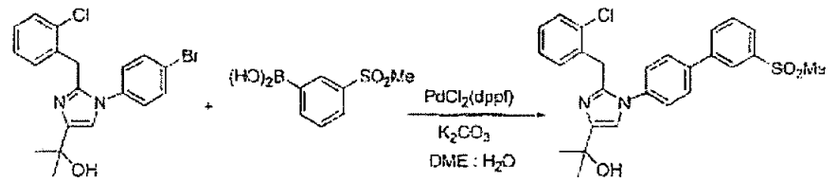


Bromuro de metilmagnesio (13 ml, 18,6 mmol, 1,4 M en tolueno/THF 75:25) se colocaron en un matraz de tres cuellos. Bajo una atmósfera de nitrógeno a 0°C se agregó una solución de éster de etilo del ácido 1-(4-bromo-fenil)-2-(2-cloro-bencil)-1H-imidazol-4-carboxílico (1,74 g, 4,1 mmol) en 15 ml de THF. Después del agregado, el baño de hielo se removió y la mezcla de la reacción se agitó a temperatura ambiente durante 3 horas. La mezcla se enfrió con cloruro de amonio saturado. Se separaron dos capas y la capa acuosa se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron en vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (30→50% de EtOAc/hexano) para dar un sólido amarillo (600 mg, 36% de rendimiento).

630

Ejemplo 11d

Preparación de 2-(2-(2-clorobencil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol



2-[1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-il]-propan-2-ol (202 mg, 0,5 mmol), ácido (3-metilsulfonil)fenilborónico, (200 mg, 1,0 mmol), carbonato de potasio (311 mg, 2,3 mmol) y $PdCl_2(dppf).CH_2Cl_2$ (42 mg, 0,05 mmol) se mezclaron con 5 ml de 9:1 DME/H_2O (v/v), luego se calentaron a 80°C toda la noche. Todo el solvente se removió en vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice (50 → 95% EtOAc/hexanos) para dar un sólido blanco (158 mg, 66% de rendimiento). ^{1}H-NMR (400 MHz, d-DMSO): δ 1,43 (s, 6H), 3,30 (s, 3H), 4,13 (s, 2H), 4,73 (q, 1H), 7,11-7,09 (m, 1H), 7,03 (m, 1H), 7,24-7,20 (m, 2H), 7,37-7,34 (m, 1H), 7,47 (m, 2H), 7,75 (t, 1H, J=7,8), 7,88-7,86 (m, 2H), 7,94-7,92 (m, 1H), 8,08-8,06 (m, 1H), 8,18 (t, 1H, J=1,9). MS (ES): 481,0 [m+H]+.

Todos los siguientes compuestos se elaboraron en forma similar usando nitrilos y anilinas apropiadas. Los reactivos ácido borónico y boronato para el acoplamiento de Suzuki, si no

632
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están disponibles comercialmente, se prepararon usando técnicas comunes que son evidentes para los expertos en el arte.

- 2-{2-[(2-fluorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 465,0 [m+H]+.
- 2-(1-[3'-(metilsulfonil)bifenil-4-il]-2-{[2-(trifluorometil)fenil]metil}-1H-imidazol-4-il)propan-ol; MS (ES): 515,3 [m+H]+.
- 2-{2-[(2-clorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 480,0 [m+H]+.
- 2-{2-[(2-clorofenil)metil]-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 495,4 [m+H]+.
- 2-{2-[(2-clorofenil)metil]-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 511,4 [m+H]+.
- 2-{2-[(2,6-diclorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 515,3 [m+H]+.

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- 2-{2-[(2,6-diclorofenil)metil]-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 529,3 [m+H]+.
- 2-{2-[(2,6-diclorofenil)metil]-1-[3'-(etilsulfonil)-4'-(hidroximetil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 545,3 [m+H]+.
- 2-{2-[(2-cloro-6-fluorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 599,5 [m+H]+.
- 2-{2-[(2-cloro-6-fluorofenil)metil]-1-[3'-(etilsulfonil)metil]-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 513,5 [m+H]+.
- 2-{2-[(2,3-diclorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 15,3 [m+H]+.
- 2-{2-[(2,3-diclorofenil)metil]-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 529,3 [m+H]+.
- 3-{2-[(2-clorofenil)metil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}pentan-3-ol, MS (ES): 509,3 [m+H]+.

- 3-{2-[(2-clorofenil)metil]-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}pentan-3-ol, MS (ES): 523,3 [m+H]+.
- 3-{2-[(2-clorofenil)metil]-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}pentan-3-ol, MS (ES): 589,2 [m+H]+.
- 2-(2-(5-cloro-2-(trifluorometil)bencil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 549,3 [m+H]+.
- 2-(2-(5-cloro-2-(trifluorometil)bencil)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 563,3 [m+H]+.
- 2-(2-(5-cloro-2-(trifluorometil)bencil)-1-4'-(hidroximetil)-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 579,2 [m+H]+.
- 2-(2-(2-(2-clorofenil)propan-2-il)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 509,0 [m+H]+.
- 2-(2-(2-(2-clorofenil)propan-2-il)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 523,3 [m+H]+.

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- 2-(2-(2-(2,3-diclorofenil)propan-2-il)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 543,3 [m+H]+.
- 2-(2-(2-(2,3-diclorofenil)propan-2-il)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 557,3 [m+H]+.
- 2-(2-(2,3-diclorobencil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 529,3 [m+H]+.
- 2-(2-(2,3-diclorobencil)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 543,3 [m+H]+.
- 2-(1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,3-diclorobencil)-1H-imidazol-4-il)propan-2-ol, MS (ES): 549,3 [m+H]+.
- 2-(1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-2-(2,3-diclorobencil)-1H-imidazol-4-il)propan-2-ol, MS (ES): 565,2 [m+H]+.
- 2-(2-(2,3-diclorobencil)-1-(3-fluoro-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 533,0 [m+H]+.
- 2-(2-(2,3-diclorobencil)-1-(3'-(etilsulfonil)-3-fluorobifenil-4-il)-1H-

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imidazol-4-il)propan-2-ol, MS (ES): 547,3 [m+H]+.

- 2-(1-(3-cloro-(3'-(metilsulfonil)bifenil-4-il)-2-(2-(2,3-diclorofenil)propan-2-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 579,3 [m+H]+.
- 2-(1-(3-cloro-(3'-(etilsulfonil)bifenil-4-il)-2-(2-(2,3-diclorofenil)propan-2-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 593,3, 595,3 [m+H]+.
- 2-(2-(5-cloro-2-fluorobencil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 521,3 [m+H]+.
- 2-(2-(5-cloro-2-fluorobencil)-1-(3'-(etilsulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol, MS (ES): 555,0 [m+H]+.
- 2-(1-(2'-cloro-3-metil-5'-(metilsulfonil)bifenil-4-il)-2-(2,3-diclorofenil)-1H-imidazol-4-il)propan-2-ol, MS (ES): 563, 565 [m+H]+.

Los siguientes compuestos se prepararon en forma similar, excepto que los reactivos ácido borónico o boronato para el

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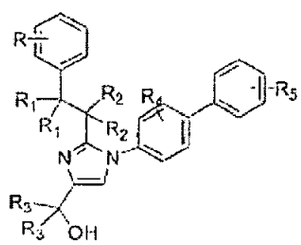
acoplamiento de Suzuki se prepararon como se describe en los Ejemplos 23-29.

- 2-{1-[3-cloro-4'-(metiloxi)-3'-(metilsulfonil)bifenil-4-il]-2-[(2,3-diclorofenil)metil]-1H-imidazol-4-il}propan-2-ol, MS (ES): 579, 581, 583 [m+H]+.
- 2-{2-[(2,3-dicloro)metil-1-[3-metil-4'-(metiloxi)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 559, 561 [m+H]+.
- 2-(1-(2'-cloro-3-metil-5'-(metilsulfonil)bifenil-4-il)-2-(2,3-diclorobencil)-1H-imidazol-4-il)propan-2-ol, MS (ES): 563, 565 [m+H]+.

Los siguientes compuestos se prepararon en forma similar, excepto que se usó propionitrilo como material inicial, en lugar de cianuro de bencilo.



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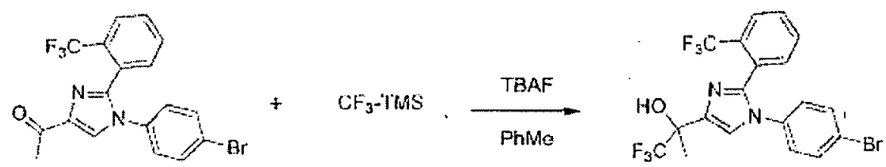
- 2-{2-[2-(2-clorofenil)etil]-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 495,4 [m+H]+.
- 2-{2-[2-(2-clorofenil)etil]-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 509,3 [m+H]+.
- 2-{2-[2-(2-clorofenil)etil]-1-[4'-(hidroximetil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol, MS (ES): 525,3 [m+H]+.

Ejemplo 12

1,1,1-trifluoro-2-(1-(3'-metilsulfonil)bifenil-4-il)-2-(2-(trifluorometil)fenil-1H-imidazol-4-il)propan-ol

Ejemplo 12a

Preparación de 1-[1-(4-bromofenil)-2-(2-trifluorometil-fenil)-1H-imidazol-4-il]-1,1,1-trifluoro-propan-2-ol



A una solución de 1-[1-(4-bromofenil)-2-(2-trifluorometil-fenil)-1H-imidazol-4-il]-etanona (0,24g, 0,59 mmol) trifluorometil-trimetilsilano (0,10 ml, 0,68 mmol) en tolueno (3 ml, anhidro) a 0°C se agregó una solución 1,0M de fluoruro

639
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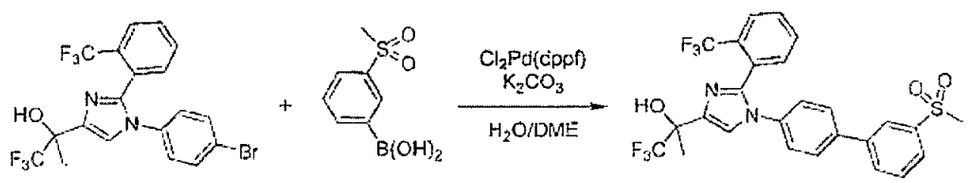
de tetrabutilamonio (TBAF) en THF (0,12 ml, 20% en moles, se secó sobre tamices moleculares de 4 A). Después de 24 horas, la mezcla de la reacción se cargó con trifluorometil-trimetilsilano adicional (0,10 ml) y 1,0 TBAF (0,12 ml)y luego se calentó a 50°C. Después de 48 horas, (totales) la mezcla de la reacción se dejó enfriar a tmeperatura ambiente, se enfrió con H_2O y se extrajo con DCM (2 x 30 ml). Los extractos combinados se secaron (Na_2SO_4), se concentraron y se purificaron mediante cromatografía (sílice, EtOAc/Hexanos, 20:80 a 60:40) para dar el compuesto del título (0,11 g, 39%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,76 (d, 1H), 7,50-7,60 (m, 2H), 7,46 (d, 2H), 7,27 (m, 2H), 7,02 (d, 2H), 4,36 (s, 1H), 1,72 (s, 3H).

Ejemplo 12b

Preparación de 1,1,1-trifuoro-2-(1-(3'-(metilsulfonil)bifenil-4-il)-2-(2-trifluorometil)fenil)-1H-imidazol-4-il)propan-2-ol



Una mezcla de 2-[1-(4-bromofenil)-2-(2-trifluorometil-fenil)-1H-imidazol-4-il]-1,1,1-trifluoro-propan-2-ol (0,11 g, 0,23 mmol), ácido 3-metanosulfonil-fenilborónico (54 mg, 0,27 mmol), K_2CO_3 (95 mg, 0,69 mmol), $Cl_2Pd(dppf).DCM$ (15 mg, 8% en

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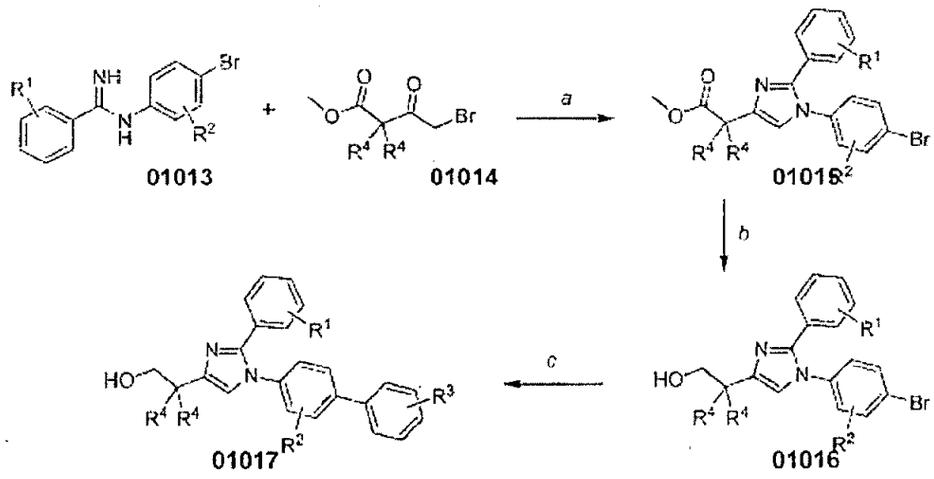
moles) y H_2O (0,25 ml) en DME (2,5 ml) se roció con Argón durante 5 minutos y luego se calentó a 80°C como un matraz sellado. Después de 90 minutos la mezcla de la reacción se dejó enfriar a temperatura ambiente, se filtró (Celite®) y el agente de filtro se enjuagó con EtOAc. Los filtrados combinados se cncentraron bajo presión reducida y se purificaron mediante cromatografía (sílice, EtOAc/Hexanos, 35:65 a 80:20) para dar el compuesto del título (116 mg, 89%) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,09 (m, 1H), 7,91 (m, 1H), 7,84 (m, 1H), 7,78 (d, 1H), 7,66 (m, 1H), 7,59 (d, 2H), 7,49-7,57 (m, 2H), 7,33 (m, 2H), 7,25 (d, 2H), 4,40 (s, 1H), 3,06 (s, 3H), 1,75 (s, 3H). MS (ES): 555 [m+H]+.

Esquema 10



(a) $NaHCO_3$, 2-PrOH, μW 180°C; (b) $LiBH_4$ 10-% en moles $B(OMe)_3$, THF; (c) $ArB(OH)_2$, $Cl_2Pd(dppf)$, K_2CO_3, HO/DME, μW 120°C.

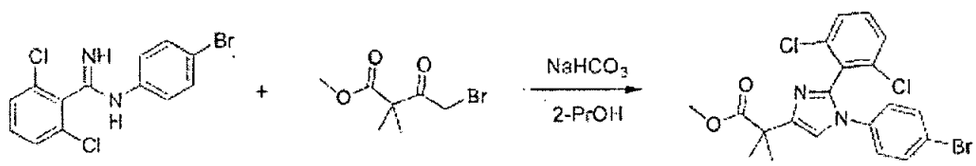
En general, los compuestos de la fórmula 01017 se pueden preparar como se ilustra en el Esquema 10. Primero, la amidina (01013) y una bromocetona (01014) puede reaccoinar en condiciones básicas y a temperatura elevada para dar el imidazol correspondiente (01015). Este intermedio 01015 se puede reducir en condiciones normales, tales como con borohidruro de litio y optativamente, borato de trimetilo catalítico, para dar el carbinol correspondiente (01016). El último intermedio 01016 puede pasar por la reacción de acoplamiento cruzado, tal como la reacción de Suzuki-Miyaura con ácidos borónicos (ésteres) para dar el imidazol deseado 01017.

Ejemplo 13

2-[2-(2,6-diclorofenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-2-metil-propan-1-ol

Ejemplo 13a

Éster de metilo del ácido Preparación de 2-[1-(4-bromofenil)-2-(2,6-diclorofenil)-1H-imidazol-4-il]-2-metil-propiónico



Una mezcla de N-(4-bromofenil)-2,6-diclorobenzamidina (1,03 g, 3,0 mmol), metil 4-bromo-2,2-dimetilacetoacetato (1,78 g, 8,0 mmol) y NaHCO (0,76 g, 9,0 mmol) en isopropanol (12 ml) se

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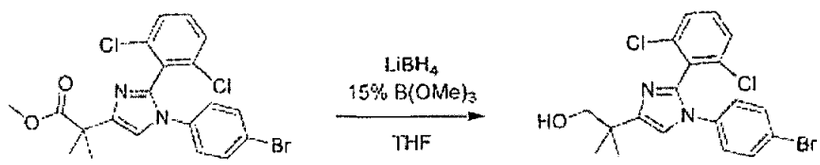
calentó en una unidad de microondas (Biotage Initiator®) a 170°C durante 25 minutos. La mezcla resultante se decantó y los sólidos se enjuagaron con EtOAc. Los filtrados combinados se concentraron y se purificaron mediante cromatografía (sílice, EtOAc/Hexano, 15:85 a 50:50) para dar el compuesto del título (0,80 g, 57%) como un sólido amarillo pálido. ^{1}H-NMR (400 MHz, DCM-d_2): δ 7,44 (d, 2H), 7,27-7,34 (m, 3H), 7,09 (m, 2H), 3,67 (s, 3H), 1,61 (s, 6H). MS (ES): 467, 469, 471 [M+H]+.

Ejemplo 13b

Preparación de 2-[1-(4-bromofenil)-2-(2,6-diclorofenil)-1H-imidazol-4-il]-2-metil-propan-1-ol



A una suspensión agitada de éster de metilo del ácido 2-[1-(4-bromofenil)-2-(2,6-dilcorofenil)-1H-imidazol-4-il]-2-metil-propiónico (0,65 g, 1,4 mmol) en Et_2O (3,5 ml, anhidro) se agregó gota a gota 2,0 M de solución de borohidruro de litio en THF (1,4 ml, 2,8 mmol) y luego se agregó borato de trimetilo (22 µl, 15% en moles). Después de 3 horas la mezcla de la reacción se enfrió con 1N NaOH (4 ml) y se extrajo con EtOAc (2 x 30 ml). Los extractos combinados se lavaron con

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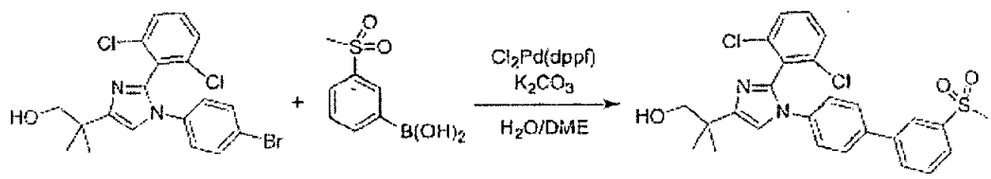
NH_4Cl saturado y solución salina, se secaron (Na_2SO_4), se concentraron y se purificaron mediante cromatografía (sílice, EtOAc/hexano, 15:85 a 50:50) para dar un sólido blanco (0,21 g) que comprende una mezcla de 2:1 del compuesto del título, MS(ES): 439, 440, 443 [M+H]+ y 2-[2-(2,6-diclorofenil)-1-fenil-1H-imidazol-4-il]-2-metl-propan-1-ol, MS(ES): 361, 363 [M+H]+.

El último derivó de la reducción excesiva del compuesto del título en las condiciones dadas. El producto aislado se usó en el paso siguiente sin nueva purificación.

Ejemplo 23c

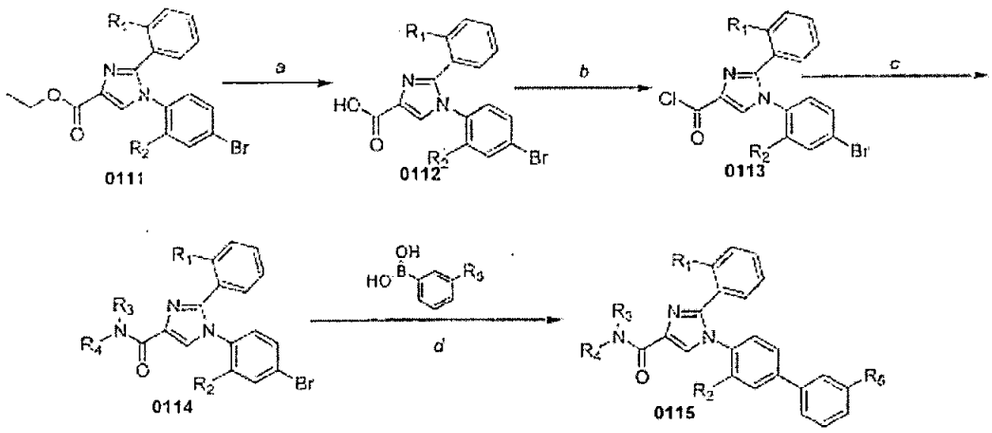
Preparación de 2-[2-(2,6-diclorofenil)-1-(3'-metanosulfonil-4-il)-1H-imidazol-4-il]-2-meti-propan-1-ol



Una mezcla agitada de 2-[1-(4-bromofenil-2-(2,6-diclorofenil)-1H-imidazol-4-il]-2-metil-propan-1-ol (202 mg, 0,46 mmol), ácido 2-metanosulfonil-fenilborónico (92 mg, 0,46 mmol), carbonato de potasio (0,19 g, 1,4 mmol), $Cl_2Pd(dppf).DCM$ (19 mg, 5% en moles) y H_2O (0,35 mL) en DME (2,5 ml) se roció con Argón durante 5 minutos y luego se calentó a 60°C como un matraz sellado. Después de 30 minutos, la mezcla de la

reacción se concentró bajo presión reducida y se purificó mediante cromatografía (sílice, EtOAc/Hexanos, 40:60 a 75:25) para dar el compuesto del título (35 mg) como un sólido blanco. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,10 (d, 1H), 7,91 (d, 1H), 7,85 (d, 1H), 7,66 (m, 1H), 7,60 (d, 2H), 7,29-7,37 (m, 5H), 7,10 (s, 1H), 3,79 (br s, 1H), 3,62 (s, 2H), 3,06 (s, 6H). MS (ES): 515, 517 [M+H]+.

Esquema 11



(a) NaOH acuoso, MeOH; (b) $(COCl)_2$, DMF; (c) R_3R_4NH, $CHCl_3$, DIEA; (d) $PdCl_2dppf$, K_2CO_3, DME, H_2O

En general, los compuestos que contienen amida de la fórmula (0115) se pueden sintetizar siguiendo la metodología mostrada en el Esquema 11. El grupo éster en el compuesto (0111) se puede hidrolizr en condiciones básicas acuosas para dar el ácido carboxílico (0112). El ácido (0112) se puede convertir

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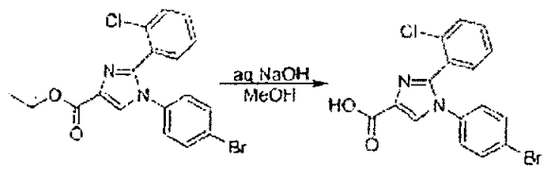
en un ácido /cloruro (0113) usando procedimientos conocidos seguidos por la reacción con una amina primaria o secundaria para proporcionar el intermedio de amida (0114). El intermedio amida (0114) puede pasar por transformaciones de acoplamiento cruzado para dar el 2-biaril-imidazol (0115) correspondiente.

Ejemplo 14

(2,2,2-trifluoro-etil)-amida del ácido 2-(2-cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-carboxílico

Ejemplo 14a



A un matraz de fondo circular de 100 ml se agregó éster de etilo del ácido 1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-carboxílico (1,03 g, 2,54 mmol), MeOH (20 ml) y 1N NaOH acuoso (10 ml). La solución de la reacción se dejó agitar a 45°C durante 1 hora antes del análisis mediante LCMC. La solución de la reacción se diluyó con EtOAc (150 ml), se vertió en un embudo separador y se reaprtió la fase orgánica. La fase acuosa se neutralizó agregando 1N HCl acuoso y se extrajo con EtOAc (70 ml x 2). Una fase orgánica combinada se secó sobre Na_2SO_4, se filtró en un matraz de fondo circular y

646
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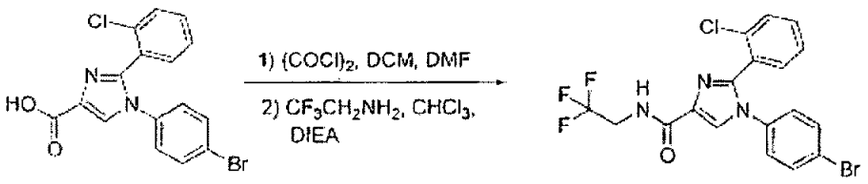
se concentró sobre el rotoevaporador. El residuo crudo se sometió a cromatografía a través de 25 g de una columna de SiO_2 usando un gradiente de fase móvil de 100% Hx a 85% EtOAc para dar 845 mg (88% de rendimiento) del intermedio ácido carboxílico. MS (ES): 378 [M+H]+.

Ejemplo 14b

Preparación de (2,2,2-trifluoro-etil)-amida del ácido 1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-carboxílico

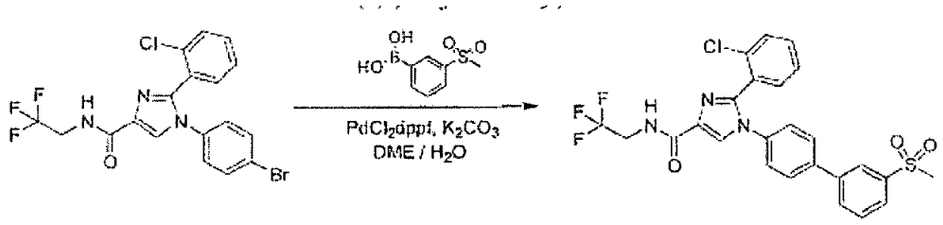


A un matraz de base circular de 100 ml purgado con N_2 se agregó ácido 1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-carboxílico (845 mg, 2,24 mmol) y (10 ml) de DCM anhidro. La solcuión se enfrió a 0°C antes de agregar cloruro de oxalilo (590 µL, 6,7 mmol) y varias gotas de DMF anhidro. La solución de la reacción se dejó agitar calentando a temperatura ambiente durante 2 horas. El solvente y el reactivo en exceso se removieron con agua. Al reiduo de cloruro de ácido crudo se agregó $CHCl_3$ anhidro (15 ml), 2,2,2-trifluoroetilamina (700 mg, 6,70 mmol) y DIEA (1,3 ml, 7,46 mmol). La soluciónde la reacción se dejó agitar a 40°C durante 1 hora. La solución de la reacción se diluyó con DCM (70 ml) y se tranasfirió a un

embudo separador. La solución se lavó con NH_4Cl acuoso (50 ml x 2) y con NaCl acuoso (50 ml). La fase orgánica sesecó sobre Na_2SO_4, se filtró, se concentró en el rotoevaporador y se sometió a cromatografía a través de una columna de 25 g de SiO usando un gradiente de fase móvil de 100% Hx a 70% EtOAc para dar 840 mg (82% de rendimiento) del producto amida. MS (ES): 461 [M+H]+.

Ejemplo 14c

Preparación de (2,2,2-trifluoro-etil)-amida del ácido 2-(2-cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-carboxílico



A un matraz de base circular de 50 ml montado con una columna de Vigreux y barra de agitación magnética se agregó (2,2,2-trifluoro-etil)-amida del ácido 1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-1-carboxílico (249 mg, 540 µmol), ácido 3-metilsulfonilfenil borónico (130 mg, 650 µmol), PdC_2dppf (40 mg, 10% en moles), K_2CO_3 (240 mg, 1,90 mmol), 1,2-dimetoxietano (14 ml) y H_2O (2 ml). La solución de la reacción se dejó agitar a 75°C durante 3 horas. La solución de la reacción se diluyó

648
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con EtOAc (150 ml) y se filtró a través de un embudo Buchner con tampón de Celita para remover Pd usado. El filtrado se transfirió a un embudo separador y se lavó con NH_4Cl acuoso (100 ml) y NaCl acuoso (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró, se concentró sobre el rotoevaporador y se sometió a cromatografía a través de una columna de 25 g de SiO_2 usando un gradiente de fase móvil de 2% EtOAc a 90% EtOAc para dar 212 mg (74% de rendimiento del compueto del título. MS (ES): 534 [M+H]+, 557 [M+Na]+. ^{1}H-NMR (400 MHz, DCM-d_2): δ 8,13 (s, 1H), 7,99 (s, 1H), 7,92 (d, 1H), 7,65 (t, 1H), 7,57 (d, 2H), 7,41-7,34 (m, 3H), 7,24 (d, 2H), 4,11 (q, 2H), 3,08 (s, 3H); ^{19}F NMR (400 MHz, $CDCl_3$) δ 7,24 ppm.

Los siguientes compuestos se prepararon en una forma similar a la descrita en el Ejemplo de procedimiento experimental 14.

- 2-(2-isopropilfenil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-N-(2,2,2-trifluorometil-1H-imidazol-4-carboxamida, MS (ES): 556,3 $[M+H]^+$
- 2-(2,6-diclorofenil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-N-(2,2,2-trifluorometil-1H-imidazol-4-carboxamida, MS (ES): 582,2, 584,2 $[M+H]^+$
- 2-(2,6-diclorofenil)-1-(3'-(etilsulfonil)-3-metillbifenil-4-il)-N-(2,2,2-trifluorometil-1H-imidazol-4-carboxamida, MS (ES): 596,3, 598,3 $[M+H]^+$

- 2-(2,6-diclorofenil)-N,N-dietil-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-carboxamida, MS (ES): 556,3, 558,3 $[M+H]^+$
- 2-(2,6-diclorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-N-(2,2,2-trifluorometil-1H-imidazol-4-carboxamida, MS (ES): 568,2, 578,2 $[M+H]^+$;
- 2-(2,6-diclorofenil)-N-(2-fluoroetil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-carboxamida, MS (ES): 532, 534 $[M+H]^+$;
- 2-(2,6-diclorofenil)-N-etil-1-(3'-(metilsulfonil)bifenil-4-il)-N-1H-imidazol-4-carboxamida, MS (ES): 514,3, 516,3 $[M+H]^+$;
- (2-(2,6-diclorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)(4-metilpiperazin-1il)metanona, MS (ES): 569,2, 571,3 $[M+H]^+$;
- 2-(2,6-diclorofenil)-N-(2-hidroxietil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-carboxamida, MS (ES): 530,3, 5302,3 $[M+H]^+$;
- 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,5-diclorofenil)-N-(2,2,2-trifluoroetil)-1H-imidazol-4-carboxamida, MS (ES): 602,0, 604,0, 606,3 $[M+H]^+$;
- 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(2-fluoroetil)-1H-imidazol-4-carboxamida, MS (ES): 566,3, 568,3, 570,2 $[M+H]^+$;

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- Ácido 2-(1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-carboxamido)acético, MS (ES): 578,3, 580,3, 582,3 $[M+H]^+$;
- 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(2,2,2-trifluoroetil)-1H-imidazol-4-carboxamida, MS (ES): 616,0, 618,0, 620,0 $[M+H]^+$;
- 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(1-hidroxi-2-metilpropan-2-il)-1H-imidazol-4-carboxamida, MS (ES): 592,0, 594,0, 596,2 $[M+H]^+$;
- 1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(1-hidroxi-2-metilpropan-2-il)-1H-imidazol-4-carboxamida, MS (ES): 606,3, 608,3, 610,0 $[M+H]^+$;
- N-terc-butil-1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-carboxamida, MS (ES): 576,3, 578,3, 580,3 $[M+H]^+$;
- 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(2-hidroxietil)-1H-imidazol-4-carboxamida, MS (ES): 564,2, 566,2, 568,3 $[M+H]^+$;
- 1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(2-hidroxietil)-1H-imidazol-4-carboxamida, MS (ES): 578,3, 580,3, 582,2 $[M+H]^+$;

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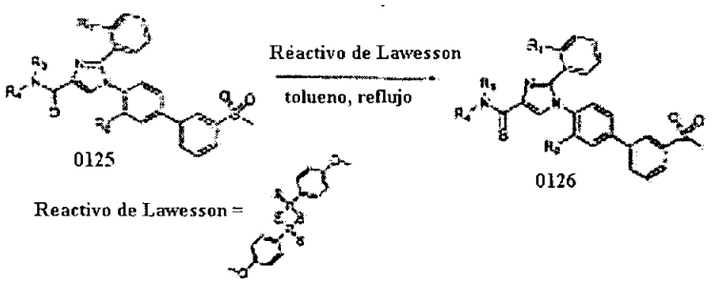
- 1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(2-hidroxi-2-metilpropil)-1H-imidazol-4-carboxamida, MS (ES): 592,3, 594,3, 596,0 $[M+H]^+$;
- 1-(3-cloro-3'-(etilsulfonil)bifenil-4-il)-2-(2,6-diclorofenil)-N-(2-hidroxi-2-metilpropil)-1H-imidazol-4-carboxamida, MS (ES): 606,2, 608,2, 610,2 $[M+H]^+$;
- 2-(2,6-diclorofenil)-N-(1-hidroxi-2-metilpropan-2-il)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-carboxamida, MS (ES): 558,3, 560,3 $[M+H]^+$;
- 2-(2,6-diclorofenil)-1-(3'-(etilsulfonil)bifenil-4-il)-N-(1-hidroxi-2-metilpropan-2-il)-1H-imidazol-4-carboxamida, MS (ES): 572,3, 574,3 $[M+H]^+$;
- N-terc-butil-2-(2,6-diclorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-carboxamida, MS (ES): 542,3, 544,3 $[M+H]^+$.

Esquema 12



En general, las amidas de ácidos carboxílicos de la fórmula (0125) se pueden convertir en el derivado de tioamida (0126)

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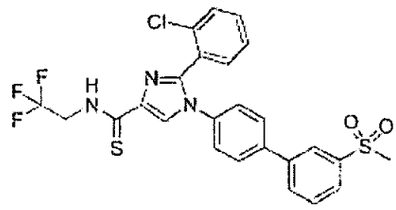
como se muestra en el Esquema 12. La transformación funcional se puede realizar usando un reactivo de tiación adecuado, tal como los reactivos de Laweson o un compuesto relacionado.

Ejemplo 15



Preparación de (2,2,2-trifluoro-etil)-amida del ácido 2-(2-cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-carboxílico

A un matraz de fondo circular de 25 ml montado con una columna de Vigreux y barra de agitación magnética se agregó (2,2,2-trifluoro-etil)-amida del ácido 2-(2-cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-carboxílico (65 mg, 127 μmol), reactivo de Laweson (230 mg, 570 μmol) y tolueno anhidro (6 ml). La solución de la reacción se dejó agitar a reflujo durante 5 horas antes de que el análisis de TLC mostrara la transformación total del material inicial. La solución de la reacción se dejó enfriar a temperatura ambiente antes de agregar una mezcla de 1:1 de benceno y Et_2O. El precipitado resultante se removió mediante filtración al vacío a través de un embudo de Buchner. El filtrado se concentró sobre el rotoevaporador y el residuo crudo se sometió a

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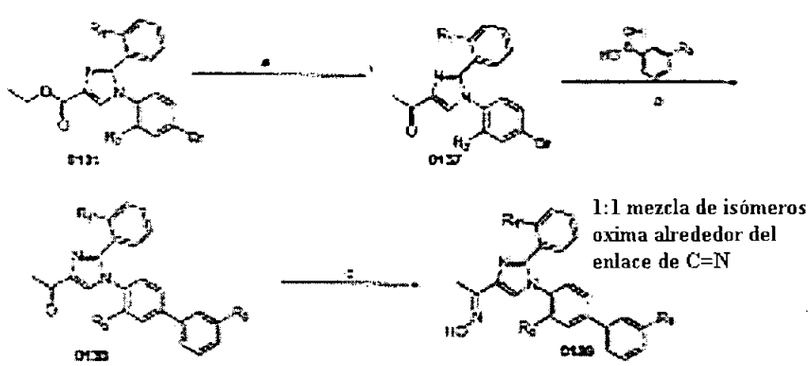
cromatografía a través de una columna de 12 g de SiO_2 usando un gradiente de fase móvil de 100% Hx a 50% EtOAc para dar 55 mg (79% de rendimiento) del compuesto del título. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9,21 (t, 1H), 8,11 (s, 1H), 8,04 (t, 1H), 7,85 (d, 1H), 7,75 (d, 1H), 7,59 (t, 1H), 7,53-7,46 (m, 4H), 7,34-7,31 (m, 3H), 7,18 (d, 2H), 4,56 (m, 2H), 3,02 (s, 3H); ^{19}F NMR (400 MHz, $CDCl_3$) δ 70,8 ppm. MS (ES): 550,3, 552,3 $[M+H]^+$.

Los siguientes compuestos se prepararon en una forma similar a la descrita en el procedimiento experimental del Ejemplo 15:

- 2-(2-isopropilfenil)-(3-metil-3'-(metilsulfonil)bifenil-4-il)-N-(2,2,2-trifluoroetil)-1H-imidazol-4-carboxamida; MS (ES): 577,2 $[M+H]^+$.
- 1-(4-bromofenil)-2-(2-clorofenil)-N-(2,2,2-trifluoroetil)-1H-imidazol-4-carboxamida; MS (ES): 474,0, 476,0 $[M+H]^+$.

Esquema 13



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(a) (i) Me_3Al, tolueno, $MeNHCH_2CH_2NHMe$, reflujo, (ii) HCl acuoso; (b) $PdCl_2dppf$, K_2CO_3, DME/H_2O; (c) H_2NOH-HCl, 2:1 MeOH/H_2O, NaOAc, reflujo

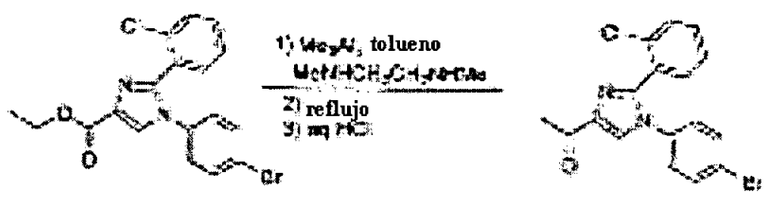
En general, los compuestos que contienen oxima de la fórmula (0139) se pueden preparar como se muestra en el Esquema 13. El intermedio éster de imidazol (0131) se puede convertir en el compuesto sustituido con metilcetona (0137) usando trimetilamonio y un quelante diamino, tal como N,N-dimetil etildiamina. El compuesto (0137) se puede someter al acoplamiento cruzado para instalar el anillo D para dar el compuesto final (0138). El producto sustituido con oxima (0139) se puede preparar mediante la reacción con hidroxilamina en condiciones conocidas.

Ejemplo 16

1-[2-(2-Cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-etanona oxima

Ejemplo 16a

Preparación de 1-[1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-il]-etanona



A un matraz RB de 100 ml purgado con N_2, secado, montado con una columna de Vigreux se agregó tolueno anhidro (20 ml) y N,N-dimetiletilendiamina (2,2 ml, 1,1 equivalente). La solución se enfrió a 0°C antes de agregar gota a gota de una solución 2,0 M de Me_3Al en hexanos (28 ml, 3,1 equivalentes). La solución de la reacción se agitó a temperatura ambiente durante 40 minutos antes de agregar de el éster de etilo del ácido 1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-carboxílico (7,41 g, 18,3 mmol) en una solución de tolueno (10 ml). La solución de la reacción se dejó agitar a reflujo durante 2 horas. La solución de la reacción se enfrió a temperatura ambiente y se enfrió agregando 1N HCl acuoso (10 ml). La solución de la reacción se diluyó con EtOAc, se repartió, se lavó con NaCl acuoso, se secó sobre Na_2SO_4, se filtró, se concentró sobre un Rotoevaporador y se sometió a cromatografía a través de una columna de 80 g de SiO_2 usando un grdiente de fase móvil de 100% Hx al 75% de EtOAc para dar 3,10 g (45% de rendimiento) del intermedio de metil cetona. MS (ES): 376 $[M+H]^+$.

Ejemplo 16b

Preparación de 1-[2-(2-cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-etanona

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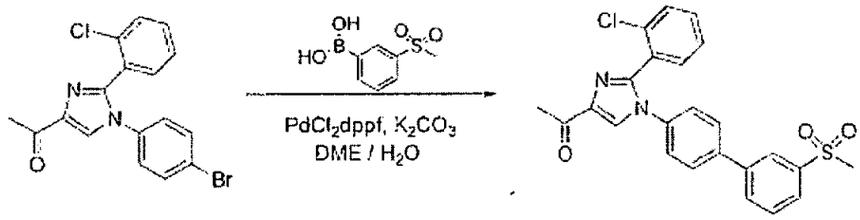

A un matraz de base circular de 50 ml montado con una columna de Vigreux y una barra de agitación magnética se agregó 1-[1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-il]-etanona (270 mg, 719 µmol), ácido 3-metilsulfonilfenil borónico (220 mg, 1,08 mmol), $PdCl_3dppf$ (55 mg, 10% en moles), K_2CO_3 (300 mg, 2,16 mmol), 1,2-dimetoxietano (11 ml) y H_2O (1 ml). La solución de la reacción se dejó agitar a 70°C durante 14 horas. La solución de la reacción se diluyó con EtOAc (150 ml) y se filtró a través de un embudo de Buchner con tampón de Celita para remover el Pd gastado. El filtrado se transfirió a un embudo separador y se lavó con NH_4Cl (100 ml) y NaCl acuoso (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró, se concentró sobre el Rotoevaporador y se sometió a cromatografía a través de una columna de SiO_2 de 25 g usando un gradiente de fase móvil de 100% Hx a 75% de EtOAc para dar 170 mg (52% de rendimiento) del producto. MS (ES): 473 $[M+Na]^+$.

Los siguientes compuestos se sintetizaron en forma similar al procedimiento precedente:

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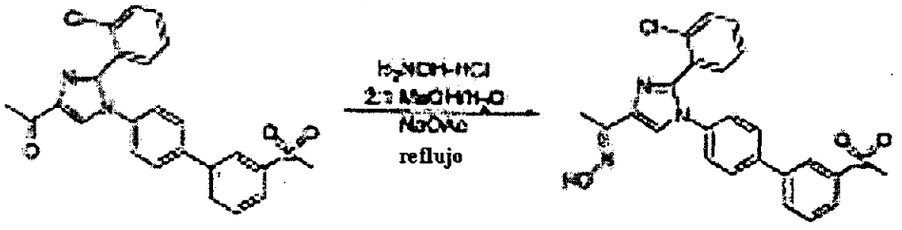
- 1-{1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}-etanona; MS (ES): 485,4 $[M+H]^+$.
- 1-(2-(2,6-diclorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)etanona; MS (ES): 485,3, 487,3 $[M+H]^+$.

Ejemplo 16c

Preparación de 1-[2-(2-Cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-etanona oxima



A un matraz de RB de 50 ml montado con una columna de Vigreux se agregó el compuesto 1-[2-(2-Cloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-etanona (162 mg, 359 µmol), HCl de hidroxilamina (200 mg, 2,87 mmol), acetato de sodio (238 mg, 2,90 mmol), MeOH (12 ml) y H_2O (6 ml). La solución de la reacción se dejó agitar a reflujo durante 2 horas antes del análisis de TLC. La solución de la reacción se diluyó con EtOAc (150 ml), se lavó con NaCl acuoso (100 ml), se repartió, se secó sobre Na_2SO, se filtró y se cncentró sobre el Rotoevaporador. El producto crudo se sometió

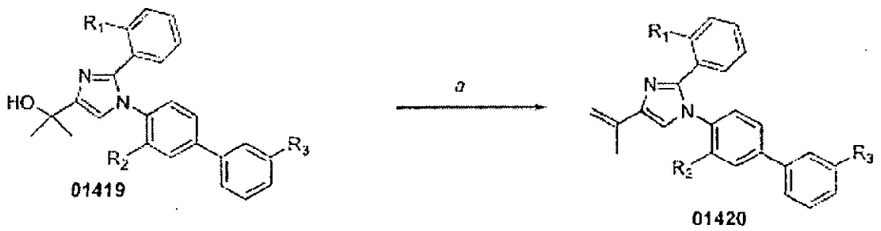
a cromatografía a través de una columna de 25 g de SiO_2 usando un gradiente de fase móvil de 100% Hx al 80% de EtOAc para dar 85 mg (51% de rendimiento) del compuesto del título como una mezcla de isómeros E y Z. Los isómeros se separaron mediante cromatografía con una HPLC de Fase Invertida usando una columna Preparativa de C_{18}. Caracterización para un solo isómero de oxima. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9,86 (s, 1H), 8,15 (t, 1H), 8,02 (d, 1H), 7,90 (d, 1H), 7,85 (s, 1H), 7,80 (d, 2H), 7,72 (t, 1H), 7,64 (d, 1H), 7,47-7,44 (m, 3H), 7,35 (d, 2H). MS (ES): 466,1 $[M+H]^+$.

Los siguientes compuestos se prepararon en forma similar a la descrita en el Ejemplo 16 de procedimiento experimental:

- 1-{1-[3'-(metilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}-etanona oxima; MS (ES): 500,2 $[M+H]^+$.
- 1-{2-(2-clorofenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona oxima; MS (ES): 480,0, 482,0 $[M+H]^+$.
- 1-{2-(2-clorofenil)-1-[3'-(etilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona oxima; MS (ES): 480,0, 482,0 $[M+H]^+$.
- 1-{2-(2-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona oxima; MS (ES): 430,0, 432,0 $[M+H]^+$.

- 1-{2-(2-clorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona oxima; MS (ES): 466,0, 468,0 $[M+H]^+$.
- 1-{2-(2-clorofenil)-1-[4'-(hidroxietil)-3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona oxima; MS (ES): 495,3, 497,3 $[M+H]^+$.
- (E)-1-{2-(2,6-diclorofenil)-1-[3'-(metilsulfonil)bifenil-4-il]-1H-imidazol-4-il}etanona oxima; MS (ES): 500,4, 502,3 $[M+H]^+$.
- (E)-1-{2-(2-etilfenil)-1-(3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)etanona oxima; MS (ES): 460,3 $[M+H]^+$.
- (E)-1-{2-(2-isopropilfenil)-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)etanona oxima; MS (ES): 483,3 $[M+H]^+$.

Esquema 14



(a) HCl, dioxano, Δ o HOAc, tolueno, Δ

En general, imidazol sustituido con carbinol de la fórmula (01419) se puede deshidratar usando métodos conocidos para proporcionar el alqueno (01420) (Esquema 14). La reacción de

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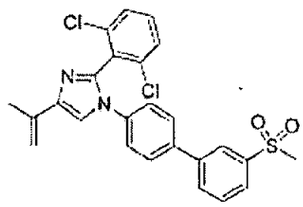
deshidratación se puede realizar usando varios catalizadores de ácidos, tales como HCl o ácido acético, en un sistema de solvente calentado y anhidro.

Ejemplo 17



Preparación de 2-(2,6-dicloro-fenil)-4-isopropil-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol

A un matraz de base circular de 25 ml montado con una columna de Vigreux se agregó 2-[2-(2,6-dicloro-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-propan-2-ol (383 mg, 764 μmol), tolueno anhidro (8 ml) y ácido acético (3,5 ml). La solución de la reacción se dejó agitar a reflujo durante 15 horas. La solución de la reacción enfriada se concentró en vacío, y el residuo se recogió en EtOAc (200 ml) y se lavó con $NaHCO_3$ acuoso (100 ml x 2) y NaCl acuoso (100 ml). La fase orgánica se repartió, se secó sobre Na_2SO_4, se filtró y se concentró en vacío. El producto crudo se sometió a cromtografía a través de una columna de 25 g de SiO_2 usando un gradiente móvil de 100% Hx a 80% de EtOAc para proporcionar

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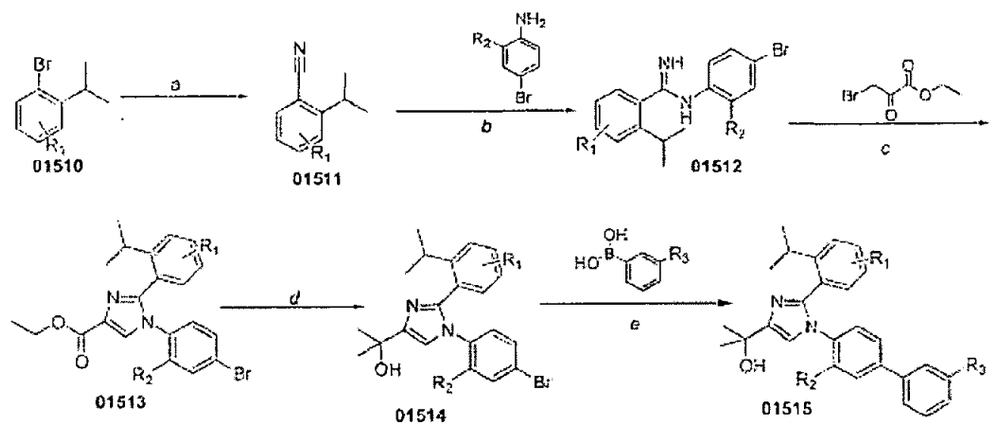
288 mg (78% de rendimiento) del compuesto del título. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8,15 (br s, 1H), 8,08-7,97 (m, 2H), 7,92 (d, 1H), 7,89 (d, 1H), 7,75 (t, 1H), 7,64-7,57 (m, 3H), 7,43 (d, 2H), 5,77 (br s, 1H), 5,10 (br s, 1H), 3,29 (s, 3H), 2,11 (s, 3H). MS (ES): 483,1, 485,1 $[M+H]^+$.

El siguiente compuesto se preparó de acuerdo con este esquema:

- 2-(2,3-diclorofenil)-1-(3'(etilsulfonil)bifenil-4-il)-4-prop-1-en-2-il)-1H-imidazol; MS(ES): 497, 499 $[M+H]^+$.

Esquema 15



(a) CuCN, DMF, reflujo; (b) (i) Me_3Al, tolueno, (ii) reflujo 1 d; (c) (i) EtOH, $NaHCO_3$, (ii) HOAc, reflujo; (d) 4 equivalentes de MeMgBr; (e) $PdCl_2dppf$, K_2CO_3, DME/H_2O

En general, los compuestos de la fórmula (01515), con sustituyentes del anillo A de alquilo de mayor tamaño que Me o

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Et se pueden sintetizar siguiendo la secuencia que se muestra en el Esquema 15. Por ejemplo, la metodología del Esquema 15 puede dar compuestos imidazol con grupos 2-iso-propilo sobre el anillo A de fenilo. En general, la metodología también puede dar compuestos con otros anillos A de fenilo mono o disustituido. Un bromuro de arilo (01510) se puede convertir en un arilnitrilo (01511) mediante la reacción con cianuro de cobre(I). El arilnitrilo puede reaccionar con anilina en la presencia de un ácido de Lewis, tal como trimetilaluminio, para dar la amidina correspondiente (01512). La amidian (1152) puede reaccionar con bromopiruvato de etilo en la presencia de bicarbonato de sodio, seguido por la deshidratación para dar el intermedio imidazol ciclado (01513). La formación de carbinol para proporcionar (01514) y el acoplamiento cruzado de Suzuki se puede usar para dar el compuesto (01515) en una forma similar a aquella descrita en el Esquema 8.

El siguiente compeusto se preparó de acuerdo con este esquema: 2-(2,3-diclorofenil)-1-(3'-(metilsulfonil)bifenil-4-il)-4-(prop-1-en-2-il)-1H-imidazol; MS(ES): 497, 499 $[M+H]^+$.

Ejemplo 18

2-[2-(2-isopropil-fenil)-1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-propan-2-ol

Ejemplo 18a

Preparación de 2-isopropilbenzonitrilo

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A un matraz de base circular de 100 ml purgado con N_2 montado con un condensador se agregó 1-bromo-2-isopropilbenceno (10,0 g, 58,2 mmol), DMF anhidra (26 ml), y CaCN (5,85 g, 65,3 mmol). La suspensión de la reacción se agitó a reflujo bajo N_2 durante 4 horas antes del análisis mediante GCMS. La mezcla de la reacción se enfrió a temperatura ambiente y se vertió en una solución de hielo / NH_4Cl acuoso. Los precipitados resultantes se removieron mediante filtración en vacío a través de un embudo de Buchner. El filtrado acuoso se extrajo con EtOAc (150 ml x 3). La fase orgánica combinada se secó sobre Na_2SO_4, se filtró y se concentró sobre el Rotoevaporador para dar 5,97 g (82% de rendimiento) de 2-isopropilbenzonitrilo. El producto se usó en el paso siguiente sin nueva purificación. GCMS m/z = 145 [M^+].

Ejemplo 18b

Preparación de N-(4-Bromo-fenil)-2-isopropil-benzamidina

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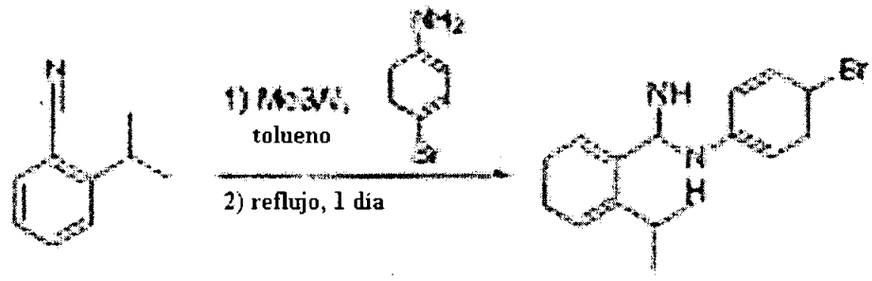

A un matraz de base circular de 100 ml purgado con N_2, seco se agregó 4-bromo-anilina (2,73 g, 15,9 mmol) y tolueno anhidro (40 ml). A la solución a 0°C se agregó, gota a gota, una solución 2,0M de Me_3Al en hexanos (9,4 ml). La solución se dejó agitar, calentando a temperatura ambiente durante aproximadamente 1 hora. A la solución de la reacción se agregó 2-isopropilbenzonitrilo (3,00 g, 20,7 mmol) en una solución de tolueno (15 ml). La solución de la reacción se agregó para agitar a 80°C durante aproximadamente 24 horas. La solución de la reacción se dejó enfriar a temperatura ambiente antes de enfriar vertiendo la solución de la reacción en un Erlenmeyer que contiene una solución 2:1 de $CHCl_3$/MeOH y 100 g de sílice. La suspensión se dejó agitar durante 30 minutos antes de la filtración en un embudo de Buchner bajo vacío. El filtrado se concentró sobre un Erlenmeyer y el residuo resultante se reprecipitó suando una mezcla 10:1 Hx / Et_2O. Los precipitados blancos resultantes se aislaron mediante filtración al vacío para dar 1,98 g (40% de rendimiento) del producto amidina. GCMS m/z = 317 [M^+].

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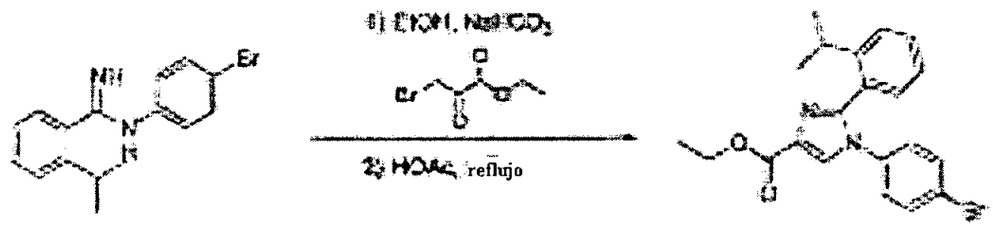
Ejemplo 18c

Preparación de éster de etilo del ácido 1-(4-Bromo-fenil)-2-(2-isopropil)-1H-imidazol-4-carboxílico



A un matraz de base circular de 250 ml montado con un condnesador se agregó N-(4-bromo-fenil)-2-isopropil-benzamidina (1,94 g, 6,11 mmol), etil bromopiruvato (1,54 ml, 12,2 mmol), bicarbonato de sodio (1,02 g, 12,2 mmol) e isopropanol (45 ml). La suspensión de la reacción se dejó agitar a 80°C durante aproximadamente 2 horas. La solución de la reacción se decantó en un matraz de base circular limpio y se concentró en vacío. El residuo resultante se disolvió en ácido acético (25 ml) y la solución se dejó agitar a reflujo durante aproximadamente 2 horas. La solución se se concentró en vacío, y el residuo producido se recogió en EtOAc (200 ml) y se lavó con NaCl acuoso (200 ml x 2) y $NaHCO_3$ acuoso (100 ml). La fase orgánica se repartió, se secó sobre Na_2SO_4, se filtró, se concentró y se sometió a cromatografía a través de una columna de 40 g de SiO2 usando un gradiente móvil de 100% Hx a 70% de

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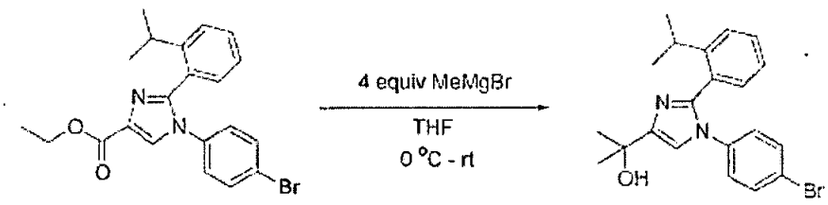
EtOAc para dar 1,90 g (75% de rendimiento) del compuesto del título. MS (ES): 414,0 $[M+H]^+$.

Ejemplo 18d

Preparación de 2-[1-(4-bromo-fenil)-2-(2-isopropil-fenil)-1H-imidazol-4-il]-propan-2-ol



A un matraz de base circular purgado con N_2, seco que contiene éster de etilo del ácido 1-(4-bromo-fenil)-2-(2-isopropil-fenil)-1H-imidazol-4-carboxílico (1,87 g, 4,52 mmol) se agregó THF anhidro (55 ml). La solución se enfrió a 0°C antes de agregar una solución 3,0 M de bromuro de metilmagnesio. La reacción se agitó 1 hora a temperatura ambiente antes de enfriar con NH_4Cl acuoso (30 ml). La fase orgánica se repartió, se secó sobre Na_2SO_4, se filtró y se concentró en vacío. El producto crudo se sometió a cromatografía a través de una columna de SiO_2 usando un gradiente móvil al 100% Hx al 80% de EtOAc para dar 1,19 g (66% de rendimiento) de 369-45.

Ejemplo 18e

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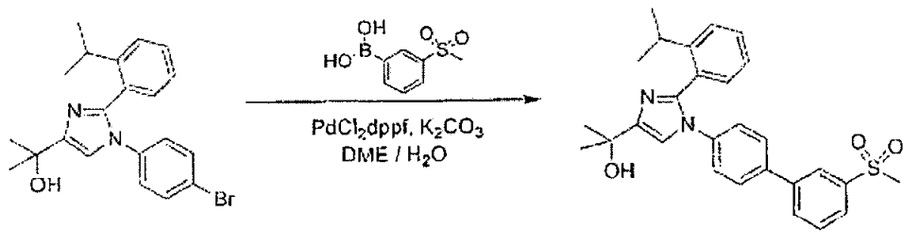
Preparación de 2-[2-(2-isopropil-fenil)1-(3'-metanosulfonil-bifenil-4-il)-1H-imidazol-4-il]-propan-2-ol



A un matraz de base circular de 50 ml montado con una columna de Vigreux y una barra de agitación magnética se agregó 2-[1-(4-bromo-fenil)-2-(2-isopropil-fenil)-1H-imidazol-4-il]-propan-2-ol (297 mg, 743 µmol), ácido 3-(metilsulfonilfenil borónico (193 mg, 968 µm), $PdCl_2dppf$ (60 mg, 10% en moles), K_2CO_3 (310 mg, 2,23 mmol), 1,2-dimetoxietano (14 ml) y H_2O (4 ml). La solución de la reacción se dejó agitar durante 80°C durante 2 horas. La solución de la reacción se diluyó con EtOAc (150 ml) y se filtró a través de un embudo de Buchner con tampón de Celita para remover el Pd gastado. El filtrado se transfirió a un embudo separador y se lavó con NH_4Cl acuoso (100 ml) y NaCl acuoso (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró, se concentró sobre un Rotoevaporador y se sometió a cromatografía a través de una columna de SiO_2 de 25 g usando un gradiente de fase móvil del 100% Hx al 90% de EtOAc para dar 303 mg (86% de rendimiento) del compuesto del título. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8,14 (s, 1H), 8,02 (d, 1H), 7,89 (d, 1H), 7,89 (d, 1H), 7,78 (d, 2H), 7,72 (t, 1H),

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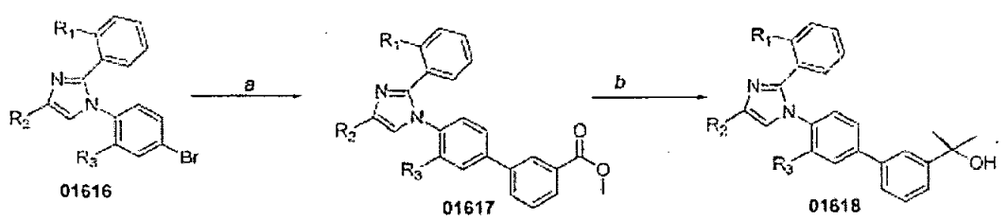
7,37-7,34 (m, 3H), 7,26 (d, 2H), 7,18-7,16 (m, 2H), 4,84 (s, 1H), 3,26 (s, 3H), 2,85 (sept, 1H), 1,50 (6H), 0,86 (d, 6H). MS (ES): 475,4 $[M+H]^+$, 497,5 $[M+Na]^+$.

Los siguientes compuestos se prepararon en forma similar a la descrita en el Ejemplo de procedimiento experimental 18:

- 2-(1-(3'-(etilsulfonil)bifenil-4-il)-2-(2-isopropilfenil)-1H-imidazol-4-il)-propan-2-ol; MS (ES): 489,4 [M+H], 511,4 $[M+Na]^+$
- 2-(1-(3-cloro-3'-(metilsulfonil)bifenil-4-il)-2-(2-isopropilfenil)-1H-imidazol-4-il)-propan-2-ol; MS (ES): 509,3, 511,3 $[M+H]^+$
- 2-(2-(2-isopropil-1-(3-metil-3'-(metilsulfonil)bifenil-4-il)-1H-imidazol-4-il)-propan-2-ol; MS (ES): 489,3, 511,4 $[M+Na]^+$
- 2-(1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-2-(2-isopropilfenil)-1H-imidazol-4-il)-propan-2-ol; MS (ES): 50,4 $[M+H]^+$

Esquema 16



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(a) Acoplamiento de Suzuki; (b) 4 equivalentes de MeMgBr, tolueno

En general, los compuestos de la fórmula (01618) se puedne sintetizar como se muestra en el Esquema 16. El método comprende usar un compuesto de anillo D sustituido con metileno, tal como el ilustrado con el compuesto (01617). El éster del anillo D (01617) se puede convertir en un compuesto dimetilcarbinol (01618) mediante la reacción con un exceso molar de bromuro de metilmagnesio. La transformación se puede realizar cuando R_2 es un grupo éster de carbinol. Cuando R_2 es un grupo éster, cuatro equivalentes de bromuro de metilmagensio se pueden uasr para preparar le versión de bis-carbinol del compuesto (01618).

Ejemplo 19

1-{2-(2-Cloro-fenil)-1-[3'-(1-hidroxi-1-metil-etil)-bifenil-4-il]-1H-imidazol-4-il}-propan-2-ol

Ejemplo 19a

Preparación de éster de metilo del ácido 4'-[2-(2-cloro-fenil)-4-(1-hidroxi-1-metil-etil)-imidazol-1-il]-bifenil-3-carboxílico

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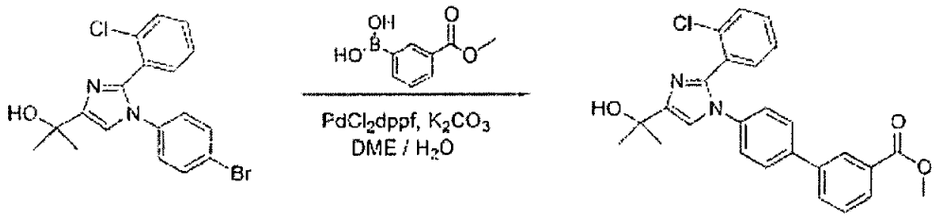
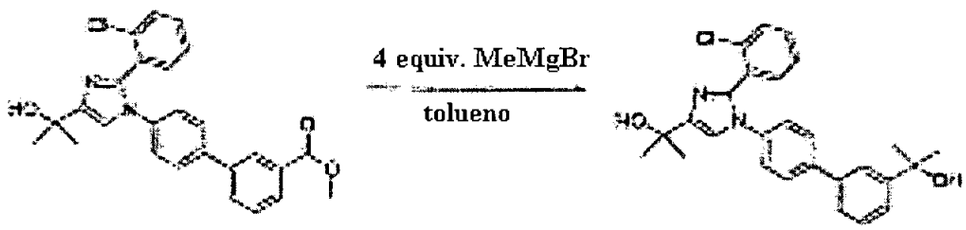


A un matraz de base circular de 50 ml montado con una columna de Vigreux y una barra de agitación magnética se agregó 2-[1-(4-bromo-fenil)-2-(2-cloro-fenil)-1H-imidazol-4-il]-propan-2-ol (275 mg, 702 µmol), ácido 3-metoxicarbonilfenil borónico (164 mg, 913 µmol), $PdCl_3dppf$ (51 mg, 10% en moles), K_2CO_3 (290 mg, 2,11 mmol), 1,2-dimetoxietano (13 ml) y H_2O (1,5 ml). La mezcla de la reacción se dejó agitar a 70°C durante aproximadamente 2 horas. La solución de la reacción se diluyó con EtOAc (150 ml) y se filtró a través de un embudo de Buchner con tampón de Celita para remover el Pd gastado. El filtrado se transfirió a un embudo separador y se lavó con NH_4Cl acuoso (100 ml) y NaCl acuoso (100 ml). La fase orgánica se secó sobre Na_2SO_4, se filtró, se concentró sobre el Rotoevaporador y se sometió a cromatografía a través de una columna de SiO_2 de 25 usando un gradiente de fase móvil de 100% Hx a 90% de EtOAc para dar 122 mg (39% de rendimiento) del producto. MS (ES): 446,3, 448,3 $[M+H]^+$.

Ejemplo 19b

Preparación de 2-{2-(2-cloro-fenil)-1-[3'-(1-hidroxi-1-metil-etil)-bifenil-4-il]-1H-imidazol-4-il}-propan-2-ol



A un matraz de fondo circular de 50 ml purgado con N_2, seco se agregó éster de metilo del ácido 4'-[2-(2-cloro-fenil)-4-(1-hidroxi-1-metil-etil)-imidazol-1-il]-bifenil-3-carboxílico (100 mg, 225 µmol), anhidro y tolueno (1 ml). A la solución a 0°C se agregó una solución 1,4 M de bromuro de metilmagnesio (640 µl). La solución de la reacción se dejó agitar a temperatura ambiente durante aproximadamente 1 hora. La reacción se enfrió agregando NH_4Cl acuoso (20 ml). La fase orgánica se repartió, se secó sobre Na_2SO_4, se filtró, y se concentró en vacío. El residuo crudo se sometió a cromatografía a través de una columna de 12 g de SiO_2 usando un gradiente del 100% Hx al 100% de EtOAc para dar 45 mg (45% de rendimiento) del compuesto del título. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7,70 (s, 2H), 7,55 (d, 2H), 7,55 (d, 2H), 7,48-7,38 (m, 5H), 7,35 (s, 1H), 7,33 (m, 1H), 7,18 (s, 1H), 7,16 (s, 1H), 1,73 (s, 6H), 1,62 (s, 6H). MS (ES): 447,4 $[M+H]^+$, 469,3 $[M+Na]^+$.

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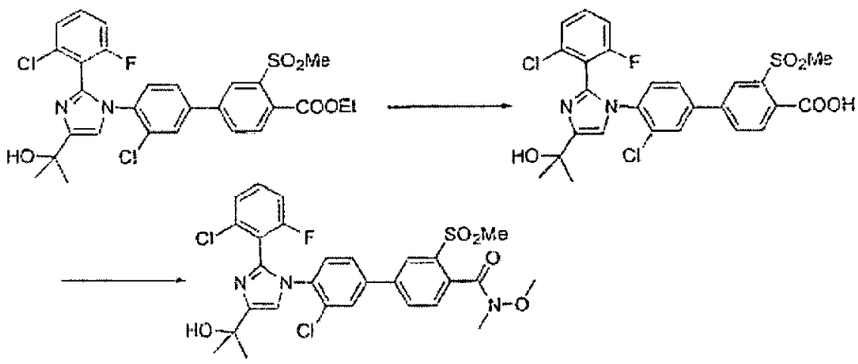
Los siguientes compuestos se prepararon en forma similar a aquella descrita en el Ejemplo de procedimiento experimental 19:

- 1-(3-cloro-3'-(2-hidroxipropan-2-il)bifenil-4-il)-2-(2,6-diclorofenil)-N-(1-hidroxi-2-metilpropan-2-il)-1H-imidazol-4-carboxamida; MS (ES): 572,3, 574,3, 576,3 $[M+H]^+$.
- 2-{2-(2,6-diclorofenl)-1-[3'-(1-hidroxi-1-metletil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS (ES): 481 $[M+H]^+$, 503 $[M+Na]^+$

Ejemplo 20

Preparación 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-N-metil-N-(metiloxi)-3-(metilsulfonil)bifenil-4-carboxamida



Etil 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-carboxilato se preparó como se describen en el Ejemplo 9. En

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un matraz de 500 ml se pesaron 11,19 g (18,92 mmol) de éster, 100 ml de THF, 100 ml de metanol y 19,0 ml de 3,0 M $LiOH-H_2O$. La suspensión resultante se agitó a temperatura ambiente durante 21 horas y luego se concentró en vacío. El residuo se trató con acetato de etilo y 1,0 M HCl y la suspensión resultante se filtró de sólidos. El filtrado se colocó en un embudo separador y el acetato de etilo se separó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. Los sólidos se recogieron mediante filtración se agregaron y los sólidos combinados sesecaron bajo alto vacío para dar ácido 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-carboxílico como un sólido incoloro, y dio 7,36 g (69%); MS (ES): 563 $[M+H]^+$.

También se recuperó como un subproducto minoritario el ácido 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-metiletenil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-carboxílico; MS (ES): 545 y 547 $[M+H]^+$.

En un frasco de 8 ml se pesaron 68 mg (697 µmol) de clorhidrato de N,O-Dimetil-hidroxilamina, y 257 m (279 µmol) de sólido. Luego los sólidos se trataron con 710 µl de 0,5 M solución de hexafluorofosfato de O-(benzotiazol-1-il)-N,N,N',N'-

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tetrametiluronio en DMF y se agregaron 200 µl de diisopropiletilamina. La reacción se agitó a temperatura ambiente durante 20 horas y luego se lavó en un embudo separador con acetato de etilo y 1M HCl. El acetato de etilo se separó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El producto se purificó mediante cromatografía rápida de gel de sílice (Biotage, 12,5 x 150 mm de SiO_2, elución de gradiente desde 100% de hexanos al 100% de acetato de etilo durante 0,5 hora). Las fracciones aproopiadas se combinaron y se concentraron en vacío para dar el producto como un aceite incoloro, rendimiento: 85 mg (47%); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8,26 (s, 1H), 8,19 (d, J=8 Hz, 1H), 8,15 (s, 1H), 7,87 (d, J= 6Hz, 1H), 7,72 (d, J= 8 Hz, 1H), 7,53 (q, J= 6 Hz, 1H), 7,4-7,5 (m, 3H), 7,31 (t, J= 8 Hz, 1H), 3,39 (s, 3H), 3,32 y 3,36 (cada s, 3H), 2,75 (s, 3H), 1,58 (s, 6H); MS (ES): 606 $[M+H]^+$.

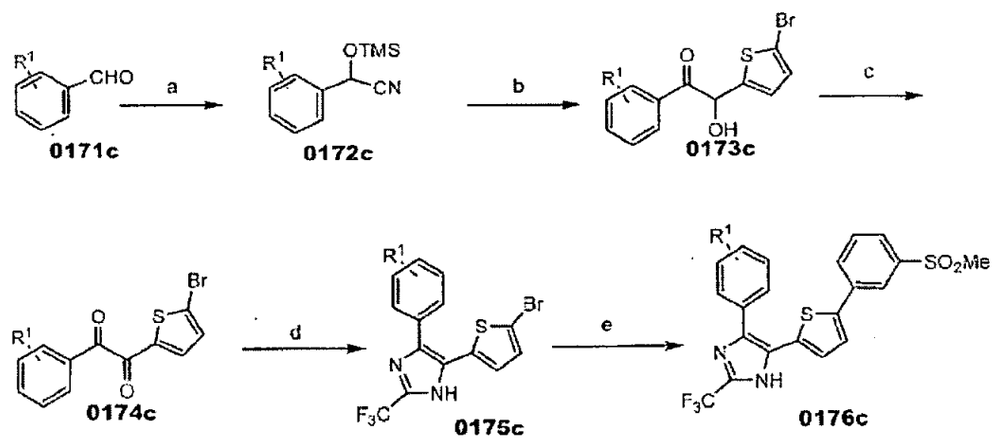
En forma similar a la descrita, los siguientes ejemplos dela invención se prepararon sustityendo un reactivo apropiado:

- 5'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)bifenil-4-carboxamida; MS (ES): 562 $[M+H]^+$;

- 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-N,N-dimetil-3-(metilsulfonil)bifenil-4-carboxamida; MS (ES): 590 $[M+H]^+$;
- 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-N-etil-3-(metilsulfonil)bifenil-4-carboxamida; MS (ES): 590 $[M+H]^+$;
- 1-{2-[2-(2-cloro-6-fluorofenil)-1-[3'-cloro-3'-(metilsulfonil)-4'-(morfolin-4-ilcarbonil)bifenil-4-il]-1H-imidazol-4-il}propan-2-ol; MS (ES): 632 $[M+H]^+$;
- 3'-cloro-4'-[2-(2-cloro-6-fluorofenil)-4-(1-hidroxi-1-metiletil)-1H-imidazol-1-il]-3-(metilsulfonil)-N-(fenilmetil)bifenil-4-carboxamida; MS (ES): 652 $[M+H]^+$.

Esquema 17

Imidazol 2,4-5-trisustituido (Isómero IIc y tautómero IId)



Reactivos y condiciones: (a) TMSCN, ZnI_2, temperatura ambiente; (b) 5-bromotiofen-2-carboxaldehído, LiHMDS, THF, -78°C; (c)

Bi_2O_3, HOAc, 90°C; (d) NH_4OAc, $CF_3CH(OH)(OH)$, AcOH, reflujo; (e) $ArB(OH)_2$, K_2CO_3, $PdCl_3(dppf)$, DME/H_2O, 80°C.

Los presentes compuestos imidazol de la fórmula (0176c) se sintetizan de acuerdo con la secuencia descrita en el Esquema 3. Un aldehído (0177c) tal como 2-clorobenzaldehído se convierte en la cianohidrina protegida de la fórmula (0172c) mediante la reacción con cianuro de trilalquilsililo, tal como cianuro de trimetilsililo (TMSCN), en la presencia de un catalizador tal como yoduro de zinc. La reacción de la cianohidrina (0172c) con un aldehído tal como 5-bromotiofeno-2-caroxaldehído, bajo una base resistente produce benzoína de la fórmula (0173c). La oxidación de la benzoina con un oxidante adecuado tal como óxido de bismuto proporciona la dicetona de la fórmula (0174c), que posteriormente reacciona con acetato de amonio y el aldehído apropiado o su equivalente tal como etil hemiacetatl de trifluoroacetaldehído para dar 1H-imidazol de la fórmula (0175c). En una reacción de acoplamiento mediada por paladio, por ejemplo una reacción Suzuki, los compuestos de la fórmula (0175c) luego reaccionan con un reactivo de boronato o ácido borónico para dar compuestos de la fórmula (0176c) después de los procedimientos de aislamiento comunes.

Ejemplo 21

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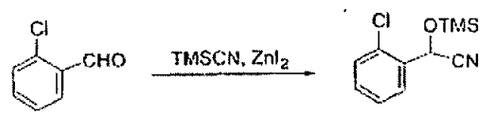
4-(2-clorofenil)-5-(5-(3-(metilsulfonil)fenil)tiofen-2-il)-2-(trifluorometil)-1H-imidazol

Ejemplo 21a

Preparación de (2-cloro-fenil)-trimetilsilanilloxi-acetonitrilo



Bajo una atmósfera de nitrógeno, se colocó yoduro de zinc anhidro (30 mg, 0,1 mmol) en un matraz seco. A 0°C se agregó cianuro de trimetilsililo (5,2 g, 52,5 mmol), seguido por 2-clorobenzaldehído (7,0 g, 50 mmol). La mezcla se agitó a 0°C durante 3 horas, luego a temperatura ambiente toda la noche. Se agregó éter etílico, y la mezcla se lavó con agua y solución salina, se secó sobre Na_2SO_4 y se concentró en vacío para dar un aceite marrón (10,95 g, rendimiento del 91%), que se usó directamente para el paso siguiente sin nueva purificación. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5,80 (s, 1H), 7,38 (m, 3H), 7,73 (dd, 1H).

Ejemplo 21b

Preparación de 2-(5-Bromo-tiofen-2-il)-1-(2-cloro-fenil)-2-hidroxi-etanona

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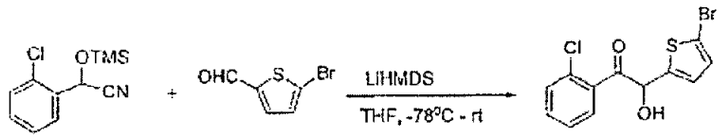

Bajo una atmósfera de nitrógeno, a una solución (-78°C) de bis(trimetilsilil)amida de litio (8,05 ml, solución 1,0M en THF, 8,05 mmol) se agregó una solución de (2-cloro-fenil)-trimetilsulfaniloxi-acetonitrilo (1,69 g, 7 mmol) en tetrahidrofurano (10 ml) gota a gota durante 10 minutos. Después de agitar durante otros 30 minutos, se agregó gota a gota una solución de 5-bromotiofen-2-carboxaldehído en tetrahidrofurano (10 ml). La reacción se agitó toda la noche desde -78°C hasta alcanzar la temperatura ambiente, luego se enfrió agregando 3N HCl (20 ml) y calentando a 40°C durante 5 horas. Después de enfriar, la mezcla se repartió entre éter etílico y agua. La capa orgánica se agitó con 1M NaOH (30 ml) durante 2 horas, y las capas se separaron. La capa orgánica se lavó con solución salina, se secó sobre Na_2SO_4 y se concentró en vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc, 8/2) para dar un aceite marrón (320 mg, 14% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4,35 (d, 1H), 6,12 (d, 1H), 7,02 (d, 1H), 7,26 (m, 2H), 7,41 (d, 1H), 7,44 (dd, 1H).

Ejemplo 21c

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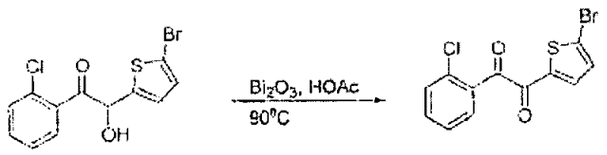
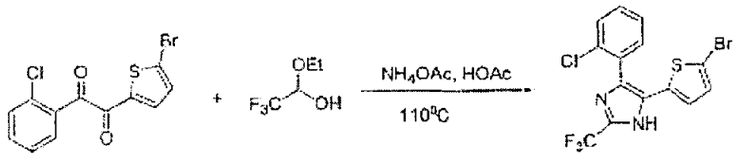
Preparación de 1-(5-bromo-tiofen-2-il)-2-(2-cloro-fenil)-etano-1,2-diona



Una mezcla de benzoína preparada como se describió anteriormente (316 mg, 0,95 mmol) y óxido de bismuto (560 mg, 1,2 mmol) en ácido acético (5 ml) se calentó a 90°C durante 5 horas. La mezcla de la reacción caliente se filtró a través de celita y el filtrado se concentró en vacío. El residuo marrón se redisolvió en metanol caliente y luego se filtró. El filtrado se evaporó para dar un aceite marrón (311 mg, 99% de rendimiento), que se usa directamente para el paso siguiente sin nueva purificación. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7,21 (d, 1H), 7,43 (m, 1H), 7,45 (m, 1H), 7,54 (m, 1H), 7,70 (d, 1H), 7,77 (dd, 1H).

Ejemplo 21d

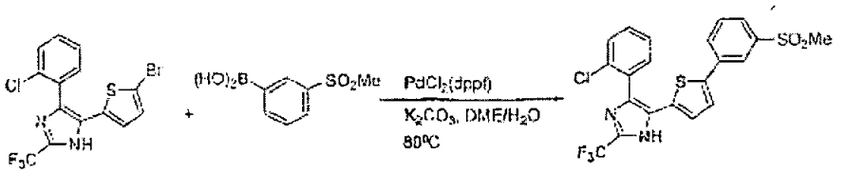
Preparación de 5-(5-bromo-tiofen-2-il)-4-(2-cloro-fenil)-2-trifluorometil-1H-imidazol



Una mezcla de dicetona (311 mg, 0,55 mmol), acetato de amonio (366 mg, 4,75 mmol) y etil hemiacetal de trifluoroacetaldehído (684 mg, 4,75 mmol) en 5 ml de ácido acético se calentó a 110°C durante 10 horas bajo una atmósfera de nitrógeno. Todo el solvente se removió bajo vacío, y el residuo se redisolvió en dicolorometano y se filtró. El filtrado se concentró, y luego se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc, 8/2) para dar un sólido rosa claro (141 mg, 36% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6,81 (d, 1H), 6,87 (d, 1H), 7,38 (t, 1H), 7,49 (m, 2H), 7,56 (d, 1H), 9,55 (s, 1H).

Ejemplo 21e

Preparación de 4-(2-cloro-fenil)-5-[5-(3-metanosulfonil-fenil)-tiofen-2-il]-2-trifluorometil-1H-imidazol



5-(5-bromo-tiofen-2-il)-4-(2-cloro-fenil)-2-trifluorometil-1H-imidazol (70 mg, 0,17 mmol), ácido (3-metilsulfonil)fenilborónico (69 mg, 0,34 mmol), carbonato de potasio (106 mg, 0,77 mmol) y $PdCl_2$(dppf).CH_2Cl_2 (14 mg, 0,017 mmol) se mezcló con 2 ml 9:1 (v/v) DME/HO, luego se calentó a 80°C durante toda la noche. Todo el solvente se removió en

680

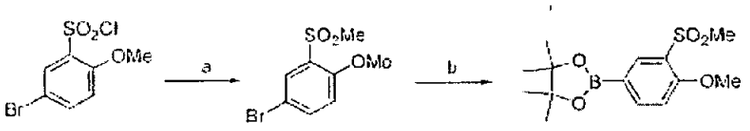
vacío. El residuo se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc, 6/4) para dar un sólido blanco (25 mg, 30% de rendimiento). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3,07 (s, 3H), 7,00 (d, 1H), 7,12 (m, 1H), 7,51 (m, 5H), 7,81 (m, 2H), 8,10 (t, 1H), 9,65 (s, 1H).

Todos siguientes compuestos se prepararon en forma similar usando aldehídos apropiados como materiales iniciales:

- 4-(2-cloro-fenil)-5-[3'-(metilsulfonil)bifenil-4-il]-2-(trifluorometil)-1H-imidazol; 477,1, 479,3 $[M+H]^+$;
- 4'-[4-(2-clorofenil)-2-(trifluorometil)-1H-imidazol]bifenil-3-sulfonamida; 478,0 $[M+H]^+$;
- 3-{5-[4-(2-clorofenil)-2-(trifluorometil)-1H-imidazol]-5-il]-2-tienil}bencenosulfonamida; 484,0 $[M+H]^+$;

Ejemplo 22

Preparación de 2-(4-metoxi-3-(metilsulfonil)fenil]-4,4,5,5-tetrametil-1,3,2-dioxaborolano



a) $NaHCO_3$, Na_2SO_3, H_2O, 85°C; b) Bis(pinacolato)diboro, Pd(dppf), KOAc, DMSO, 100°C

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En un matraz de 1L se pesaron 41,4 g de sulfito de sodio, 29 g de bicarbonato de sodio y 175 ml de agua. La suspensión se agitó a 80°C-85°C y cloruro de sulfonilo (50 g) se agregó en porciones durante 3 horas. Se continuó calentando durante 3 horas luego la reacción se dejó reposar a temperatura ambiente durante 3 días. El intermedio sulfinato se recogió mediante filtración y se agregó agua luego se secó bajo alto vacío. Los sólidos secos (45 g) se devolvieron a un matraz de 1 L junto con 28,0 g de bicarbonato de sodio, 25 ml de sulfato de dimetilo y 63,75 ml de agua. La suspensión resultante se calentó a 120°C-130°C donde se hizo una solución, durante 20 horas y luego se se enfrió y se lavó en un embudo separador con acetato de etilo y agua. El acetato de etilo se separó, se lavó con solución salina, se secaron (Na_2SO_4) y se concentró en vacío. El producto se precipitó desde diclorometano con hexanos y se secó bajo alto vacío para dar el intermedio 4-bromo-2-metanosulfonil-1-metoxi-benceno como un polvo incolor; rendimiento: 31,1 g (67%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,08 (2, 1H), 7,69 (d, J=8 Hz, 1H), 6,96 (d, J=8 Hz, 1H), 4,00 (s, 3H), 3,21 (s, 3H).

En un matraz de 500 ml se pesaron 15,48 g (58,4 mmol) de bromuro, 23 g de boronato, 21 g de acetato de potasio, 5 g de diclorometano de dicloro[1,1'-bis(difenilfosfonio)ferroceno]paladio (II) agregado y 150 ml

de DMSO. La suspensión resultante se calentó a 100°C durante 20 horas, luego se enfrió y se diluyó con 200 ml de acetato de etilo y 200 ml de agua. La suspensión se filtró a través de celita para remover los sólidos y el filtrado se transfirió a un embudo separador. La fase acuosa se separó y se lavó con acetato de etilo. Los lavados de acetato de etilo se cmbinaron, se lavaron con solución salina, se secaron (Na_2SO_4) y se concentraron en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm SiO_2, elución de gradiente desde 100% de hexanos a 100% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío. El producto purificado parcialmente se disolvió en acetato de etilo y se precipitó con hexanos. El 2-(3-metanosulfonil-4-metoxi-fenil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano se recuperó como un polvo débilmente amarillo, rendimiento: 12,56 g (77%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,43 (s, 1H), 8,01 (d, J=8 Hz, 1H), 7,03 (d, J=8 Hz, 1H), 4,02 (s, 1H), 3,20 (s, 3H), 1,33 (s, 12H).

Ejemplo 23

Preparación de etil 2-(metilsulfonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxoborolan-2-il)benzoato

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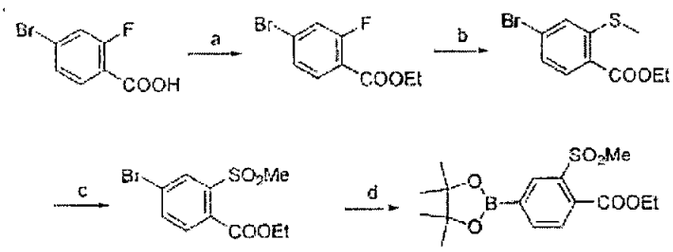

a) EDCI, DMAP, EtOH, CH_2Cl_2, 45°C; b) NaSMe, THF, 80°C; c) MCPBA, CH_2Cl_2, 25°C; d) Bis(picolinato)diboro, Pd(dppf), KOAc, DMSO, 85°C.

En un matraz de 1 L se pesaron 24,66 g (113 mmo) de ácido, 26,3 g (138 mmol) de EDCI, 1,7 g de DMAP, 425 ml de diclorometano, y 25 ml de etanol. La solución resultante se calentó a 40°C-45°C durante 24 horas, luego se concentró en vacío para remover diclormetano. El residuo se lavó en un embudo separador con acetato de etilo y 1M HCl. El acetato de etilo se separó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El intermedio éster de etilo del ácido 4-bromo-2-fluoro-benzoico como un aceite incoloro, rendimiento. 24,99 g (89,8%).

El éster se trató con 12,2 de tiometóxido de sodio y 200 ml de THF y la suspensión resultante se calentó a 80°C-85°C durante 5 horas. La reacción luego se concentró para remover THF y se lavó en un embudo separador con acetato de etilo y 1 M HCl. El acetato de etilo se separó, se lavó con solución salina, se

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secó (Na_2SO_4) y se concentró en vacío y dio el intermedio éster de etilo del ácido 4-bromo-2-metilsulfonil-benzoico como un sólido gris claro, rendimiento: 27,5 g (99%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7,86 (d, J= 8 Hz, 1H), 7,86 (s, 1H), 7,28 (d, J=8 Hz, 1H), 4,38 (q, J=7 Hz, 2H), 2,45 (s, 3H), 1,39 (t, J= 7 Hz, 3H).

En un matraz de 1 L se pesaron 15,0 g de éster de etilo del ácido 4-bromo-2-metilsulfonil-benzoico (54,5 mmol), 200 ml de diclorometano y 28,0 g de MCPBA (77% max, Aldrich) se agregó en porciones a temperatura ambiente. La suspensión resultante se agitó a temperatura ambiente durante tres días, luego se concentró en vacío para remover diclorometano. El residuo se lavó en un embudo separador con acetato de etilo y 1,0 M NaOH. El acetato de etilo se separó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El éster de etilo del ácido intermedio 4-bromo-2-metanosulfonil-benzoico se recuperó como un aceite incoloro que se cristalizó en reposo, rendimiento: 16,3 g (97%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,27 (s, 1H), 7,82 (d, J= 8 Hz, 1H), 7,60 (d, J=8 Hz, 1H), 4, 44 (q, J=7 Hz, 2H), 3,38 (s, 3H), 1,41 (t, J= 7 Hz, 3H).

El éster de etilo del ácido 4-bromo-2-metanosulfonil-borónico (16,3 g, 53 mmol) se pesó en un matraz con 21 g de

686
685

bis(pinacolato) diboro, 19 g de acetato de potasio, 5 g de diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) agregado, y 150 ml de DMSO. La suspensión resultante se calentó a 80°C-86°C durante 2 horas, luego se diluyó con 200 ml de agua, 200 ml de acetato de etilo, y la mezcla de la reacción se filtró a través de celita para remvoer sólidos. El filtrado se se transfirió a un embudo separador y la fase acuosa se separó y se lavó con acetato de etilo. El acetato de etilo se combinó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm de SiO_2, elución de gradiente desde 100% de hexanos al 40% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío dando el producto como un sólido incoloro, rendimiento: 12,65 g (67%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,52 (s, 1H), 8,08 (d, J= 8 Hz, 1H), 7,65 (d, J=8 Hz, 1H), 4,45 (q, J=7 Hz, 2H), 3,33 (s, 3H), 1,42 (t, J= 7 Hz, 3H), 1,35 (s, 12H).

Ejemplo 24

Preparación de (2-(metilsulfonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)metanol

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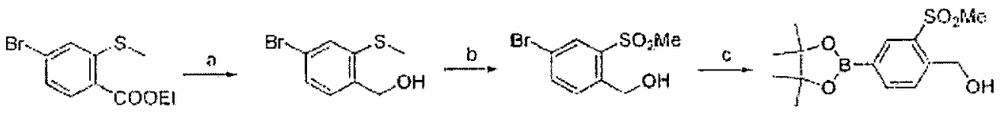

a) $LIBH_4$, THF, 85°C; b) MCPBA, CH_2Cl_2, 25°C; c) bis(pinacolato)diboro, Pd(dppf), KOAc, DMSO, 100°C.

El éster de etilo del ácido 4-bromo-2-metanosulfonil-borónico se preparó como se describió en el Ejemplo 23. En un matraz de 1L se pesaron 27,5 g de éster (99,9 mmol) y 150 ml de THF. Luego se agregó una solución de 2,0M $LiBH_4$ en THF (50 ml, 100 mmol) y la reacción se calentó a 80°C-85°C donde permaneció durante 23 horas. La reacción luego se removió desde calor y se enfrió en un baño de hielo cuando se templó agregando acetna. La reacción luego se concentró en vacío y se lavó en un embudo separador con acetato de etilo y 1M HCl. El acetato de etilo se separó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El intermedio (4-bromo-2-metilsulfonil-fenil)-metanol se recuperó como un aceite incoloro que se solidificó en reposo, rendimiento: 25,5 g (100+%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7,24-7,34 (m, 3H), 4,69 (s, 2H), 2,50 (s, 3H).

El alcohol luego se disolvió en 250 ml de diclorometano, se enfrió a 0°C-3°C en un baño de hielo, y se agregaron 44 g de ácido 3-cloroperbenzoico (77% máximo, Aldrich) en porciones.

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La reacción luego se dejó calentar a temperatura ambiente a la cual permaneció durante 22 horas. La reacción luego se concentró en vacío para remover diclorometano y el residuo se lavó en un embudo separador con acetato de etilo y 1M NaOH. El acetato de etilo se separó, se lavó con 1M NaOH, se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm SiO_2), elución de gradiente desde 100% de hexanos hasta 100% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío para dar el intermedio (4-bromo-2-metanosulfonil-fenil)-metanol como un sólido semicristalino, incoloro, rendimiento: 171,13 g (65%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,18 (s, 1H), 7,77 (d, J= 8 Hz, 1H), 7,46 (d, J=8 Hz, 1H), 4,92 (s, 2H), 3,19 (s, 3H), 2,94 (br s, 3H).

En un matraz de 1L se pesaron 17,13 g de bromuro, 25 g de bis(pinacolato)diboro, 5,0 g de diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) agregado, 23 g de acetato de potasio y 175 ml de DMSO. La suspensión resultante se calentó a 98°C-102°C durante 18 horas, luego se diluyó con 200 ml de acetato de etilo y 200 ml de agua. la suspensión resultante se filtró a través de celita para remover los sólidos y el filtrado se transfirió a un embudo separador. La fase acuosa se separó y se lavó con acetato de etilo. El

687
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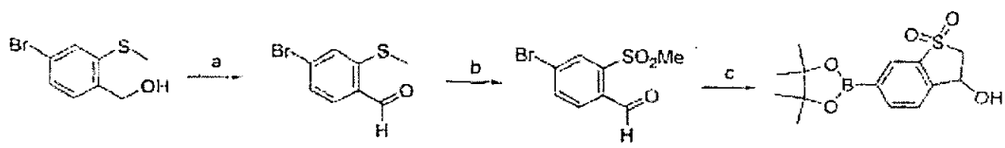
acetato de etilo se combinó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm de SiO, elución de gradiente desde 100% al 40% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío. El producto purificado se disolvió en diclorometano y se precipitó con hexanos. El [2-metanosulfonil-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-fenil]-metanol se recuperó como un polvo blancuzco, rendimiento: 8,78 g (43%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,45 (s, 1H), 8,04 (d, J= 8 Hz, 1H), 7,57 (d, J=8 Hz, 1H), 4,96 (s, 2H), 3,17 (s, 3H), 1,35 (s, 6H), 1,24 (s, 6H).

Ejemplo 25

Preparación de 1,1-dióxido de 6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2,3-dihidro-1-benzotiofeno-3-ol



a) DMSO, cloruro de oxalilo, CH_2C_2, -78°C; b) MCPBA, CH_2C_2; c) Bis(picolinato)diboro, Pd(dppf), KOAc, DMSO, 100°C.

El (4-bromo-2-metilsulfonil-fenil)-metanol se preparó como se describió en el Ejemplo 24. En un matraz de 500 ml se

689

colocaron 220 ml de diclorometano y 5,66 ml de cloruro de oxalilo bajo nitrógeno. La solución se enfrió a una temperatura de -70°C a -78°C y se agregaron 9,80 ml de DMSO gota a gota. La suspensión resultante se agitó a -78°C durante 15 minutos. Se preparó una solución de alcohol (10,0 g, 42,9 mmol) en 30 ml de diclorometano y se agregó a la suspensión a través de una cánula. La reacción se agitó a -78°C durante 0,5 hora, luego se agregaron 30 ml de trietilamina a través de una jeringa. La reacción se agitó a -78°C durante 30 minutos, luego se enfrió agregando cloruro de amonio saturado. La mezcla se lavó en un embudo separador agregando agua y diclorometano. El diclorometano se evaporó, se secó (Na_2SO_4)y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm de SiO_2, elución de gradiente desde el 100% de hexanos hasta 200% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío para dar el producto como un sólido amarillo limón, rendimiento: 6,78 g (88% basado en el material inicial recuperado). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10,19 (s, 1H), 7,65 (d, J= 8 Hz, 1H), 7,40-7,54 (m, 2H), 2,50 (s, 3H).

En un matraz de 250 ml se pesaron 6,78 g (25,8 mmol) de aldehído y 60 ml de diclorometano. La reacción se enfrió a una temperatura de 0°C-3°C en un baño de hielo y 10 g de MCPBA

690

(77% máximo, Aldrich) se agregó en porciones. La reacción se dejó calentar a temperatura ambiente a la cual se mantuvo durante 21 horas. La reacción luego se concentró en vacío para remover diclorometano y se lavó en un embudo separador con acetato de etilo y 1 M NaOH. El acetato de etilo se separó, se lavó con 1,0 M NaOH, solución salina, se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 45 x 150 mm de SiO_2, elución de gradiente desde 100% de hexanos hasta 20% de acetato de etilo durante 1 hora. Las fracciones apropiadas se combinaron y se concentraron en vacío para dar el producto como un sólido incoloro, rendimiento: 5,32 g (89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10,71 (s, 1H), 8,30 (s, 1H), 7,95 (s, 2H), 3,29 (s, 3H).

En un matraz de 250 ml se pesaron 5,32 g (20,2 mmol) de aldehído, 7,13 g de acetato de potasio, 7,85 g de bis(pinacolato)diboro, 1,88 g de diclorometano de dicloro[1,1'-bis(difosfino)ferroceno]paladio (II) agregado, y 55 ml de DMSO. La suspensión resultante se calentó a 98°C-102°C durante 20 horas, luego se diluyó con 100 ml de acetato de etilo y 100 ml de de agua. la suspensión resultante se filtró a través de celita para remover sólidos y el filtrado se transfirió a un embudo separador. La fase acuosa se separó y se lavó con acetato de etilo. El acetato de etilo se combinó

695
691

y se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm SiO_2, gradiente de elución desde 100% de hexanos hasta 40% de acetato de etilo durante 0,5 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío. El producto purificado se disolvió en diclorometano y se precipitó con hexanos. El 1,1-dioxo-6-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-2,3-dihidro-1H-1λ*6*-benzo[b]tiofen-3-ol se recuperó como un polvo tostado, rendimiento: 1,88 g (30%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8,21 (s, 1H), 8,08 (d, J=8 Hz, 1H), 7,64 (d, J=8 Hz, 1H), 5,49 (m, 1H), 3,80 (d, J=7,13 Hz, 1H), 3,45 (dd, J=5, 13 Hz, 1H), 2,79 (d, J=8 Hz, 1H), 1,34 (s, 12H).

693
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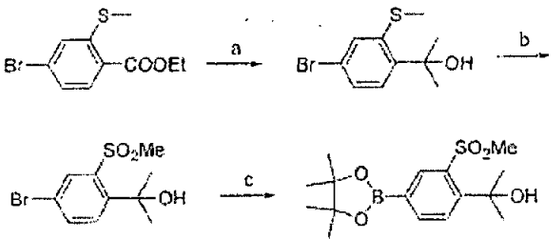
Ejemplo 26

Preparación de 2-(2-(metilsulfonil)-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)propan-2-ol



a) MeMgBr, THF, -78°C; b) MCPBA, CH_2C_2, 50°C; c) Bis(pinacolato) diboro, Pd(dppf), KOAc, DMSO, 100°C.

El éster de etilo del ácido 4-bromo-2-metanosulfonil-benzoico se preparó como se describió en el Ejemplo 25. En un matraz de 500 ml se pesaron 10,2 g (37,1 mmol) de éster y 100 ml de THF anhidro. La solución resultante se enfrió a -78°C y se agregaron 80 ml de 1,4M MeMgBr en THF (Aldrich) en porciones. La reacción se dejó calentar a temperatura ambiente a la cual se mantuvo durante 3 horas. La reacción luego se enfrió agregando cloruro de amonio saturado y la mezcla se lavó en un embudo separador con acetato de etilo y cloruro de amonio saturado. El acetato de etilo se separó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El intermedio 2-(4-bromo-2-metilsulfanil-fenil)-propan-2-ol se transportó al paso siguiente sin purificación adicional.

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El alcohol crudo se disolvió en 100 ml de diclorometano, se enfrió a 0°C-3°C en un baño de hielo y se agregaron 20 g de MCPBA (77% máximo, Aldrich) en porciones. La reacción luego se removió a un baño de aceite donde se calentó a 50°C durante 18 horas. La reacción luego se enfrió y se concentró en vacío para remover diclorometano. El residuo se lavó en un embudo separador con acetato de etilo y 1,0 M NaOH. El acetato de etilo se separó, se lavó con 1,0 M NaOH, solución salina, y se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage 45 x 150 mm de SiO_2, elución de gradiente desde 100% de hexanos hasta 40% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío y dieron el intermedio 2-(4-bromo-2-metanosulfonil-fenil)-propan-2-ol como un sólido incoloro, rendimiento: 10,02 g (92% para ambos pasos). ^1H NMR (400 MHz, $CDCl_3$): δ 8,33 (s, 1H), 7,68 (d, J=8 Hz, 1H), 7,33 (d, J=8 Hz, 1H), 3,41 (s, 3H), 1,76 (s, 1H), 1,69 (s, 6H).

En un matraz de 500 ml se pesaron 9,88 g (33,7 mmol) de bromuro, 12 g de acetato de potasio, 13,1 g de bis(pinacolato)diboro, 3,0 g de diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) agregado y 90 ml de DMSO. La suspensión resultante se calentó a 98°C-102°C durante 20 horas, luego se diluyó con 200 ml de acetato de etilo y 200

695
694

ml de agua. la suspensión resultante se filtró a través de celita para remover sólidos y el filtrado se transfirió a un embudo separador. La fase acuosa se separó y se lavó con acetato de etilo. El acetato de etilo se combinó, se lavó con solución salina, se secó (Na_2SO_4) y se concentró en vacío. El residuo se purificó mediante cromatografía rápida de gel de sílice (Biotage, 65 x 200 mm de SiO_2, elución de gradiente desde 100% de hexanos hasta 100% de acetato de etilo durante 1 hora). Las fracciones apropiadas se combinaron y se concentraron en vacío dando 2-[2-metanosulfonil-4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-fenil]-propan-2-ol como un sólido gris, rendimiento: 10,0 g (87%). ^1H NMR (400 MHz, $CDCl_3$): δ 8,61 (s, 1H), 7,96 (d, J=8 Hz, 1H), 7,45 (d, J=8 Hz, 1H), 3,39 (s, 3H), 1,70 (s, 6H), 1,34 (s, 12H).

Varis boronatos diferentes se pueden sintetizar mediante métodos generales descritos en el Esquema 18 y ejemplificados en el Ejemplo 27. Un sustrato aromático adecuado, tal como 2-halopiridina, puede reaccionar para producir un intermedio con un grupo "director" unido. Dicho sistema puede entonces halogenarse para dar un halógeno dispuesto *para*. Dicho sistema puede entonces convertirse en un boronato usando métodos tales como aquellos que se describen a continuación. Alternativamente, se pueden usar varios intermedios disponibles comercialmente, tales como 2,4-Dibromo-3-

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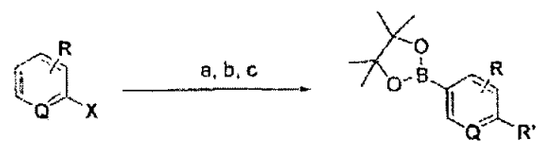
metilpiridina, 4-bromo-2-cloropirimidina, y varios anillos de benceno sustituido.

Esquema 18



Q = Usado para identificar cualquier sistema de anillo aromático que se puede hacer adecuadamente funcional como sería rápidamente evidente para un experto en el arte.

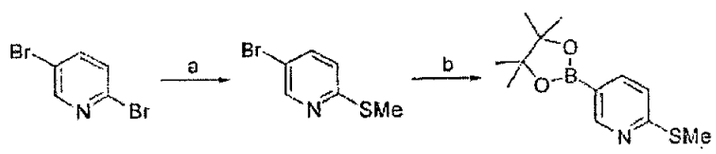
X = halógeno o grupo "director" preexistente

R' = "grupo director"

R = cualquier funcionalidad que no interfiera con el efecto director del grupo R'

Ejemplo 27

Preparación de 2-(metiltio)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina



Condiciones de la reacción: a) NaSMe, DMF, 60°C; b) Bis(pinacolato)diboro, Pd(dppf), KOAc, DMSO, 80°C.

697
696

2,5-Dibromo-piridina (3,0 g, 12,7 mmol) y tiometóxido de sodio (0,84 g, 12 mmol) se disolvieron en 18 ml de N,N-dimetilformamida anhidra. La mezcla se calentó a 160°C bajo nitrógeno durante 6 horas. Después de enfriar a temperatura ambiente, se agregaron agua y acetato de etilo a la mezcla de la reacción. La capa acuosa se extrajo varias veces con acetato de etilo. El extracto combinado se lavó con solución salina, se secó sobre sulfato de sodio, y se concentró en vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (0→6% de EtOAc/Hexano) para dar 5-bromo-2-metilsulfanil-piridina como un sólido blanco (2,18 g, 84% de rendimiento). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2,55 (s, 3H), 7,09 (dd, 1H, J= 0,7, 8,6), 7,59 (dd, 1H, J=2,4, J=8,6), 8,50 (m, 1H).

Catalizador de paladio (completo de [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (II) (1:1), 167 mg, 0,21 mmol), acetato de potasio (1,81 g, 18,5 mmol, Aldrich) y bis(pinacolato)diboro (1,56 g, 6,1 mmol) se colocaron en un frasco y se desgasificaron con una corriente de nitrógeno durante 20 minutos. En un frasco separado, 5-bromo-2-metilsulfanilpiridina (N° 2) (836 mg, 4,1 mmol) se disolvió en 8 ml de DMSO anhidro y se desgasificó con una corriente de nitrógeno durante 20 minutos. Esta solución en

698
697

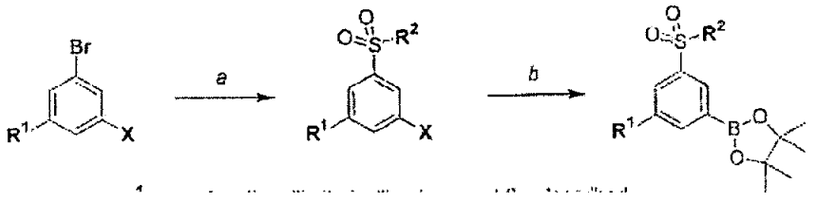
DMSO se agregó al frasco de "catalizador", y luego se calentó a 80°C toda la noche. Después de enfriar a temperatura ambiente, se agregaron agua y acetato de etilo a la mezcla de la reacción. La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre sulfato de sodio y se concentraron en vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice (10→20% de EtOAc/Hexanos, 0,25% de Et_3N en hexanos) para dar 2-Metilsulfanil-5-(4,4,5,5)-tetrametil-[1,3,2]dioxaborolan-2-il]piridina como un aceite incoloro (1,00 g, 97% de rendimiento). ^1H NMR (400 MHz, $CDCl_3$): δ 1,35 (s, 12H), 2,58 (s, 3H), 7,16 (dd, 1H, J=1,0 J=8,0), 7,83 (dd, 1H, J=1,8, J=8,0), 8,50 (dd, 1H, J= 1,7, J=1,0).

En forma similar a la mencionada se prepararon los siguientes ejemplos de la invención sustituyendo un reactivo apropiado.

- 2-metilsulfanil-3-metil-5-(4,4,5,5-tetrametil)-[1,3,2]dioxoborolan-2-piridina. ^1H NMR (400 MHz, $CDCl_3$): δ 1,35 (s, 12H), 2,24 (s, 3H), 2,59 (s, 3H), 7,64 (d, J=0,8, 1H), 8,63 (d, J=1,0, 1H).
- 2-etilsulfanil-3-metil-5-(4,4,5,5-tetrametil)-[1,3,2]dioxoborolan-2-piridina. ^1H NMR (400 MHz, $CDCl_3$): δ 1,35 (s, 12H), 1,38 (t, J=7,4, 3H), 2,22 (s, 3H), 3,23 (q, J=7,4,

2H), 7,64 (d, J=0,8, 1H), 8,61 (d, J=1,0, 1H); MS(ES): 280,2, 282,1 $[M+H]^+$.

Esquema 19



R^1 = cualquier funcionalidad que no impida que ocurra la reacción química descrita

R^2 = alquilo, arilo, u otros grupos unidos apropiados

X = halógeno

a) NaO_2SR^2, 10% en moles CuI, 20% en moles de prolina, 20% en mole de NaOH, DMSO, μW 210°C; b) bis(pinacolato)-diboro, KOAc, $Cl_2Pd(dppf)$, DMSO, μW 130°C.

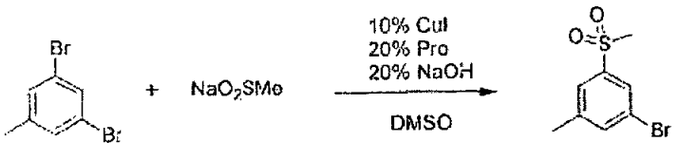
En general, los compuestos de la fórmula sistemas dearilo 1,3 (o 3,5-) disustituido se pueden preparar como se describió en el Esquema 19. Un dibromoareno puede reaccionar con una sal de sodio del ácido sulfínico (NaO_2SR^2) en la presencia de yoduro de cobre catalítico y la sal de sodio de prolina a temperatura elevada para dar la sulfona correspondiente. El intermedio luego se puede convertir en el arilboronato o ácido borónico

699

correspondiente en condiciones comunes que son evidentes para un experto en el arte.

Ejemplo 28

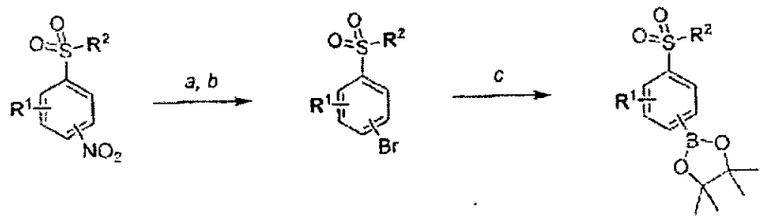
Preparación de 1-bromo-3-metanosulfonil-3-metil-benceno



Una mezcla de 3,5-dibromotolueno (2,0 g, 8,0 mmol), metanoslffinato de sodio (0,92 g, 9,0 mmol), yoduro de cobre(II) (152 mg, 0,8 mmol), prolina (0,18 g, 1,6 mmol) e hidróxido de sodio (64 mg, 1,6 mmol) en DMSO (15 ml, anhidro) se calentó en una unidad de microondas (Biotage Initiator®) a 210°C durante 20 minutos. La reacción se repitió dos veces más y las mezclas de la reacción se combinaron, se diluyeron con H_2O y se extrajeron con EtOAc. Los extractos combinados se lavaron con H_2O solución salina, luego se secaron (Na_2SO_4), se concentraron y se purificaron mediante cromatografía (sílice, EtOAc/Hexanos, 0:100 a 40:60) para dar el compuesto del título (1,2 g, 20% de rendimiento combinado) como un sólido blanco. GC-MS(EI): 248, 250.

2-(3-Metanosulfonil-5-metil-fenil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano se preparó desde 1-bromo-3-metanosulfonil-3-metil-1-benceno en forma similar a otras síntesis descritas previamente.

Esquema 20

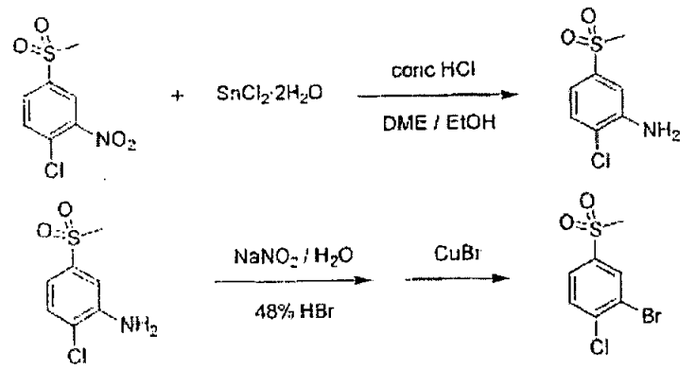


a) $SnCl_2 \cdot 2H_2O$, HCl concentrado, DME/EtOH; b) $NaNO_2$, 48% HBr, H_2O; luego CuBr; c) bis(pinacolato)diboro, KOAc, $Cl_2Pd(dppf)$, DMSO, μW 130°C.

En general, varios boronatos diferentes se pueden preparar como se describen el Esquema 20. Un nitroareno se puede reducir en condiciones normales, tales como con cloruro de estaño, para dar la arilamina correspondiente, que se puede convertir en el bromoareno correspondiente a través de la reacción de Sandmeyer. Los bromuros de arilo se pueden convertir fácilmente en boronatos usando condiciones que son evidentes para un experto en el arte.

Ejemplo 29

Preparación de 2-bromo-1-cloro-4-metanosulfonil-benceno



A una mezcla agitada de 1-cloro-4-metanosulfonil-2-nitrobenceno (5,2 g, 22 mmol) y 3x4 DME/EtOH (77 ml) se agregó gota a gota una solución de cloruro de estaño(II) dihidratado (15,3 g, 68 mmol) en 9N HCl (36 ml). Después de 3 horas la mezcla de la reacción se vertió en hielo y se trató con 10% de NaOH hasta que se alcanzó un pH 11. La mezcla resultante se extrajo con EtOAc (4 x 75 ml) y los extractos combinados se lavaron con solución salina, se secaron (Na_2SO_4) y se concentraron para dar el compuesto del título (4,5 g, cuantitativo) como un sólido blanco, que se usó sin purificación en el paso siguiente. GC-MS(EI): 205.

A una suspensión de 2-cloro-5-emtanosulfonil-anilina (4,50 g, 21,9 mmol) en 48% de HBr (12 ml) a 0°C se agregó gota a gota una solución de nitrito de sodio (2,28 g, 33 mmol) en H_2O (8 ml) a una velocidad tal que la temperatura nunca supere 5°C. La mezcla amarilla resultante se dejó agitar durante 20 minutos a 0°C y luego se cargó con bromuro de cobre(I) (3,3 g,

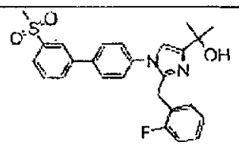
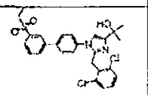
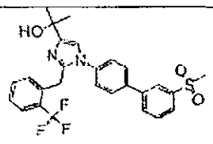
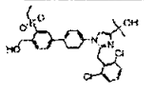
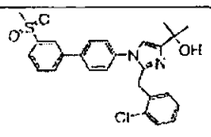
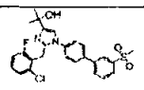
23 mmol). Después de 30 minutos, la mezcla resultante se extrajo con EtOAc (2 x 100 ml) y los extractos combinados se lavaron sucesivamente con dicho NH_4Cl, 3N HCl y solución salina, luego se secaron (Na_2SO_4) y se concentraron bajo presión reducida. El residuo resultante se purificó mediante cromatografía (sílice, EtOAc/Hexano, 0:100 a 50:50) para dar el compuesto del título (4,92 g, 83%) como un sólido blanco. GC-MS(EI): 268, 270.

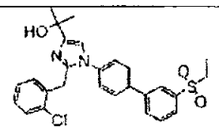
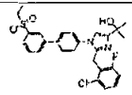
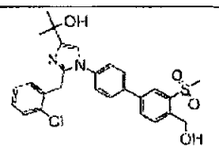
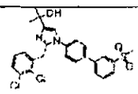
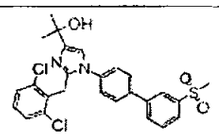
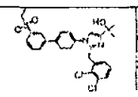
2-(2-Cloro-5-metanosulfonil-fenil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano se preparó desde 2-bromo-1-cloro-4-metanosulfonil-benceno en una forma similar a otras síntesis de boronato descritas previamente.

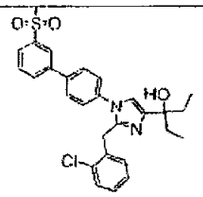
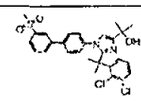
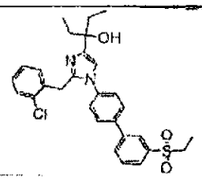
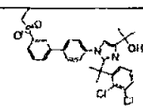
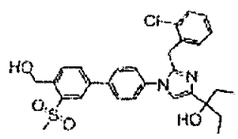
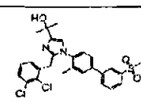
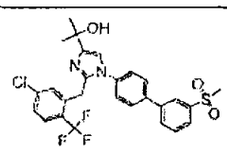
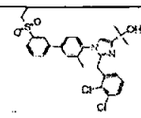
Ejemplo 30

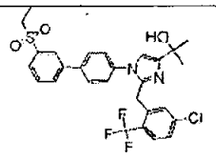
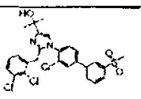
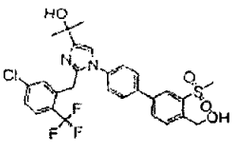
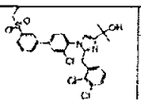
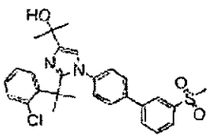
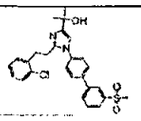
Los siguientes compuestos de la invención, en las Tablas 1 y 2, se prepararon de acuerdo con uno de los Ejemplos previos 1-29.

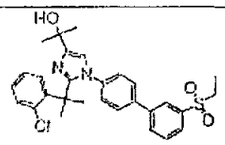
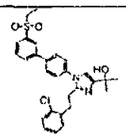
Tabla 1

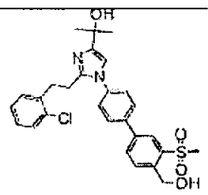
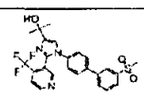
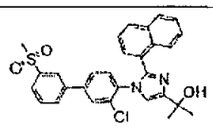
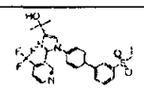
Comp	Estructura	Nombre	Comp	Estructura	Nombre
1		2-(2-(2-fluorobencil)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	7		2-(2-(2,6-diclorobencil) -1-(3'-dietilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
2		2-(1-(3'-(tetrametilsulfoni) bifenil-4-il)-2-(2-(trifluorometil) bencil)-1H-imidazol-4-il)propan-2-ol	8		2-(2-(2,6-diclorobencil) -1-(3'-(etilsulfonil) -4'-(hidroximetil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
3		2-(2-(2-clorobencil)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	9		2-(2-(2-cloro-6-fluoro bencil)1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol

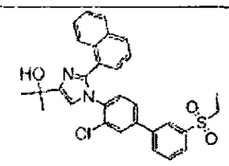
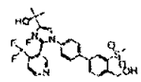
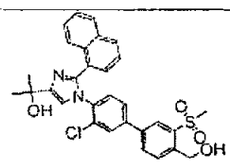
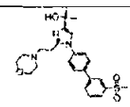
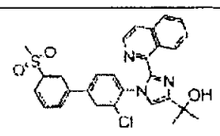
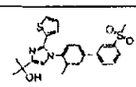
4		2-(2-(2-clorobencil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il) propan-2-ol	10		Q2-(2-(2-cloro-6-fluorobencil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
5		2-(2-(2-clorobencil)-1-(4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	11		2-(2-(2,3-diclorobencil) -1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
6		2-(2-(2,6-diclorobencil)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol4-il)propan-2-ol	12		2-(2-(2,3-diclorobencil) -1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol

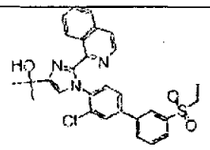
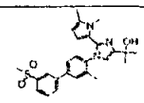
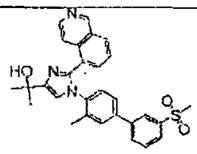
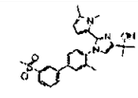
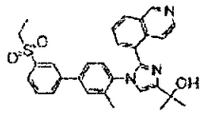
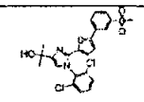
Comp	Estructura	Nombre	Comp	Estructura	Nombre
13		3-(2-(2-clorobencil)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	21		2-(2-(2-(2,3-diclorofenil) propan2-il)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
14		3-(2-(2-clorobencil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	22		2-(2-(2-(2,3-diclorobencil) propan-2-il)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
15		3-(2-(2-clorobencil)-1-(4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)pentan-3-ol	23		2-(2-(2,3-diclorobencil) -1-(3-(metil-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
16		2-(2-(5-cloro-2-(trifluorometil) benzil)-1-(3'-(metilsulfonil)	24		2-(2-(2,3-diclorobencil) -1-(3'-(etilsulfonil)

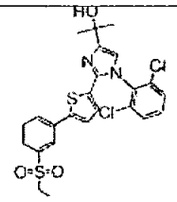
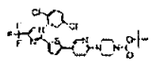
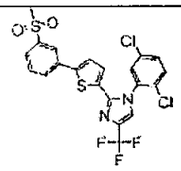
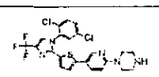
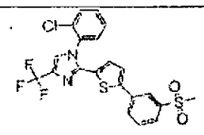
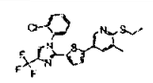
		bifenil-4-il)-1H-imidazol-4-il)propan-2-ol			-3-metilbifenil)-4-il)-1H-imidazol-4-il)propan-2-ol
17		2-(2-(5-cloro-2-(trifluorometil) bencil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	25		2-(1-(3-cloro-3'-(metil sulfonil) bifenil-4-il)-2-(2,3-diclorobencil) 1H-imidazol-4-il)propan-2-ol
18		2-(2-(5-cloro-2-(trifluorometil) bencil)-1-(4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il) propan-2-ol	26		2-(1-(3-cloro-3'-(etil sulfonil) bifenil-4-il)-2-(2,3-diclorobencil) -1H-imidazol-4-il)propan-2-ol
19		2-(2-(2-(2-clorofenil)propan-2-il)-1-(3'-etil-4-il)-1H-iimdazol-4-il)propan-2-ol	27		2-(2-(2-cloro fenil)-1-(2-(metilsulfo nil)bifenil-4-il)-1H-imidazol-4-il)-propan-2-

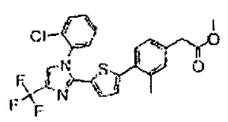
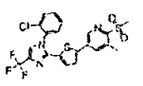
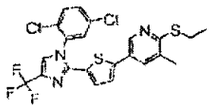
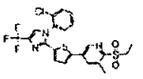
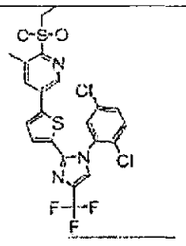
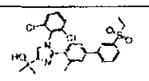
					ol
20		2-(2-(2-(2-clorofenil)propan-2-il)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	28		2-(2-(2-clorofenetil)-1-(3'-(etilsulfonil) bifenil-4-il) -1H-imidazol-4-il)propan-2-ol

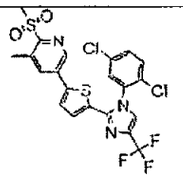
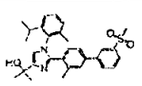
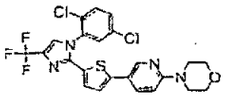
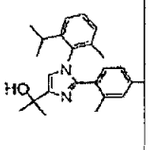
Comp	Estructura	Nombre	Comp	Estructura	Nombre
29		2-(2-(2-clorofenetil)-1-(4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	37		2-(1-(3'-(metilsulfonil) bifenil-4-il)-2-(4-(trifluoro metil)piridin-3-il)-1H-imidazol-4-il)propan-2-ol
30		2-(1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(naftalen-1-il)-1H-imidazol-4-il) propan-2-ol	38		2-(1-(3'-(etilsulfonil) bifenil-4-il)-2-(4-(trifluoro metil)piridin-3-il)-1H-imidazol-4-il))propan-2-

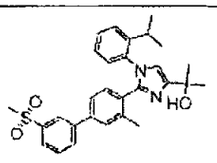
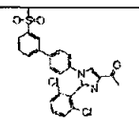
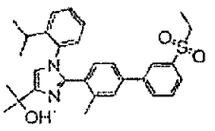
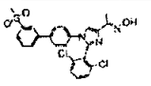
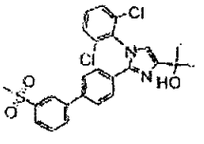
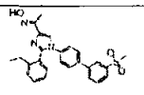
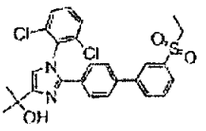
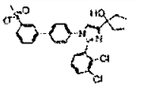
					ol
31		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(naftalen-1-il)-1H-imidazol-4-il)prpan-2-ol	39		2-(1-(4'-(hidroximetil) -3'-(metilsulfonil) bifenil-4-il)-2-(4-(trifluoro metil)piridn-3-il)-1H-imidazol-4-il)-propan-2-ol
32		2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-2-naftalen-1-il)-1H-imidazol-4-il)-propan-2-ol	40		2-(1-(3'-metilslfonil) bifenil-4-il)-2-(2-morfolino etil)-1H-imidazol-4-il) propan-2-ol
33		2-(1-(3-cloro-3'-(trimetilsulfonil) bifenil-4-il)-2-(isoquinolin-1-il)-1H-imidazol-4-il)propan-2-ol	41		2-(1-(3-metil-3'-(metilsulfonl) bifenil-4-il)-2-tiofen-2-il)-1H-imiazol-4-il)propan-2-ol

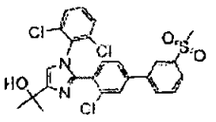
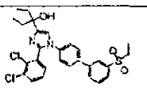
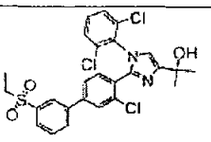
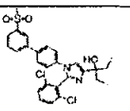
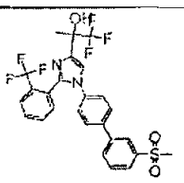
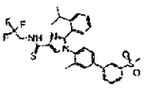
34		2-(1-(3-cloro-3'-(etilsufonil) bifenil-4-il)-2-(isoquinolin-1-il)-1H-imidazol-4-il)propan-2-ol	42		2-(2-(1,5-dimetil-1H-pirrol-2-il)-1-(3-metil-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
35		2-(2-(isoquinolin-5-il)-1-(3-metil-3' (metilsulfonil) bifenil-4-il)-1H-imidazol-4-il) propan-2-ol	43		2-(2-(1,5-dimetil-1H-pirrol-2-il)-1-(3-metil-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
36		2-(1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-2-(isoquinolin-5-il)-1H-imidazol-4-il)propan-2-ol	44		2-(1-(2,6-diclorofenil)-2-(5-(3-(metil sulfonil) fenil)tiofen-2-il)-1H-imidazol-4-il)-prpan-2-ol

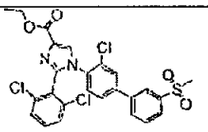
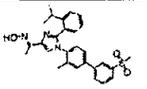
Comp	Estructura	Nombre	Comp	Estructura	Nombre
45		2-(1-(2,6-diclorofenil)-2-(5-(3-(etilsulfonil) fenil)tiofen-2-il) -1H-imidazol-4-il)-propan-2-ol	53		1,1-dimetiletil 4-(5-{5-[1-(2,5-diclorofenil)-4-(trifluoro metill)-1H-imidazol-2-il]-2-tienil} piridin-2-il) piperazina-1-carboxilato
46		1-(2,5-diclorofenil)-2-{5-[3-(metilsulfonil) fenil]-2-tienil}-4-(trifluorometil) -1H-imidazol	54		1-(5-{5-[1-(2,5-dicloro fenil)-4-(trifluoro metil)-1H-imidazol-2-il]-2-tienil} piridin-2-il) piperazina
47		1-(2-clorofenil)-2-{5-[3-(metil sulfonil)fenil]-2-tienil}-4-(trifluorometil)-1H-imidazol	55		5-{5-[1-(2-clorofenil)-4-(trifluoro metil)-1H-imidazol-2-il]-2-tienil}-3-(etiltio)-3-metilpiridina

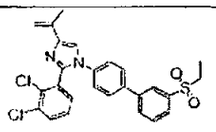
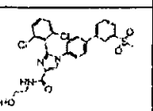
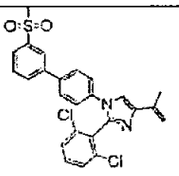
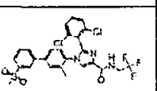
48		Metil (4-{5-[1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-3-metilfenil)acetato	56		5-{5-[1-(2-clorofenil)-4-(rifluoro metil)-1H-imidazol-2-il]-3-tieni}-3-metl-2-(metil sulfonil) piridina
49		5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-2-(etiltio)-3-metil piridina	57		5-{5-[1-(2-clorofenil)-4-(trifluoro metil)-1H-imidazol-2-il]-2-tienil}-2-(etilsulfonil) -3-metilpiridina
50		5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}-2-(etilsulfonil)-3-metilpiridina	58		2-(5-(1-(2,6-diclorofenil) -2-(3'-(etilsulfonil) 3-metilbifenil -4-il)-1H-imidazol-4-il) propan-2-ol

51		5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imiazol-2-il]-2-tienil}-3-metil-2-(metilsulfonil) piridina	59		2-(2-(3'-(etilsulfonil) 3-metilbifenil-4-il)-1-(2-isopropil-6-metilfenil)-1H-imidazol-4-il) propan-2-ol
52		4-(5-{5-[1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol-2-il]-2-tienil}piridin-2-il)morfolina	60		2-(2-(3'-(etilsulfonil) -3-metilbifenil-4-il)-1-(2-isopropil-6-metilsfenil)-1H-imidazol-4-il)propan-2-ol

Comp	Estructura	Nombre	Comp	Estructura	Nombre
61		2-(1-(2-isopropil fenil)-2-(3-metil-3'-(metilsulfonil) bifenil)-4-il)-1H-imidazol4-il) propan-2-ol	69		1-(2-(2,6-diclorofenil)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)etanona
62		2-(2-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1-(2-isopropil fenil)1H-imidazol-4-il)propan-2-ol	70		(E)-1-(2-(2,6-diclorofenil)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)etanona oxima
63		2-(1-(2,6-diclorofenil)-2-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	71		(E)-1-(2-(2-etilfenil)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)etanona oxima
64		2-(1-(2,4-diclorofenil)-2-(3'-(etilsulfonil) bifenil-4-il)-1H-	72		3-(2-(2,3-diclorofenil)-1-(3'-(metil sulfonil)

		imidazol-4-il)propan-2-ol			bifenil-4-il)-1H-imidazol-4-il)pentan3-ol
65		2-(2-(2-cloro-3'-(metilsulfonil) bifenil-4-il)-1-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol	73		3-(2-(2,3-diclorofenil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)petan-3-ol
66		2-(2-(2-cloro-3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	74		3-(2-(2,6-diclorofenil)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)-pentan-3-ol
67		1,1,1-trifluoro-2-(3'-(etilsulfonil) bifenil-4-il)-2-(2-(trifluorometil) fenil)-1H-imidazol-4-il)propan-2-ol	75		2-(2-isopropil)-1-(3-metil-3'-(metil suflonil) bifenil-4-il)-N-(2,2,2-trifluoroetil) -1H-imiazol-4-carboxamida

68		Etil 1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-carboxilato	76		(E)-1-(2-(2-isopropil fenil)-1-(3-metil-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)etanona oxima

Comp	Estructura	Nombre	Comp	Estructura	Nombre
77		2-(2,3-diclorofenil)-(3'-(etilsulfonil) bifenil-4-il)-4-(prop-1-en-2-il)-1H-imidazol	84		2-(2,6-diclorofenil)-N-(2-hidroxietil)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-carboxamida
78		2-(2,6-diclorofenil)-1-(3'-(metilsulfonil) bifenil-4-il)-4-(prp-1-en-2-il)-1H-imidazol	85		2-(2,6-dicloro fenil)-4-(3-metil-3'-(metlsulfonil) bifenil-4-il)-N-(2,2,2-trifluoroetil) -1H-imidazol-

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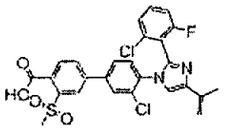
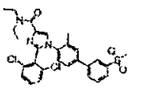
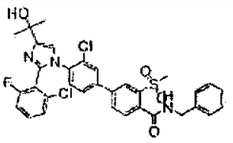
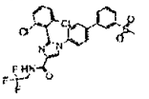
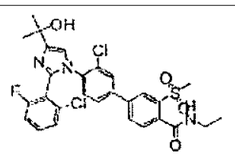
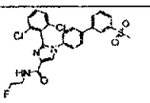
79		Ácido 3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(prop-1-en-2-il)-1H-imidazol-1-il)-3-(metilsulfonil) bifenil-4-carboxílico	86		2-(2,6-diclorofenil)-N,N-dietil-1-(3-metil-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il-carboxamida
80		N-bencil-3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(2-hidroxipropan-2-il)-1H-imidazol-1-il)-3-(metilsulfonil) bifenil-1-carboxamida	87		2-(2,6-diclorofeni)-1-(3'-(metil sulfonil) bifenil-4-il)-N-(2,2,2-trifluoroetil) -1H-imidazol-4-carboxamida
81		3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(2-hidroxipropan-2-il)-1H-imidazol-1-il)-N-etil-3-(metilsulfonil) bifenil-4-carboxamida	88		2-(2,6-dicloro fenil)-N-(2-fluoroetil)-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-carboxamida

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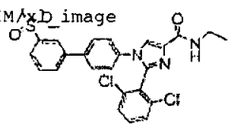
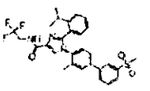
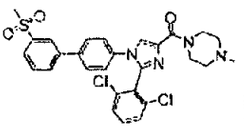
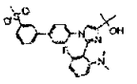
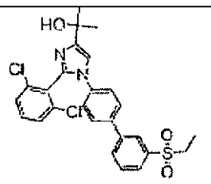
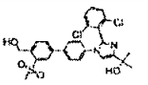
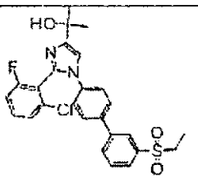
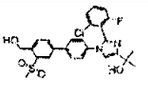
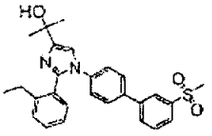
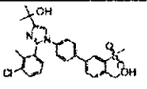
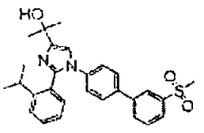
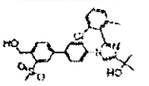
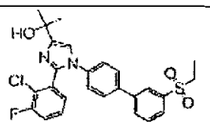
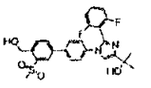
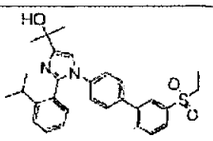
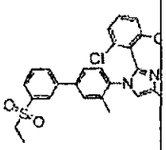
SYSTEM : H6FWSIM/xD_image

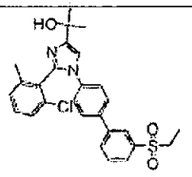
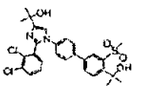
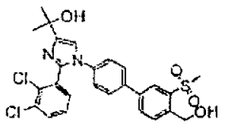
LINE : 605

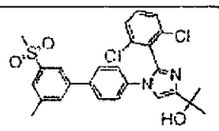
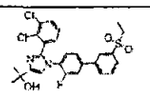
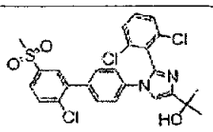
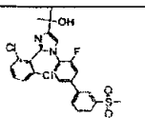
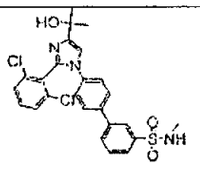
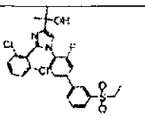
VERSION : QPDL 1.24 02-28-2005

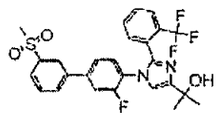
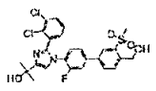
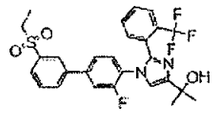
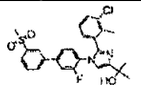
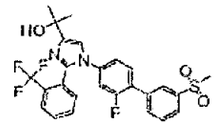
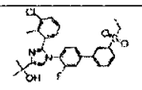
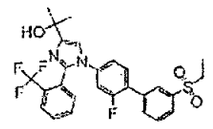
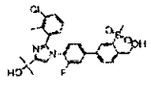
82		2-(2,6-diclorofenil)-N-etil-1-(3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-carboxamida	89		2-(2-isorpopil fenil)-1-(3-metil-3'-(metil sulfonil) bifenil-4-il)-N-(2,2,2-trifluoro etil)-1H-imidazol-4-carboxamida
83		(2-(2,6-dicloro-fenil)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il) (4-metilpiperazina-1-il)metanona	90		2-(2-(2-(dimetilamino) -6-fluoro fenil)-1-(3'-(metil sulfonil) bifenil-1-il)-1H-imidazol-4-il)propan-2-ol

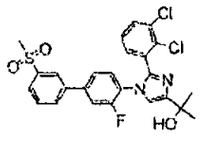
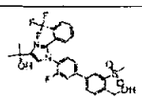
Comp	Estructura	Nombre	Comp	Estructura	Nombre
91		2-(2-(2,6-dicloro fenil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il) propan-2-ol	99		2-(2-(2,6-diclorofenil)-1-(4'-(hidroximetil) 3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
92		2-(2-(2-cloro-6-fluorofenil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il) prpan-2-ol	100		2-(2-(2-cloro-6-fluorofenil) -1-(4'-(hidroximetil) -3'-(metil sulfonil) bifenil-4-il)-1H-iidazol-4-il)propan-2-ol
93		2-(2-(2-etilfenll)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	101		2-(2-(3-cloro-2-metilfenil)-1-(4'-(hidroximetil) -3'-(metil sulfonil)) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol

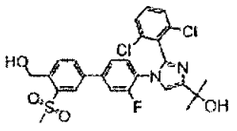
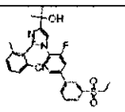
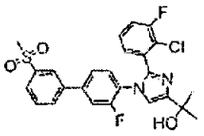
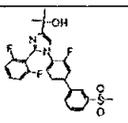
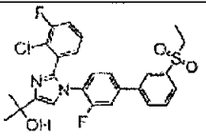
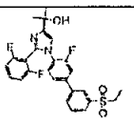
94		2-(2-(2-isopropil)-1-(3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	102		2-(2-(2-cloro-6-metilfenil)-1-(4'-(hidroximetil))-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
95		2-(2-(2-cloro-3-fluorofenil)-1-(3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)prpan-2-ol	103		2-(2-(2,6-difluorofenll)-1-(4'-(hidroximetil) 3'-(metil sulfonil) bifenil)-4-il)-1H-imidazol-4-il)propan-2-ol
96		2-(1-(3'-(etilsulfonil) bifenil-4-il)-2-(2-isopropilfenil)-1H-imidazol-4-il)propan-2-ol	104		2-(2,6-diclorofenil)-1-(3'-(etilsulfonil) -3-metil bifenil-4-il)-N-(2,2,2-trifluoro metil)-1H-imidazol-4-

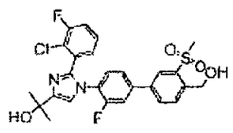
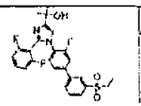
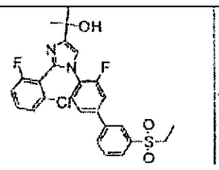
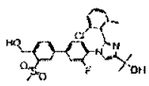
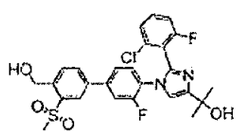
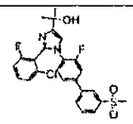
					carboxamida
97		2-(2-(2-cloro-6-metilfenil)-1-(3'-(etilsulfoniil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	105		2-(2-(2,3-diclorofenli)-1-(4'-(2-hidroxipropan-2-il)-3'-(metils sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
98		2-(2-(2,3-diclorofenil)-1-(4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol			

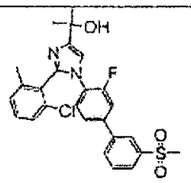
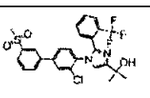
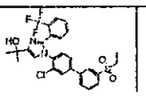
Comp	Estructura	Nombre	Comp	Estructura	Nombre
106		1-(2-(2,6-dicloro fenil)-1-(3'-metil-5'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	114		2-(2-(2,3-diclorofenli)-1-(3'-(etilsulfonil)-3-fluoro bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
107		2-(1-(2'-cloro-5'-(metilsulfonil) bifenil-4-il)-2-(2,6-diclorofenli)-1H-imidazol-4-il) propan-2-ol	115		2-(2-(2,6dicloro fenil)-1-(3-fluoro-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
108		4'-(2-(2,6-dicloro fenil)-4-(2-hidroxipropan-2-il)-1H-imidazol-1-il)-N-metilsulfonil-3-sulfonamida	116		2-(2-(2,6-diclorofenil)-1-(3'-(etilsulfonil)-3-fluorofenil-4-il)-1H-imidazol-4-il)propan-2-ol

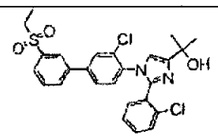
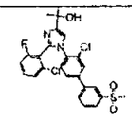
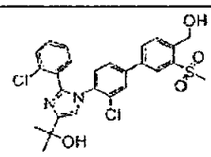
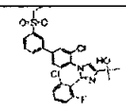
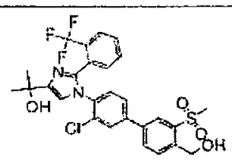
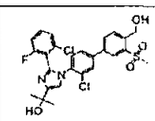
109		2-(1-(3-fluoro-3'-(metilsulfonil) bifenil-4-il)-2-(2-(trifluoro metil)fenil)-1H-imidazol-4-il)propan-2-ol	117		2-(2-(2,3-diclorofenil) -1-(3-fluoro-4'-(hidroxi metil)-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
110		2-(1-(3'-(etilsulfonil)-3-fluorobifenil-4-il)-2-(2-(trifluorometil) fenil)-1H-imidazol-4-il)propan-2-ol	118		2-(2-(3-cloro-2-metilfenil)-1-(3-fluoro-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
111		(2-(1-(2-fluoro-3'-(metilsulfonil) bifenil-4-il)-2-(2-(trifluoro metil)fenil)-1H-imidazol-4-il) propan-2-ol	119		2-(2-(3-cloro-2-metilfenil)-1-3'-(etil sulfonil)-3-fluorofenli-4-il)-1H-imiazol-4-il)propan-2-ol
112		2-(1-(3'-(etil sulfonil)-2-fluorofenil-4-il)-	120		2-(2-(3-cloro-2-metilfenil) -1-(3-fluoro-

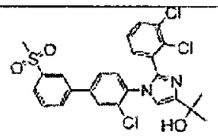
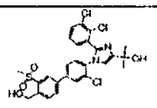
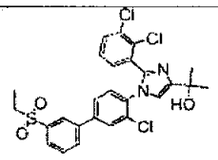
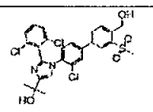
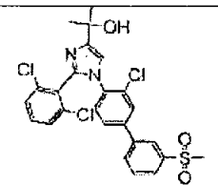
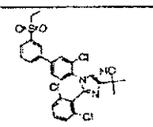
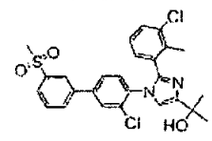
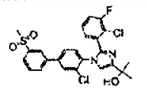
		2-(2-(trifluoro metil)fenil)-1H-imidazol-4-il) propan-2-ol			4-(hidroxi metil)-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)prpan-2-ol
113		2-(2-(2,3-dicloro fenil)-1-(3-fluoro-3'-(metil sulfonil) bifenil-4-ll)-1H-imidazol-4-il)propan-2-ol	121		2-(1-(3-fluoro-4'-(hidroximetil) -3'-(metil sulfonil) bifenil-4-il)-2-(2-trifluoro metil)fenil)-1H-imidazol-4-il)propan-2-ol

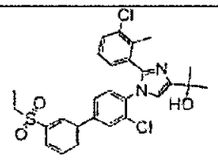
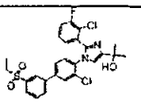
Comp	Estructura	Nombre	Comp	Estructura	Nombre
122		2-(2-(2,6-diclorofenil)-1-(3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	129		2-(2-(cloro-6-metilfenil)-1-(3'-(etilsulfonil) -3-fluoro bifenil-4-il)-1H-imidazol-4-il)propan-3-ol
123		2-(2-(2-cloro-3'-fluorofenil)-1-(3-fluoro-3'-(metil sulfonil) bifenil-4-il)-1H-imiazol-4-il)propan-2-ol	130		2-(2-(2,6-difluorofenil) -1-(3-fluoro-3'-metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
124		2-(2-(2-cloro-3-fluorofenil)-1-(3'-(etil sulfonil)-3-fluoro bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	131		2-(2-(2,6-difluorofenil) -1-(3'-(etilsulfonil) 3-fluoro bifenil-4-il)-1H-imidazol-4-il)propan-2-ol

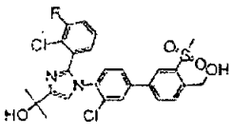
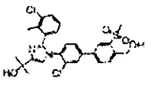
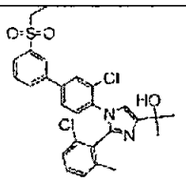
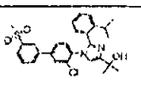
125		2-(2-(2-cloro-3-fluorofenil)-1-(3-fluoro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imiazol-4-il)propan-2-ol	132		2-(2-(2,6-difluorofenil) -1-(3'-fluoro bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
126		2-(2-(2-cloro-6-fluorofenil)-1-(3'-(etilsulfonil) -3-fluorobifenil-4-il)-1H-imiazol-4-il)propan-2-ol	133		1-(2-(2-cloro-6-metilfenil)-1-(3-fluoro-4'-(hidroximetil) -3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
127		2-(2-(2-cloro-6-fluorofenil)-1-(3-fluoro-4'-(hidroxi metil)-3'-(metil sulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	134		2-(2-(2-cloro-6-fluorofenil)-1-(3-fluoro-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol

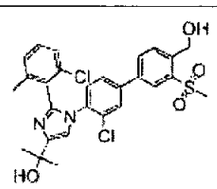
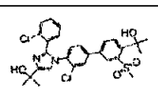
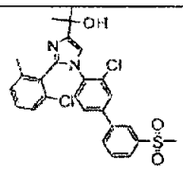
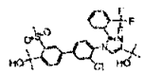
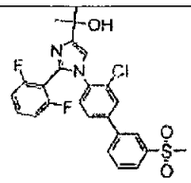
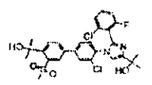
128		2-(2-(2-cloro-6-metilfenil)-1-(3-fluoro-3'-(metil sulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	135		2-(1-(3-cloro-3'-(metil sulfonil) bifenil-4-il)-2-(2-trifluoro metil)fenil)-1H-imidazol-4-il)propan-2-ol
			136		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2-(tri fuorometil) fenil)-1H-imidazol-4-il)propan-2-ol

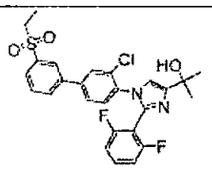
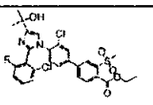
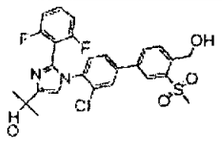
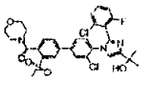
Comp	Estructura	Nombre	Comp	Estructura	Nombre
137		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2-clorofenil)-1H-imidazol-4-il)propan-2-ol	145		2-(1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(2-cloro-6-fluoro fenil)-1H-imidazol-4-il)propan-2-ol
138		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2-diclorofenil)-1H-imidazol-4-il)propan-2-ol	146		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2-cloro-6-fluorofenil)-1H-imidazol-4-il)propan-2-ol
139		2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-2-(2-trifluorometil) fenil)-1H-imidazol-4-il)propan-2-ol	147		2-(1-(3-cloro-4'-(hidroxi metil)-3'-(metilsulfonil) bifenil-4-il)-2-(2-cloro-6-fluorofenil)-1H-imidazol-4-il)propan-2-ol

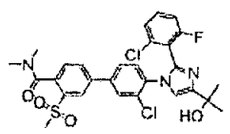
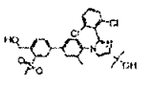
140		2-(1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(2,3-diclorofenil)-1H-imidazol-4-il)propan-2-ol	148		2-(1-(3'-cloro-4'-(hidroxi metil)bifenil-4-il)-2-(2,3-diclorofenil)-1H-imiazol-4-il)propan-2-ol
141		2-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2,3-diclorofeni)-1H-imidazol-4-il)propan-2-ol	149		2-(1-(3'-cloro-4'-(hidroxi metil)-3'-(metilsulfonil) bifenil-4-il)-2-(2,6-dicloro fenil)-1H-imidazol-4-il)propan-2-ol
142		2-(1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(2,6-diclorofenil) -1H-imidazol-4-il)propan-2-ol	150		2-(1-(3-cloro-3'-(etil sulfonil) bifenil-4-il)-2-(2,6-diclorofenil)-1H-imidazol-4-il)propan-2-ol
143		2-(2-(3-cloro-2-(metilsulfonil)-1-(3-cloro-3'-(metil sulfoni)bifenil-4-il)-1H-imidazol-4-	151		2-(1-(2-cloro-3'-(metil sulfonil) bifenil-4-il)-2-(2-cloro-3-

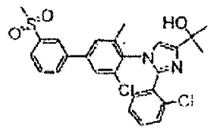
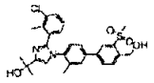
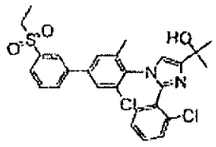
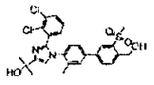
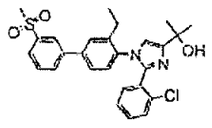
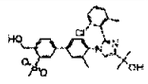
		il)propan-2-ol			fluorofenil)-1H-imiazol-4-il)propan-2-ol
144		2-(2-(3-cloro-2-metilfenil)-1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	152		2-(1-(3-cloro-3'-(etil sulfonil) bifenil-4-il)-2-(2-cloro-3-fluorofenil)-1H-imidazol-4-il)propan-2-ol

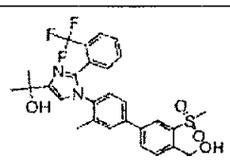
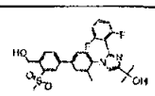
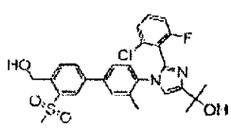
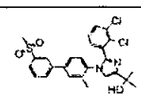
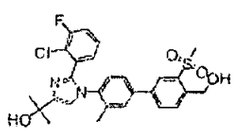
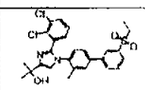
Comp	Estructura	Nombre	Comp	Estructura	Nombre
153		2-(2-(2-cloro-3-fluorofenil)-1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il) propan-2-ol	160		2-(2-(3-cloro-2-metilfenil)-1-(3-cloro-4'-(hidroximetil)-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
154		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2-cloro-6-metilfenil)-1H-imidazol-4-il)propan-2-ol	161		2-(1-(3-cloro-3'-(metil sulfonil) bifenil-4-il)-2-(2-isopropil fenil)-1H-imidazol-4-

					il)propan-2-ol
155		2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-2-(2-cloro-6-metilfenil)-1H-imidazol-4-il)prpan-2-ol	162		2-(3'-cloro-4'-(2-(2-cloro fenil)-4-(2-hidroxipropan-2-il)-1H-imidazol-4-il)-3-(metil sulfonil) bifenil-4-il)-propan-2-ol
156		2-(1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(2-cloro-6-metilfenil)-1H-imidazol-4-il)propan-2-ol	163		2-(1-(3-cloro-4'-(2-hidroxi propan-2-il)-3'-(metil sulfonil) bifenil-4-il)-2-(2-(trilfuoro metil)fenil)-1H-imidazol-4-ilpropan-2-ol
157		2-(1-(3-cloro-3'-(metilsulfonil) bifenil-4-il)-2-(2,6-difluoro fenil)-1H-imidazol-4-il)propan-2-ol	164		2-(3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(2-hidroxi propan-2-il)-1H-imidazol-4-il)-3-(metil sulfonil)

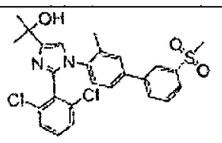
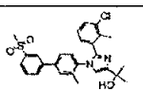
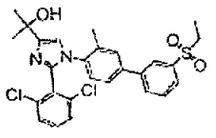
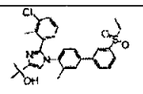
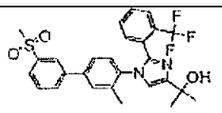
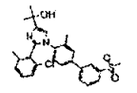
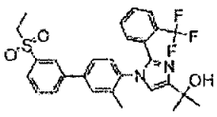
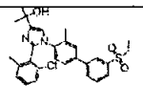
					bifenil-4-il)propan-2-ol
158		2-(1-(3-cloro-3'-(etilsulfonil) bifenil-4-il)-2-(2,6-difluoro fenil)-1H-imidazol-4-il)propan-2-ol	165		Etil 3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(2-hidroxi propan-2-il)-1H-imidazol-4-il)-3-(metilsulfonil) bifenil-4-carboxilato
159		2-(1-(3-cloro-4'-(hidroximetil)-3'-(metilsulfonil) bifenil-4-il)-2-(2,6-difluorofenil)-1H-imidazol-4-il)propan-2-ol	166		(3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(2-hidroxi propan-2-il)-1H-imidazol-1-il)-3-(metilsulfonil) bifenil-4-il) (morfolino) metanona

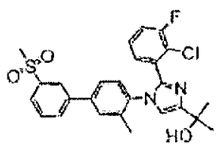
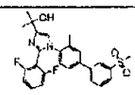
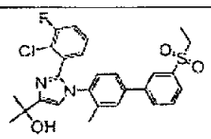
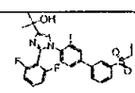
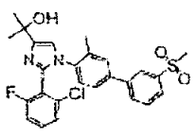
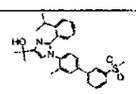
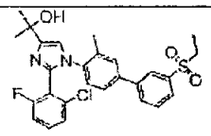
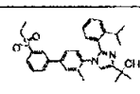
Comp	Estructura	Nombre	Comp	Estructura	Nombre
167		3'-cloro-4'-(2-(2-cloro-6-fluorofenil)-4-(2-hidroxipropan-2-	174		2-(2-(2,6-diclorofenil)-1-(4'-(hidroxi metil)-3-fenil-

		il)-1H-imidazol-1-il)-N,N-dimetil-3-(metilsulfonil) bifenil-4-carboxamida			3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
168		2-(1-(3-cloro-5-metil-3'-(metil sulfonil)bifenil-4-il)-2-(2-clorofenil)-1H-imidazol-4-il)propan-2-ol	175		2-(2-(3-cloro-2-metilfenil)-1-(4'-(hidroximetil)-3-metil-3'-(metil sulfonil) bifeni-4-il)-1H-imidazol-4-il)propan-2-ol
169		2-(1-(3-cloro-3'-(etilsulfonil)-5-metilbifenil-4-il)-2-(2-clorofenil)-1H-imidazol-4-il)propan-2-ol	176		2-(2-(2,3-diclorofenil)-1-(4'-(hidroximetil)-3-metil-3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
170		2-(2-(2-clorofenil)-1-(3-etil-3'-(metil sulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	177		2-(2-(2-cloro-6-metilfenil)-1-(4'-(hidroximetil)-3-metil-3'-(metil sulfonil)

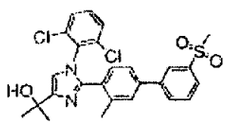
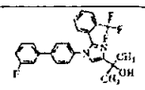
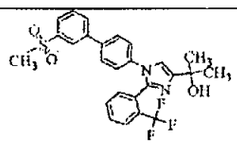
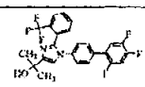
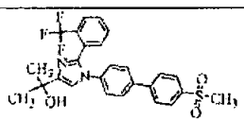
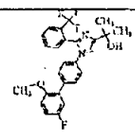
					bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
171		2-(1-(4'-(hidroximetil)-3-metil-3'-(metilsulfonil) bifenil-4-il)-2-(2-(trifluoro metil)fenil-1H-imidazol-4-il)propan-2-ol	178		2-(2-(2,6-difluorofenil)-1-(4'-(hidroxi metil)-3-metil3'-(metil sulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
172		2-(2-(2-cloro-6-fluorofenil)-1-(4'-(hidroximetil)-3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	179		2-(2-(2,3-diclorofenil)-1-(3-metil-3'-(metilsulfonil) bofenil-4-il)-1H-imidazol-4-il)propan-2-ol
173		2-(2-(2-cloro-3-fluorofenil)-1-(4'-(hidroximetil)-3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-	180		2-(2-(2,3-diclorofenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol

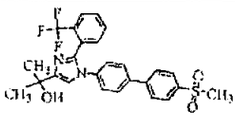
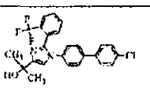
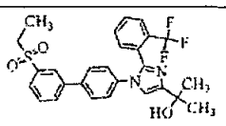
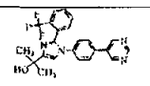
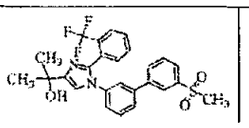
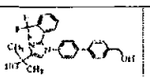
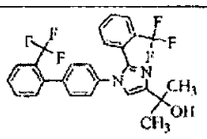
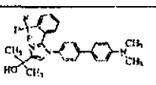
		il)propan-2-ol			

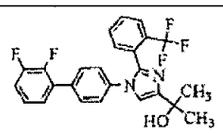
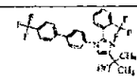
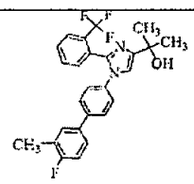
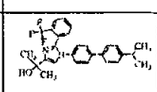
Comp	Estructura	Nombre	Comp	Estructura	Nombre
181		2-(2-(2,6-diclorofenil)-1-(3-metil-3'-(metil sulfonil)bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	189		2-(2-(2-cloro-2-metilfenil)-1-(3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
182		2-(2-(2,6-diclorofenil)-1-(3'-(etilsulfonil) -3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol	190		2-(2-(3-cloro-2-metilfenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-iidazol-4-il)propan-2-ol
183		2-(1-(3-metil-3'-(metilsulfonil) bifenil-4-il)-2-(2-(tifluorometil) fenil)-1H-imidazol-4-il)propan-2-ol	191		2-(2-(2-cloro-6-metilfenil)-1-(3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
184		2-(1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-2-(2-trifluoro	192		2-(2-(2-cloro-6-metilfenil)-1-(3'-(etilsulfonil)-

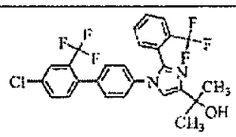
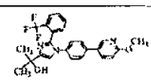
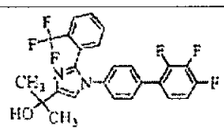
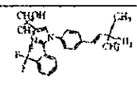
		metil)fenil)-1H-imidazol-4-il)propan-2-ol			3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol
185		2-(2-(2-cloro-3-fluorofenil)-1-(3-metil-3'-(metil sulfonil)bifenil-4-il)-1H-imidazol-4-il)prpan-2-ol	193		2-(2-(2,6-difluorofenil)-1-(3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
186		2-(2-(2-cloro-3-fluorofenil)-1-(3'-(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol	194		2-(2-(2,6-difluorofenil)-1-(3'-etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol
187		2-(2-(2-cloro-6-fluorofenil)-1-(3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	195		2-(2-(2-isopropilfenil) -1-(3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol
188		2-(2-(2-cloro-6-fluorofenil)-1-(3'-	196		2-(1-(3'-(etilsulfonil)-3-

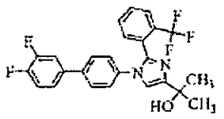
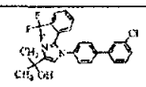
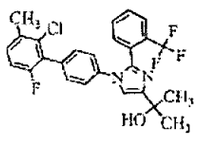
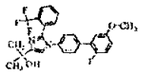
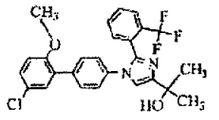
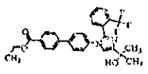
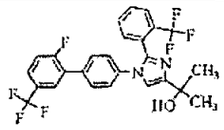
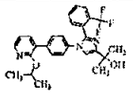
		(etilsulfonil)-3-metilbifenil-4-il)-1H-imidazol-4-il)propan-2-ol			metilbifenil)-4-il)-2-(2-isopropilfenil)-1H-imidazol-4-il)propan-2-ol

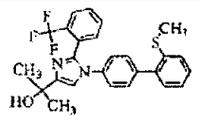
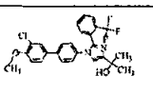
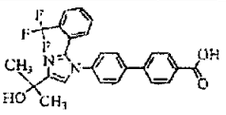
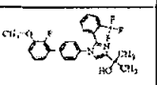
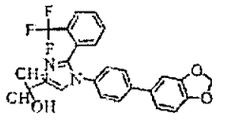
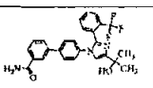
Comp	Estructura	Nombre	Comp	Estructura	Nombre
197		2-(1-(2,6-diclorofenil)-2-(3-metil-3'-(metilsulfonil) bifenil-4-il)-1H-imidazol-4-il)propan-2-ol	206		2-{1-(3'-fluoro bifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
198		2-{1-[3'-(metilsulfonil) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	207		2-{1-(2',4',5'-trifluoro bifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
199		2-{1-[4'-(metilsulfonil) bifenil-4-il}-3-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	208		2-{1-[5'-fluoro-2'-(metiloxi) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}prpan-2-ol

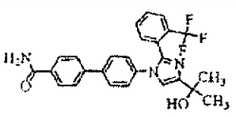
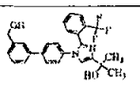
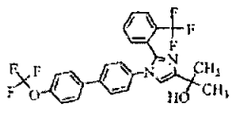
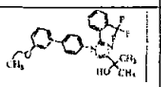
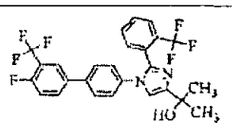
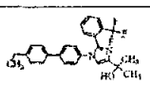
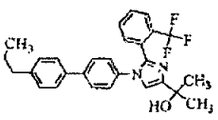
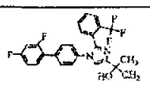
200		2-{1-[3'-(etilsulfonil) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	209		2-{1-(4'-clorobifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}prpan-2-ol
201		2-{1-[3'-(metilsulfonil) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	210		2-{1-(4-pirimidin-5-ilfenil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
202		2-{1-[2'-(trifluorometil) bifenil]-4-il]-2-[2-(trifluoro metil)fenil]-1H-imiazol-4-il}propan-2-ol	211		2-{1-[4'-(hiroximetil) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
203		2-{1-(2',3'-difluorofenil-4-il)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	212		2-{1-[4'-(dimetilamino) bifenil-4-il]-2-[2-(trfluoro metil)fenil}-1H-imidazol-4-il}prpan-2-ol

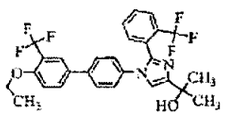
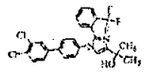
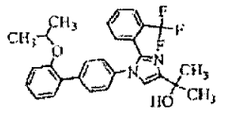
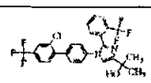
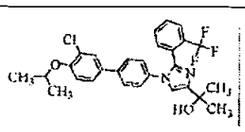
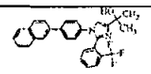
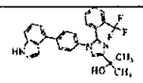
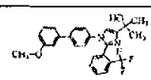
204		2-(1-{4'-[(1-metiletil)oxi] bifenil-4-il}-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)-propan-2-ol	213		2-{1-[4'-(trifluoro metil)bifenil-4-il]-2-[3-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
205		2-{1-(4'-fluoro-3'-trimetil bifenil-4-il)-2-[2-trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	214		2-{1-[4'-(1-metiletil) bifenil-4-il]-2-[2-(trifluoro metil)feni]-1H-imidazol-4-il)prpan-2-ol

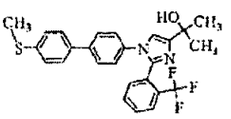
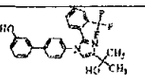
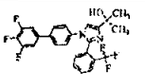
Comp	Estructura	Nombre	Comp	Estructura	Nombre
215		2-(1-[4'-cloro-2'-(trifluorometil) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	224		2-(1-{4-[6-(metiloxi) piridin-3-il]fenil}-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)propan-2-ol
216		2-(1-(2',3',4'-trifluorobifenil-4-il)-2-[2-(trifluorometil)-	225		2-(1-{4-[(E)-3,3-dimetilbut-1-en-1-]fenil}-2-[2-(trifluoro

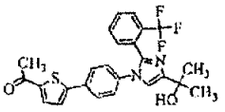
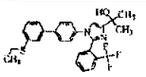
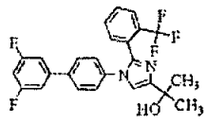
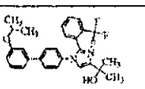
		1H-imidazol-4-il}propan-2-ol			metil)fenil]-1H-imiadazol-4-il)propan-2-ol
217		2-{1-(3',4'-difluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	226		2-{1-(3'-clorobifenil-4-il)-2-[2-(trifluoro metil)fenil}-1H-imidazol-4-il}propan-2-ol
218		2-{1-(2'-cloro-6'-fluoro-3'-metilbifenil-4-il)-2-[3-(trifluorometil)fenil]-1H-imidazol-4-il}-propan-2-ol	227		2-{1-[2'-fluoro-5'-(metiloxi) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
219		2-{1-[5'-cloro-2'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}-propan-2-ol	228		Etil 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}bifenil-4-carboxilato
220		2-{1-[2'-fluoro-5'-(trifluoro metil)bifenil-4-	229		2-{1-(4-{2-[(1-metiletil)oxi] piridin-3-

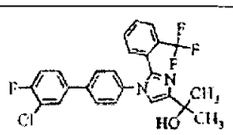
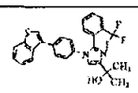
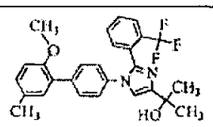
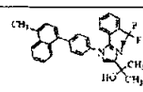
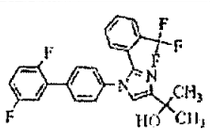
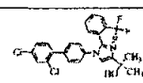
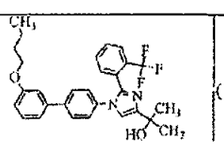
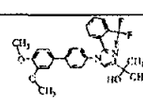
		il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol			il}fenil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
221		2-{1-[2'-(metiltio)bifenil-4-il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	230		2-{1-[3'-cloro-4'-(metiloxi) bifenil-4-il]- 2-[2-(trifluoromtil) fenil]-1H-imidazol-4-il} propan-2-ol
222		Ácido 4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imidazol-1-il} bifenil-4-carboxílico	232		2-{1-[2'-fluoro-3'-(metiloxi) bifenil-4-il]-2-[2-(trilfuoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
223		2-{1-[4-(1,3-benzodioxol-5-il)fenil]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	233		4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida

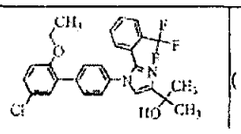
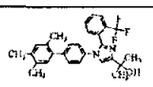
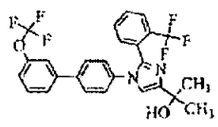
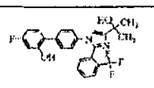
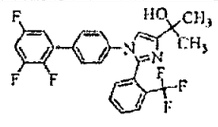
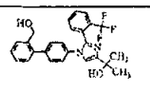
Comp	Estructura	Nombre	Comp	Estructura	Nombre
234		4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}bifenil-4-carboxamida	243		2-{1-[3'-(hidroximetil) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
235		2-(1-{6'-{(trifluorometil) oxi]bifenil-4-il}-3-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)propan-2-ol	244		2-{1-[3'-(etiloxi) bifenil-4-il]-2-[2-(trifluoro metil)fenil}-1H-imidazol-4-il}propan-2-ol
236		2-{1-[4'-fluoro-3'-(trifluoro metil)bifenil-4-il]-1-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	245		2-{1-(4'-etilbifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
237		2-{1-(4'-propil bifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	246		2-{1-(2',4'-difluorobifenil -4-il)-1-[2-(trifluoro metil)fenil]-1H-imidazol-4-

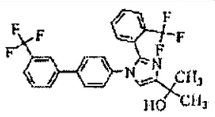
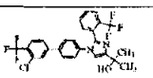
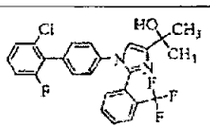
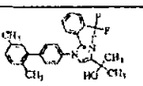
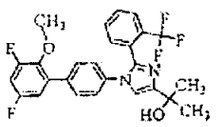
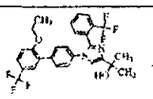
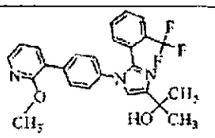
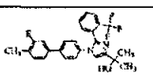
					il)propan-2-ol
238		2.{1-[4'-(etiloxi)-3'-(trifluorometil) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	247		2-{1-(3',4'-diclorobifenil-4-il)-2-[2-(trifluoro metil)bifenil]-1H-imidazol-4-il}propan-2-ol
239		2-(1-{2'-[(1-metiletil)oxi] bifenil-4-il}-2-[2-(trifluoro metil)fenil}-1H-imidazol-4-il)propan-2-ol	248		2-{1-[2'-cloro-4'-(trifluoro metil)bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
240		2-(1-{3'-cloro-4'-[(1-metiletil)oxi] bifenil-4-il}-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)-propan-2-ol	249		2-{1-(4-naftalen-2-ilfenil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}-propan-2-ol
241		2-{1-[4-(1H-indol-4-il)fenil]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-	250		2-{1-[3'-(metiloxi) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-

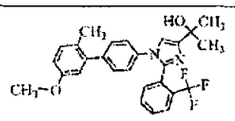
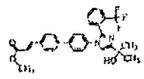
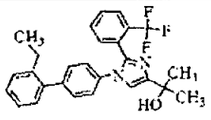
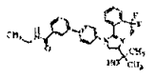
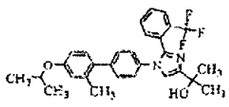
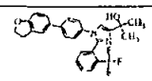
		il}propan-2-ol			1H-imidazol-4-il}propan-2-ol
242		2-{1-[4'-(metiltio)bifenil-4-il]2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	251		4'-{4'-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}bifenil-3-ol
			252		2-{1-(3',4',5'-trifluoro bifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-l}propan-2-ol

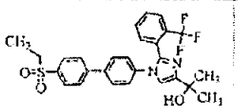
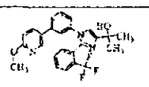
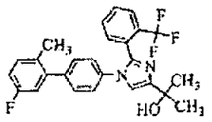
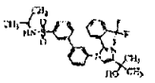
Comp	Estructura	Nombre	Comp	Estructura	Nombre
253		1-[5-(4-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imidazol-1-il}fenil)-2-tienil]etanona	262		1-{1-[3'-(etiltio) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
254		2-{1-(3',5'-difluorobifenil-4-il)-2-[2-	263		2-(1-{3'-[(1-metiletil)oxi] bifenil-4-il}-

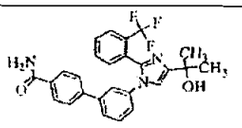
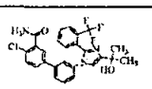
		(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol			2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)propan-2-ol
255		2-{1-(3'-cloro-4'-fluorofenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	264		2-{1-[4-(1-benzotien-3-il)fenil]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
256		2-{1-[5'-metil-2'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	265		2-{1-[4-(4-metilnaftalen-1-il)fenil]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
257		2-{1-(2',5'-difluorofenil-4-il)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	266		2-{1-(2',4'-diclorobifenil-4-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol} propan-2-ol
258		2-{1-[3'-(butiloxi)bifenil-4-il]-2-[2-(trifluorometil)	267		2-{1-[3',4'-bis(metiloxi) bifenil-4-il]-2-[2-(trifluoro

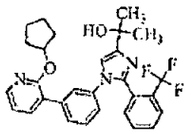
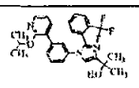
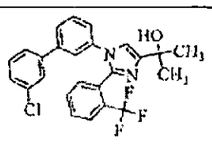
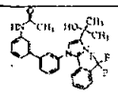
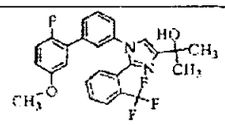
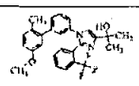
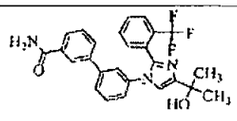
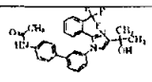
		fenil]-1H-imidazol-4-il}propan-2-ol			metl)fenil]-1H-imidazol-4-il}propan-2-ol
259		2-{1-[5'-cloro-2'-(etiloxi) bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	268		2-{2-[2-(trifluoro metil)benil]-1-(2',4',5'-trimetilbifenil-4-il)-1H-imidazol-4-il}propan-2-ol
260		2-(1-{3'-[(trifluorometil) oxi]bifenil-4-il}-2-[2-(rifluorometil) fenil]-1H-imidazol-4-il)propan-2-ol	269		4-fluoro-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}bifenil-2-ol
261		2-{1-(2',3',5'-trifluorobifenil-4-il)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	270		2-{1-[2'-(trifluoro metil)bifenil-4-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol

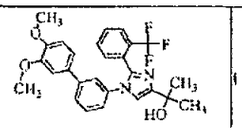
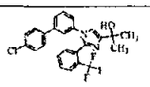
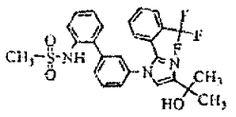
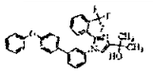
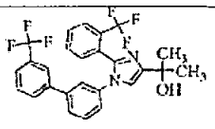
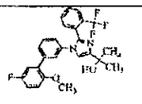
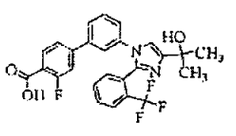
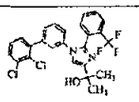
Comp	Estructura	Nombre	Comp	Estructura	Nombre
271		2-{1-[3'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	280		2-{1-[3'-cloro-4'-(trifluorometil]bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol
272		2-{1-(2'-cloro-6'-fluorobifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	281		2-{1-(5'-cloro-2'-metilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-3-il}propan-2-ol
273		2-{1-[3',5'-difluoro-2'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	282		2-{1-[2'-(etiloxi)-5'-(trifluorometil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}prpan-2-ol
274		2-(1-{4-[2-(metiloxi)piridin-3-il]fenil}-2-[2-(trifluorometil)	283		2-{1-3'-fluoro-4'-metilbifenil 4-il)-2-[2-(trifluoro

		fenil]-1H-imidazol-4-il}propan-2-ol			metil)fenil]-1H-imidazol-4-il}propan-2ol
275		2-{1-[2'-metil-5'-(metiloxi)bifenil-4-il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	284		Metil (2E)-3-(4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}bifenil-4-il)-2-enoato
276		2-{1-(2'-etilbifenil-4-il)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	285		N-etil-4'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida
277		2-(1-{2'-metil-4'-[(1-metiletil)oxi] bifenil-4-il}-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)propan-2-ol	286		2-{1-[4-(j2,3-dihidro-1-benzofuran-5-il)fenil]-2-{2-(trifluro metil)fenl]-1H-imidazol-4-il}propan-2-ol

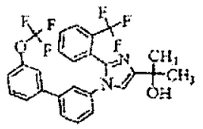
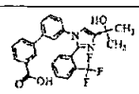
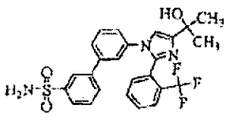
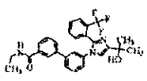
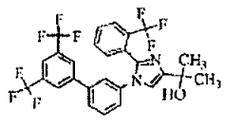
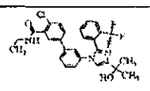
278		2-{1-[4'-(etilsulfonil)bifenil-4-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	287		2-(1-{3-[6-(metiloxi)piridin-3-il]fenil}-3-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol
279		2-2-{1-(5'-fluoro-2'-metilbifenil-4-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	288		3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-3-sulfonamida

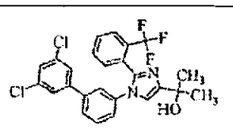
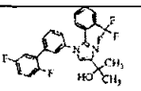
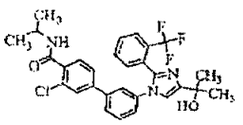
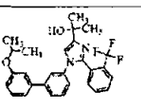
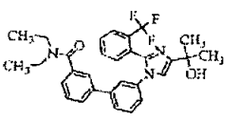
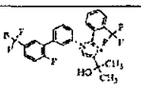
Comp	Estructura	Nombre	Comp	Estructura	Nombre
289		3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-l}bifenil-4-carboxamida	298		4-cloro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxmamida

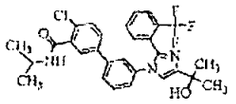
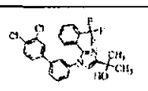
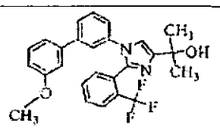
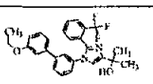
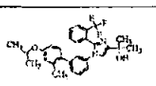
290		2-(1-{3-[2-ciclopentiloxi) piridin-3-il]fenil}-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il)propan-2-ol	299		2-{1-(2-{2-[(1-metiletil)oxi] piridin-3-il} fenil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
291		2-{2-(3'-clorobifenil-3-il)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	300		N-(3'-{3-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}bifenil-3-il)acetamida
292		2-{1-[2'-fluoro-5'-(metiloxi) bifenil-3-il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	301		2-{1-[2'-metil-5'-(metiloxi) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
293		3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imidazol-1-	302		N-(3'-{4-(1-hidroxil-metiletil)-2-[2-(trifluoro metil)fenil]-

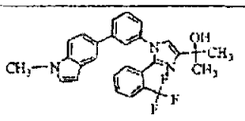
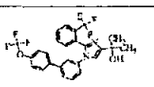
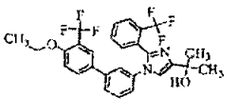
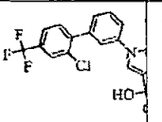
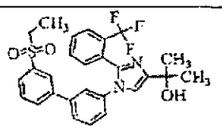
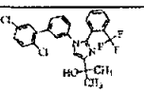
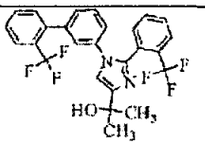
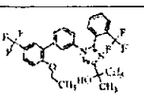
		il}bifenil-3-carboxamida			1H-imidazol-4-il}acetamida
294		2-{1-[3',4'-bis(metiloxi) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol	303		2-{1-(4'-clorobifenil-3-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
295		N-(3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imiazol-1-i}bifenil-2-il) metanosulfonamida	304		2-{1-[4'-(feniloxi) bifenil-3-il]-[2-(trifluoro metil)fenil]-1H-imidazol-4-il]-1H-imidazol-4-il}propan-2-ol
296		2-{1-[3'-(trifluorometil) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}prpan-2-ol	305		2-{1-[5'-fluoro-2'-(metiloxi) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
297		Ácido 3-fluoro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-	306		2-{1-(2',3'-diclorobifenil-3-il)-2-[2-

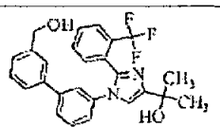
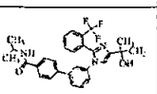
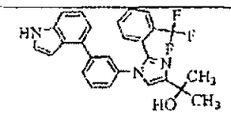
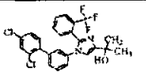
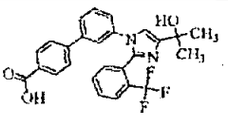
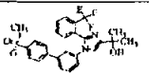
		(trifluorometil) fenil]-1H-imidazol-4-carboxílico			(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol

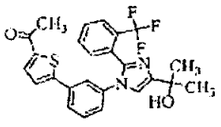
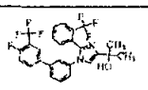
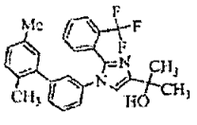
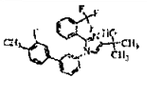
Comp	Estructura	Nombre	Comp	Estructura	Nombre
307		2-(1-{3'-[(trifluorometil) xoi]bifenil-3-il}-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il)propan-2-ol	315		Ácido 3'-{4-(1-hidroxi-1-metil etil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}bifenl-3-carboxílico
308		3'-{4-(1-hidroxi-1-metiletil)2-[2-(trifluorometil) fenil]-1H-imidazol-1-il}bifenil-3-sulfonamida	316		N-etil-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifuoro metil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida
309		2-{1-[3',5'-bis (trifluorometil) bifenil-3-il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-	317		4-cloro-N-etil-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-

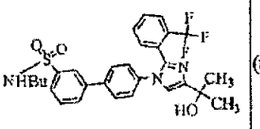
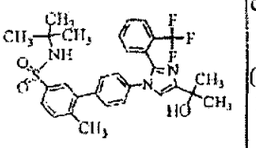
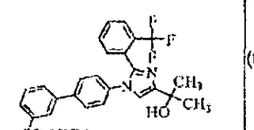
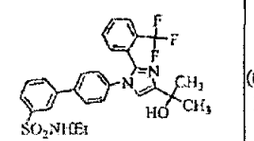
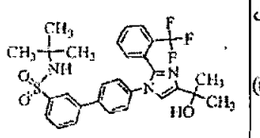
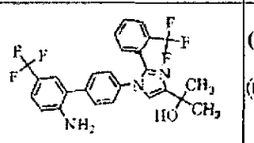
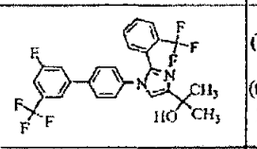
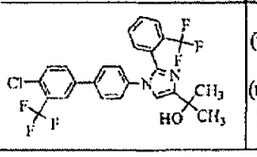
		il}propan-2-ol			il}bifenil-3-carboxamida
310		2-{1-(3',5'-diclorobifenil-3-il)-2-{2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	318		2-{1-(2',5'-difluorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol
311		3-cloro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-4-carboxamida	319		2-(1-{3'-[(1-metiletil)oxi]bifenil-3-il}-2-{2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol
312		N,N-dietil-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-3-carboxamida	320		2-{1-[2'-fluoro-5'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol

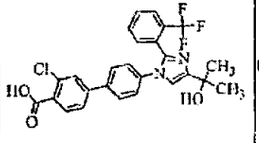
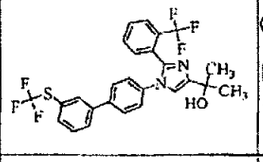
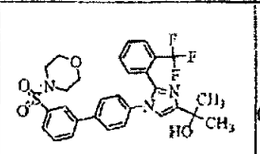
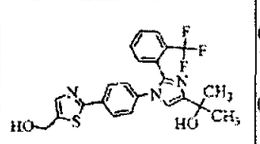
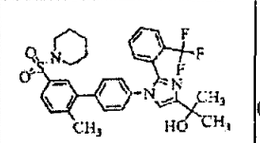
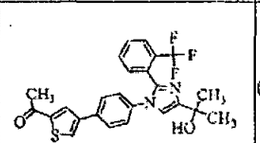
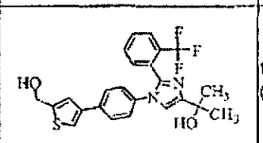
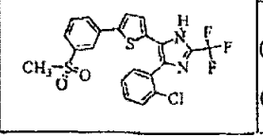
313		4-cloro-3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imidazol-1-il}-N-(1-metiletil) bifenil-3-carboxamida	321		2-{1-(3',4'-diclorobifenil-3-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
314		2-{1-[3'-(metiloxi)bifenil-3-il]-2-[2-(trifluorometil) fenil]-1H-imidazol-4-ilpropan-2-ol	322		2-{1-[3'-(etiloxi) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
			323		2-(1-{2'-metil-4'-[(1-metiletil)oxi] bifenil-3-il}-2-[2-(trifuoro metil)fenil]-1H-imidazol-4-il)propan-2-ol

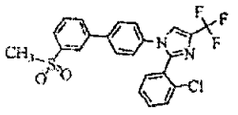
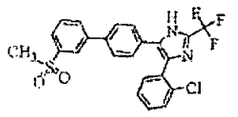
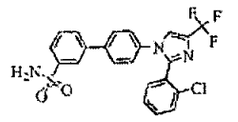
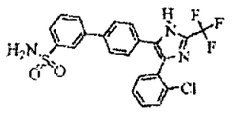
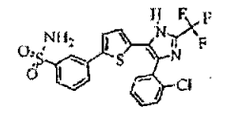
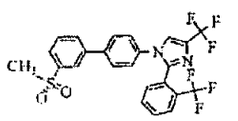
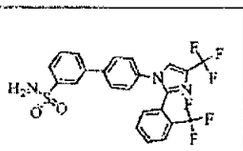
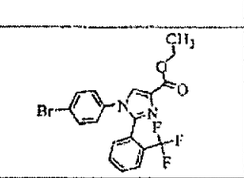
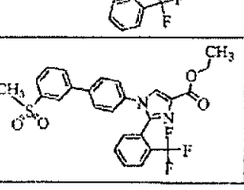
Comp	Estructura	Nombre	Comp	Estructura	Nombre
324		2-{1-[3-(1-metil-1H-indol-5-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	333		2-(1-{4'-[(trifluorometil)oxi]bifenil-3-il}-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il)propan-2-ol
325		2-{1-[4'-(etiloxi)-3'-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	334		2-(1-[2'-cloro-4'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol
326		2-{1-(3'-(etilsulfonil)bifenil-3-il]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	335		2-{1-(2',5'-diclorobifenil-3-il)-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol
327		2-{1-[2'-(trifluorometil)bifenil-3-il]-2-[2-(trifluorometil)	336		2-{1-[2-(etiloxi)-5'-(tifluorometil)bifenil-3-il]-2-[2-(trifluoro

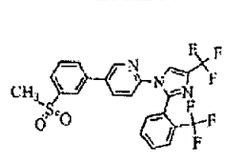
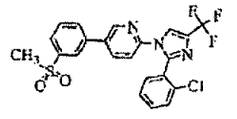
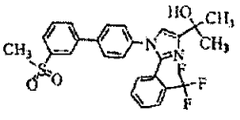
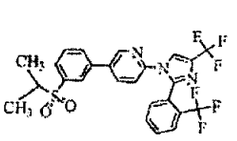
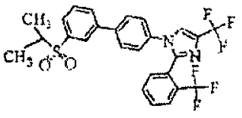
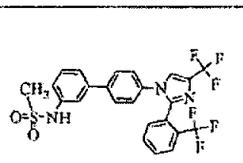
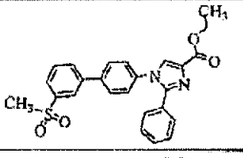
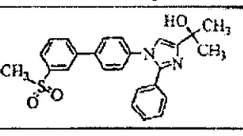
		fenil]-1H-imidazol-4-il}propan-2-ol			metil)fenil]-1H-imiazol-4-il}propan-2-ol
328		2-{1-[3'-(hidroximetil)bifenil-3-il]-2-[2-(trifluorometil)feniil]-1H-imidazol-4-il}propan-2-ol	337		3'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluoro metil)fenil]-1H-imidazol-1-il}-N-(1-metiletil)bifenil-4-carboxamida
329		2-{1-[3-(1H-indol-4-il)fenil]-2-[2-(trifluorometil)fenil]-1H-imidazol-4-il}propan-2-ol	338		2-{1-(2',4'-diclorobifenil-3-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
330		Ácido 5'-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}bifenil-4-carboxílico	339		2-{1-[4'-(etilsulfonil) bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol

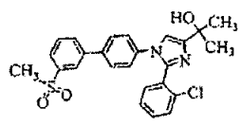
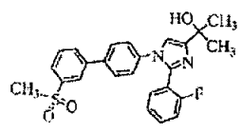
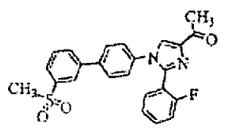
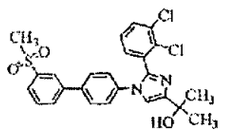
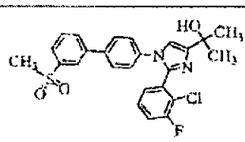
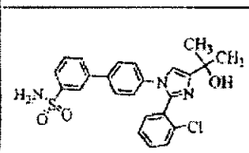
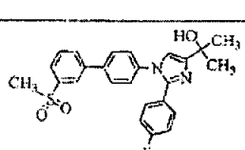
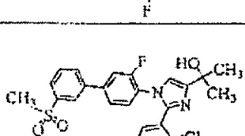
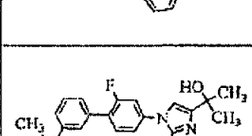
331		1-[5-(3-{4-(1-hidroxi-1-metiletil)-2-[2-(trifluorometil) fenil]-1H-imidazol-1-il}fenil)-2-tienil}etanona	340		2-{1-[4'-fluoro-3'-(trifluoro metil)bifenil-3-il]-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol
332		2-{1-(5'-cloro-2'-metilbifenil-3-il)-2-[2-(trifluorometil) fenil]-1H-imidazol-4-il}propan-2-ol	341		2-{1-(3'-fluoro-4'-metilbifenil-3-il)-2-[2-(trifluoro metil)fenil]-1H-imidazol-4-il}propan-2-ol

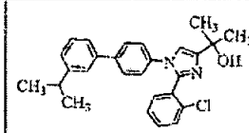
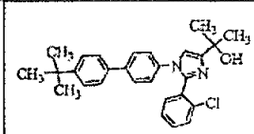
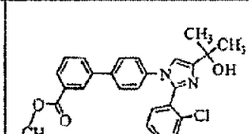
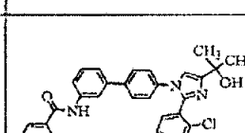
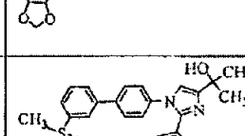
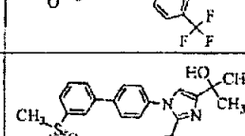
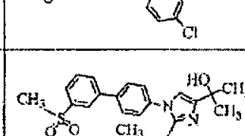
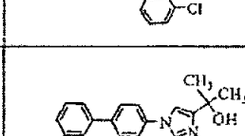
Cpd #	Structure	Name
342		N-butyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
343		N-(1,1-dimethylethyl)-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-6-methylbiphenyl-3-sulfonamide;
344		4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-N-methylbiphenyl-3-sulfonamide;
345		N-ethyl-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
346		N-(1,1-dimethylethyl)-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
347		2-{1-[2'-amino-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
348		2-{1-[3'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
349		2-{1-[4'-chloro-3'-(trifluoromethyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

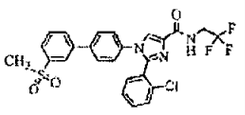
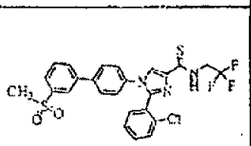
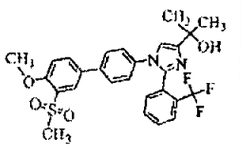
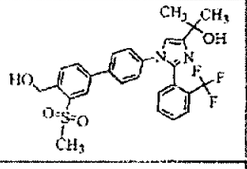
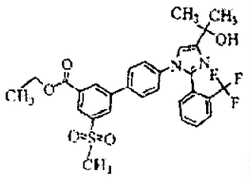
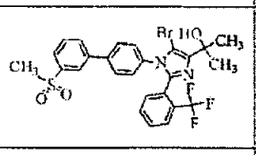
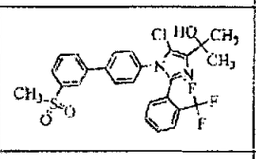
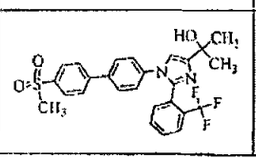
Cpd #	Structure	Name
350		3-chloro-4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-4-carboxylic acid;
351		2-(2-[2-(trifluoromethyl)phenyl]-1-{3'-[(trifluoromethyl)thio]biphenyl-4-yl}-1H-imidazol-4-yl)propan-2-ol;
352		2-{1-[3'-(morpholin-4-ylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
353		2-(1-{4-[5-(hydroxymethyl)-1,3-thiazol-2-yl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
354		2-{1-[2'-methyl-5'-(piperidin-1-ylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
355		1-[4-(4-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}phenyl)-2-thienyl]ethanone;
356		2-(1-{4-[5-(hydroxymethyl)-3-thienyl]phenyl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
357		4-(2-chlorophenyl)-5-{5-[3-(methylsulfonyl)phenyl]-2-thienyl}-2-(trifluoromethyl)-1H-imidazole;

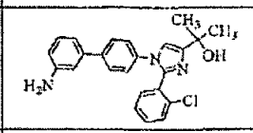
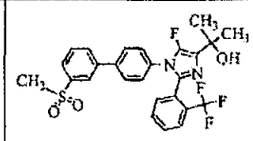
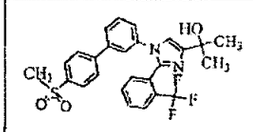
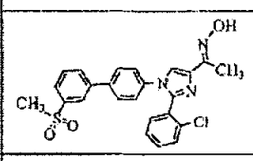
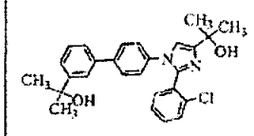
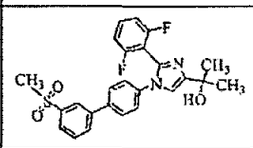
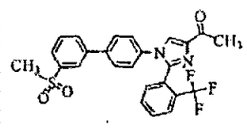
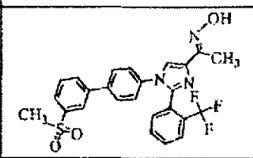
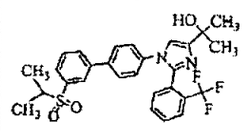
Cpd #	Structure	Name
358		2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-4-(trifluoromethyl)-1H-imidazole;
359		4-(2-chlorophenyl)-5-[3'-(methylsulfonyl)biphenyl-4-yl]-2-(trifluoromethyl)-1H-imidazole;
360		4'-[2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]biphenyl-3-sulfonamide;
361		4'-[4-(2-chlorophenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl]biphenyl-3-sulfonamide;
362		3-{5-[4-(2-chlorophenyl)-2-(trifluoromethyl)-1H-imidazol-5-yl]-2-thienyl}benzenesulfonamide;
364		1-[3'-(methylsulfonyl)biphenyl-4-yl]-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole;
365		4'-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-sulfonamide;
366		ethyl 1-(4-bromophenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxylate;
367		ethyl 1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxylate;

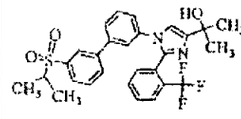
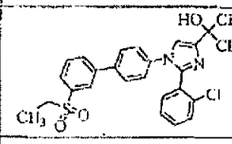
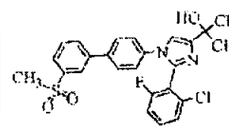
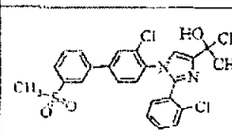
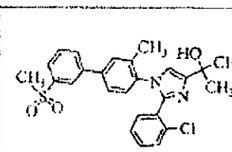
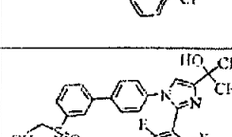
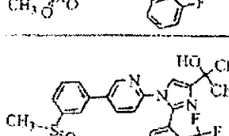
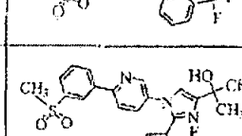
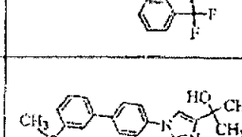
Cpd #	Structure	Name
369		5-[3-(methylsulfonyl)phenyl]-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine;
370		2-[2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]-5-[3-(methylsulfonyl)phenyl]pyridine;
371		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
372		5-{3-[(1-methylethyl)sulfonyl]phenyl}-2-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}pyridine;
373		1-{3'-[(1-methylethyl)sulfonyl]biphenyl-4-yl}-4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole;
375		N-(4'-{4-(trifluoromethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}biphenyl-3-yl)methanesulfonamide;
376		ethyl 1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-phenyl-1H-imidazole-4-carboxylate;
378		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-phenyl-1H-imidazol-4-yl}propan-2-ol;

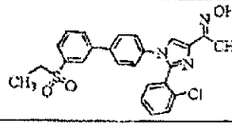
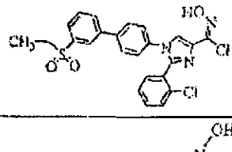
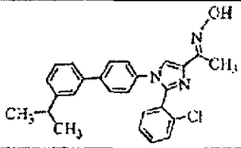
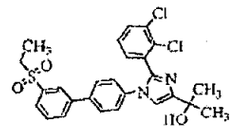
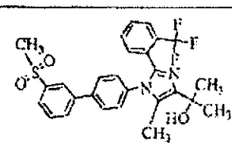
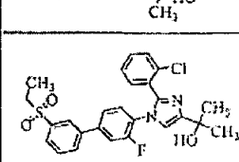
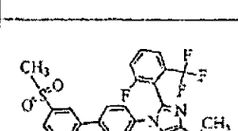
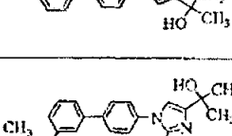
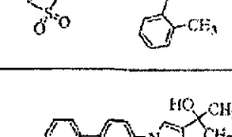
Cpd #	Structure	Name
379		2-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
380		2-{2-(2-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
381		1-{2-(2-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone;
382		2-{2-(2,3-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
383		2-{2-(2-chloro-3-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
384		4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-sulfonamide;
385		2-{2-(4-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
386		2-{2-(2-chlorophenyl)-1-[3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
387		2-{2-(2-chlorophenyl)-1-[2-fluoro-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;

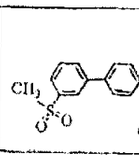
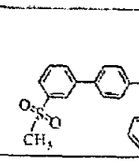
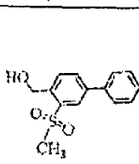
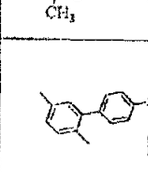
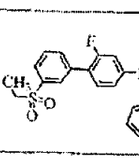
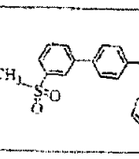
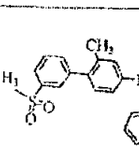
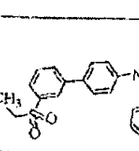
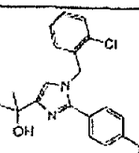
Cpd #	Structure	Name
388		2-{2-(2-chlorophenyl)-1-[3'-(1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
389		2-{2-(2-chlorophenyl)-1-[4'-(1,1-dimethylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
390		methyl 4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-carboxylate;
391		N-{4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-yl}-1,3-benzodioxole-5-carboxamide;
392		2-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[3-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
393		2-{2-(3-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
394		2-{2-(2-chloro-6-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
395		4'-[2-(2-chlorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]biphenyl-3-carboxylic acid;

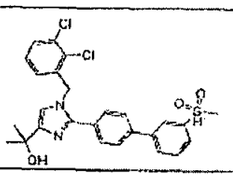
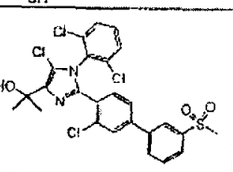
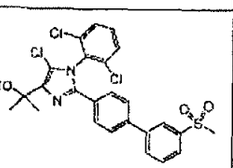
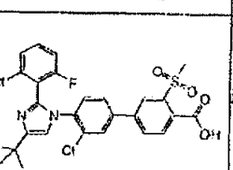
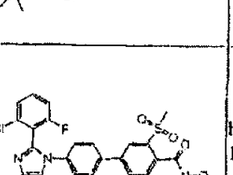
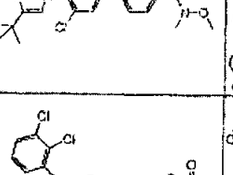
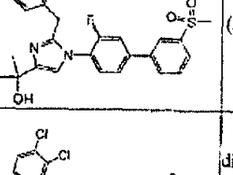
Cpd #	Structure	Name
397		2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide;
398		2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carbothioamide;
399		2-{1-[4'-(methyloxy)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
400		2-{1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
401		ethyl 4'-{4-(1-hydroxy-1-methylethyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-1-yl}-5-(methylsulfonyl)biphenyl-3-carboxylate;
402		2-(5-bromo-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
403		2-{5-chloro-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
404		2-{1-[4'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;

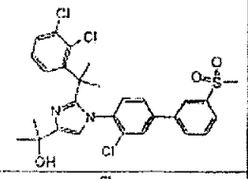
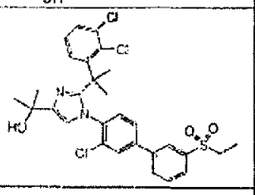
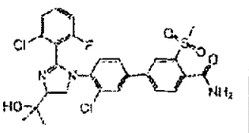
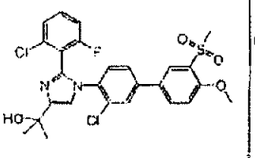
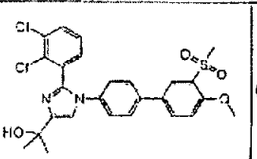
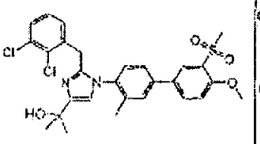
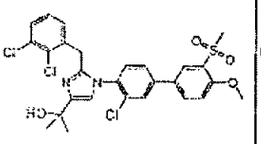
Cpd #	Structure	Name
405		2-[1-(3'-aminobiphenyl-4-yl)-2-(2-chlorophenyl)-1H-imidazol-4-yl]propan-2-ol;
406		2-{5-fluoro-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
407		2-{1-[4'-(methylsulfonyl)biphenyl-3-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
408		1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
409		2-{2-(2-chlorophenyl)-1-[3'-(1-hydroxy-1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
410		2-{2-(2,6-difluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
411		1-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}ethanone;
412		1-{1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}ethanone oxime;
413		2-(1-{3'-[(1-methylethyl)sulfonyl]biphenyl-4-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;

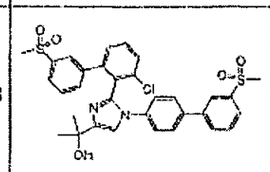
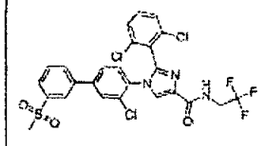
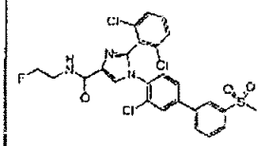
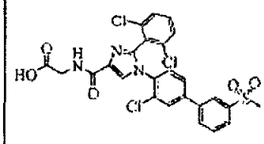
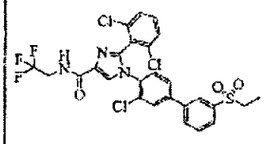
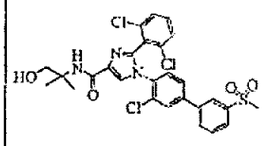
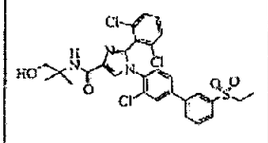
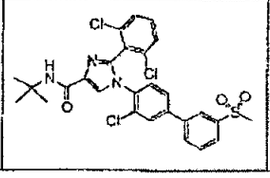
Cpd #	Structure	Name
414		2-(1-{3'-[(1-methylethyl)sulfonyl]biphenyl-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
415		2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
416		2-{2-(2-chloro-6-fluorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
417		2-{1-[3-chloro-3'-(methylsulfonyl)biphenyl-4-yl]-2-(2-chlorophenyl)-1H-imidazol-4-yl}propan-2-ol;
418		2-{2-(2-chlorophenyl)-1-[3-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
419		2-{2-(2,6-difluorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
420		2-(1-{5-[3-(methylsulfonyl)phenyl]pyridin-2-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
421		2-(1-{6-[3-(methylsulfonyl)phenyl]pyridin-3-yl}-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl)propan-2-ol;
422		2-{2-(2,6-dichlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;

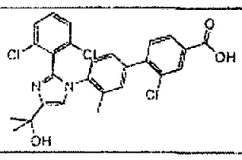
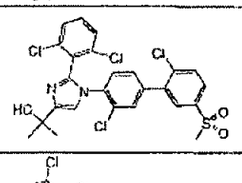
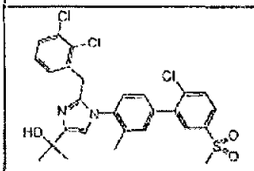
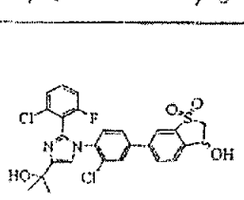
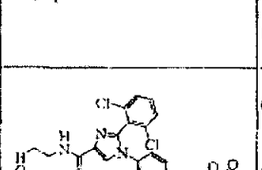
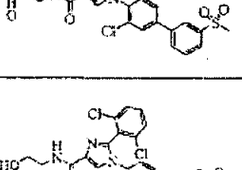
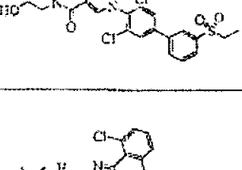
Cpd #	Structure	Name
424		1-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
425		1-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
426		1-{2-(2-chlorophenyl)-1-[3'-(1-methylethyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
427		2-{2-(2,3-dichlorophenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
428		2-{5-methyl-1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}propan-2-ol;
429		2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
430		2-{2-[2-fluoro-6-(trifluoromethyl)phenyl]-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
431		2-{2-(2-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
432		2-(1-[3'-(methylsulfonyl)biphenyl-4-yl]-2-{2-[(trifluoromethyl)oxy]phenyl}-1H-imidazol-4-yl)propan-2-ol;

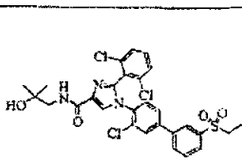
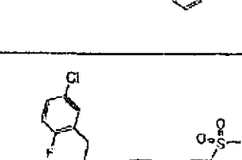
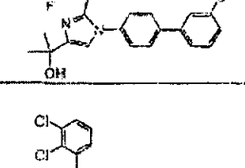
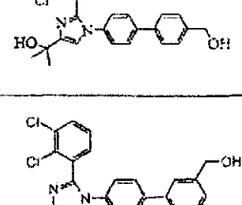
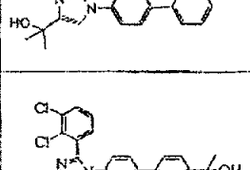
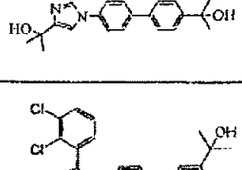
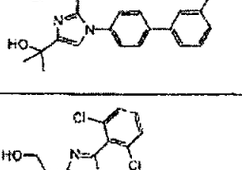
Cpd #	Structure	Name
433		1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
434		1-{2-(2-chlorophenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
435		1-{2-(2-chlorophenyl)-1-[4'-(hydroxymethyl)-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}ethanone oxime;
436		2-(1-(2',5'-dimethylbiphenyl-4-yl-2-(2-trifluoromethyl)phenyl)1H-imidazol-4-yl)propan-2-ol;
437		2-{2-(2-chlorophenyl)-1-[3'-(ethylsulfonyl)-2-fluorobiphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
438		2-{2-(3-chloro-2-methylphenyl)-1-[3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
439		2-{2-(2-chlorophenyl)-1-[2-methyl-3'-(methylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
440		2-{2-(3-chloro-2-methylphenyl)-1-[3'-(ethylsulfonyl)biphenyl-4-yl]-1H-imidazol-4-yl}propan-2-ol;
443		2-(1-(2-chlorobenzyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol

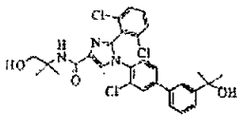
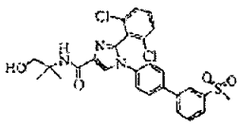
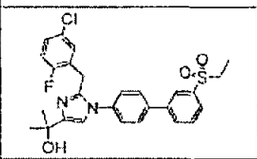
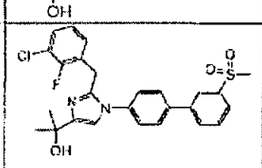
Cpd #	Structure	Name
444		2-(1-(2,3-dichlorobenzyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
445		2-(5-chloro-2-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-1-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol
446		2-(5-chloro-1-(2,6-dichlorophenyl)-2-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
447		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxylic acid
448		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-N-methoxy-N-methyl-3-(methylsulfonyl)biphenyl-4-carboxamide
449		2-(2-(2,3-dichlorobenzyl)-1-(3-fluoro-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
450		2-(2-(2,3-dichlorobenzyl)-1-(3'-(ethylsulfonyl)-3-fluorobiphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol

Cpd #	Structure	Name
451		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-(2,3-dichlorophenyl)propen-2-yl)-1H-imidazol-4-yl)propan-2-ol
452		2-(1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2-(2,3-dichlorophenyl)propen-2-yl)-1H-imidazol-4-yl)propan-2-ol
453		3'-chloro-4'-(2-(2-chloro-6-fluorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3-(methylsulfonyl)biphenyl-4-carboxamide
454		2-(1-(3-chloro-4'-methoxy-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2-chloro-6-fluorophenyl)-1H-imidazol-4-yl)propan-2-ol
455		2-(2-(2,3-dichlorophenyl)-1-(4'-methoxy-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
456		2-(2-(2,3-dichlorobenzyl)-1-(4'-methoxy-3-methyl-3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
457		2-(1-(3-chloro-4'-methoxy-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol

Cpd #	Structure	Name
458		2-(2-(3-chloro-3'-(methylsulfonyl)biphenyl-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
459		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide
460		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-fluoroethyl)-1H-imidazole-4-carboxamide
461		2-(1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxamido)acetic acid
462		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2,2,2-trifluoroethyl)-1H-imidazole-4-carboxamide
463		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
464		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
465		N-tert-butyl-1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazole-4-carboxamide

Cpd #	Structure	Name
466		2-chloro-4'-(2-(2,6-dichlorophenyl)-4-(2-hydroxypropan-2-yl)-1H-imidazol-1-yl)-3'-methylbiphenyl-4-carboxylic acid
467		2-(1-(2',3-dichloro-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-1H-imidazol-4-yl)propan-2-ol
468		2-(1-(2'-chloro-3-methyl-5'-(methylsulfonyl)biphenyl-4-yl)-2-(2,3-dichlorobenzyl)-1H-imidazol-4-yl)propan-2-ol
469		6-(3-chloro-4-[2-(2-chloro-6-fluorophenyl)-4-(1-hydroxy-1-methylethyl)-1H-imidazol-1-yl]phenyl)-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide
470		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1H-imidazole-4-carboxamide
471		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxyethyl)-1H-imidazole-4-carboxamide
472		1-(3-chloro-3'-(methylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-4-carboxamide

Cpd #	Structure	Name
473		1-(3-chloro-3'-(ethylsulfonyl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1H-imidazole-4-carboxamide
474		2-(2-(5-chloro-2-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
475		2-(2-(2,3-dichlorophenyl)-1-(4'-(hydroxymethyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
476		2-(2-(2,3-dichlorophenyl)-1-(3'-(hydroxymethyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
477		2-(2-(2,3-dichlorophenyl)-1-(4'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
478		2-(2-(2,3-dichlorophenyl)-1-(3'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
479		2-(2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)-2-methylpropan-1-ol

Cpd #	Structure	Name
480		1-(3-chloro-3'-(2-hydroxypropan-2-yl)biphenyl-4-yl)-2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
481		2-(2,6-dichlorophenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide
482		2-(2-(5-chloro-2-fluorobenzyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol
483		2-(2-(3-chloro-2-fluorobenzyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazol-4-yl)propan-2-ol

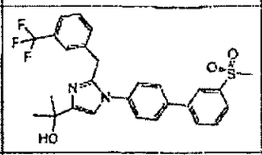
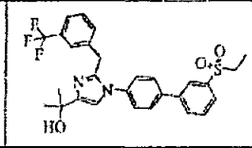
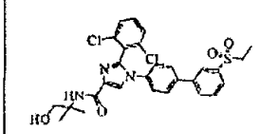
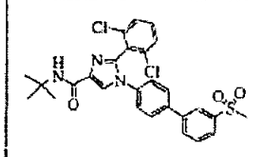
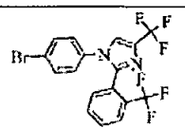
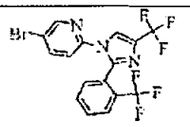
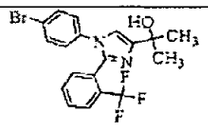
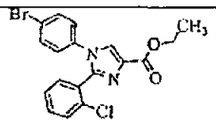
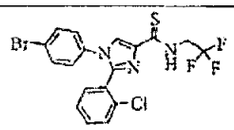
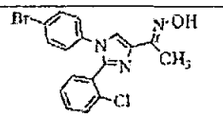
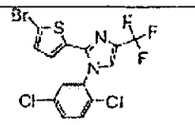
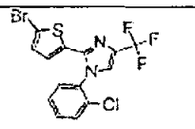
Cpd #	Structure	Name
484		2-(1-(3'-(methylsulfonyl)biphenyl-4-yl)-2-(3-(trifluoromethyl)benzyl)-1H-imidazol-4-yl)propan-2-ol
485		2-(1-(3'-(ethylsulfonyl)biphenyl-4-yl)-2-(3-(trifluoromethyl)benzyl)-1H-imidazol-4-yl)propan-2-ol
486		2-(2,6-dichlorophenyl)-1-(3'-(ethylsulfonyl)biphenyl-4-yl)-N-(1-hydroxy-2-methylpropan-2-yl)-1H-imidazole-4-carboxamide
487		N-tert-butyl-2-(2,6-dichlorophenyl)-1-(3'-(methylsulfonyl)biphenyl-4-yl)-1H-imidazole-4-carboxamide

Tabla 2

363		1-4-bromofenil)-4-(trifluorometil)-2-[2-(trifluorometil)fenil-1H-imidazol
368		5-bromo-2-{4-(trifluorometil)-2-[2-(trifluorometil)fenil]-1H-imidazol-1-il}-piridina
374		2-{1-(4-bromofenil)-2-[2-(trifluorometil)-1H-imidazol-4-il}propan-2-ol

377		Etil 1-(bromofenil)-2-(2-clorofenil)-1H-imidazol-4-carboxilato
396		1-(4-bromofenil)-2-(2-clorofenil)-N-(2,2,2-trifluoroetil)-1H-imidazol-4-carbotioamida
423		1-[1-(4-bromofenil)-2-(2-clorofenil)-1H-imidazol-4-il]etanona oxima
441		2-(5-bromo-2-tienil)-1-(2,5-diclorofenil)-4-(trifluorometil)-1H-imidazol
442		1-(5-bromo-2-tienil)-1-(2-clorofenil)-4-(trifluorometil)-1H-imidazol

Ejemplo 31

Ensayo de Coactivador FRET

El ensayo de coactivador FRET mide la capacidad de los ligandos de LR de promover las interacciones de proteína a proteína entre el dominio de unión al ligando (LBD) de LXR y las proteínas de coactivador transcripcional. El ensayo coniste en el uso de una proteína de fusión del dominio de unión al ligando (LBD) de receptor nuclear de Glutationa-S-Transferasa (GST) recombiante y una secuencia de péptido biotinilada sintética derivada del dominio que interactúa con

receptor de un péptido de coactivador tal como el coactivador 1 del receptor de esteroide (SRC-1). Generalmente, el GST-LBD está rotulado con un quelato de europio ((donador) a través de un anticuerpo anti-GST marcado con europio y el péptido de coactivador está rotulado con aloficocianina a través de una ligadura de estreptavidina-biotina.

En la presencia de un agonista para el receptor nuclear, se recluta el péptido hacia el GST-LBD que acerca el europio y la aloficocianina para permitir la transferencia de energía desde el quelato de europio a la aloficocianina. Al excitar el complejo con luz a 340 nm la energía de la excitación absorbida por el quelato de europio se transmite al grupo aloficocianina que deriva en la emisión a 665 nm. Si el quelato de europio no se acerca al grupo aloficocianina hay escasa o ninguna energía y la excitación del quelato de europio deriva en la emisión a 615 nm. Por lo tanto la intensidad de la luz emitida a 665 nm da una indicación de la resistencia de la interacción de proteína a proteína.

Materiales necesarios:

Proteína recombinante parcialmente purificada que comprende glutationa-S-transferasa fusionada en un marco al dominio de unión al ligando de LXR (que comprende los aminoácidos 188-447 del LXRalfa humano, o los aminoácidos 198-461 del LXRbeta

humano). Péptido biotinilado que contiene un motivo de interacción del receptor de SRC-LXXLL. Anticuerpo anti-GST conjugado a un quelato de Europio (alfa GST-K) (de Wallc/PE Life Science Ca N° AD0064). Aloficocianina unida a Estreptavidina (SA-APC) (de Wallac/PE Life Science CAT# AD0059A). 1x Tampón FRET (20 mM KH_2PO_4/K_2HPO_4 pH 7,3, 150 mM NaCl, 2,5 mM CHAPS, 2 mM EDTA, 1 mM DTT (agregar nuevo)). Placas de varios receptáculos de 96 o 384 recpetáculos (de LJL).

Soluciones de Material:

0,5 M KH_2PO_4/K_2HPO_4: pH 7,3; 5 M NaCl; 80 mM (5%) CHAPS; 0,5 M EDTA pH 8,0; 1 M DTT (mantener a -20°C).

Preparación de reactivos de selección:

Preparar la mezcla de la reacción para el número apropiado de receptáculos combinando los siguientes reactivos: 5 nM/receptáculo GST-hLXRalfaLBD, 5 nM/receptáculo GST-hLXRbetaLBD, 5 nM/receptáculo anticuerpo anti-GST (Eu), 12 nM/receptáculo péptido de biotina-SRC-1, 12 nM/recpetáculo APC-SA ajustar el volumen 10 uL/receptáculo con 1x tampón FRET.

Procedimiento:

Agregar 0,5 uL de un compuesto de material 1 mM (a una concentración final de 10' uM) o el solvente a cada recpetáculo en una placa negra de 96 o 384 receptáculso (LJL). Agregar 10 uL de la mezcla de la reacción (prepararada anteriormente) a cada receptáculo de la placa de varios receptáculos. Incubar cubierto o a la sombra (el APC es sensible a la luz) a temperatura ambiente durante 1-4 horas. Después de este tiempo si las reacciones no se leen se pueden almacenar a 4°C durante varias horas sin demasiada pérdida de señal.

Leer la placa usando un Analizador LJL, o un instrumento similar, usando las siguientes condiciones: Canal 1: La Excitación es 330 nm la emisión es de 615. Esto es para el quelato de Eu; Canal 2: La Excitación es de 330 nm y la emisión es de 665. Esto es para APC; Para el canal 1: Destellos por receptáculo: 100; tiempo de integración = 1000 us; intervalo entre destellos = 1x10 ms; Retardo después de destello: 200 us; Para el Canal 2: Destellos por receptáculo : 100; tiempo de integración: 100 us; intervalo entre destellos: 1x10 ms; Retardo después de destello: 65 us.

Ejemplo 32

Ensayo de Proximidad de Centelleo (SPA)

El ensayo SPA mide la señal reflectora generada por la unión de ^{3}H-24,25-epoxicolesterol a XRRalfa o LXRbeta. La base del ensayo es el uso de cuentas de SPA que contienen un centelleador, de manera tal que cuando la unión al receptor acerque el ligando rotulado a la cuenta, la energía desde el rótulo estimule al centelleador a emitir luz. La luz se mide usando un lector de centelleo de microplaca común. La capacidad de un ligando de unirse a un receptor se puede medir evaluando el nivel al cual el compuesto puede competir con un ligando radiorotulado con afindad conocida para el receptor.

Materiales Necesarios:

Rótulo: ^{3}H-24,25-epoxi-colesterol (Amersham)

LXRalfa lisado: heterodímero de LXRalfa/RXR expresado por Baculovirus con RXR que tiene un marcador de 6-HIS producido como un lisado crudo.

LXRbeta lisado: heterodímero de LXRbeta/RXR expresado por Baculovirus cn RXR que tiene un marcador de 6-HIS producido como un lisado crudo.

Cuentas de SPA: cuentas de SPA con marcardor de HIS de cobre Ysi (Amersham)

Placas: placa de 96 recpetáculos con superficie no ligante (Corning).

Tampón de dilución de lisado de proteína: (20 mM Tris-HCl pH 7,9; 500 mM NaCl, 5 mM Imidazol). 2x Tampón de SPA (40 mM

K_2HPO_4/KH_2PO_4 pH 7,3, 100 mM NaCl, 0,05% de Tween 20, 30% de glicerol, 4 mM EDTA) 2x Tampón de SPA con EDTA (40 mM K_2HPO_4/kH_2PO_4 pH 7,3,100 mM NaCl, 0,05% de Tween 20, 20% de glicerol).

Soluciones de material:

0,5 M K_2HPO_4/KH_2PO_4 pH 7,3; 0,5 M EDTA pH 8,0; 5 M NaCl; 10% de Tween 20; Glicerol

Preparación de lisados de proteínas

Los plásmidos de expresión de Baculovirus para RXR alfa humano, acceso N° NM_002957) (LXR alfa acceso N° U22662), LXR beta acceso N° U07132) se prepararon clonando los cADN de longitud completa apropiados en el vector pBacPakhis1 (Clontech, CA) siguiendo procedimientos comunes. La inserción de los cADN en el poligador de vector pBAcPakhis1 creó una fusión de marco al cADN a un marcador poli-His de extremo de N en pBacPakhis. La clonación correcta se confirmó mediante mapeo de restricción y/o secuenciación.

Se prepararon lisados de células infectando células de insectos Sf9 sanas a una densidad de aproximadamente $1,25x10^6$/ml a 27°C, en un volumen total de 500 ml por matraz de 1 L, se cultivaron en condiciones estándar. Para preparar el lisado de LXRalfa, las células de insectos se co-transfectaron

con el cassette de expresión de LXRalfa a un M.O.I. de 0,5 a 0,8 y con el cassette de expresión de RXR a un M.O.I. de aproximadamente 1,6. Para preparar el lisado de LXRbeta, las células de insectos se cotransfectaron con el cassette de expresión de LXRbeta a un M.O.I. de aproximadamente 1,6 y con los cassettes de expresión de RXR a un M.O.I. de aproximadamente 1,6. En ambos casos las células se incubaron durante 48 hors a 27°C agitando constantemente antes de cosechar.

Después de la incubación, las células se cosecharon mediante centrifugación y se graficaron. Las pelotillas decélulas se resuspendieron en dos volúmenes de tampón de extracción recién preparado helado (20 mM Tris pH 8,0, 10 mM Imidazol, 400 mM NaCl, que contiene una tableta de inhibidor de proteasa libre de EDTA (Roche Catálogo N° 1836170) por 10 ml de tampón de extracción). Las células se homogeneizaron lentamente sobre hielo usando un Douncer para alcanzar un 80%-90% de lisis de células. El producto homogeneizado se centrifugó en un rotor previamente enfriado (Ti50 o Ti70, o un equivalente) a 45.000 rpm durante 30 minutos a 4°C. Se congelaron alícuotas del sobrenadante sobre hielo seco y se almacenaron congeladas a -80°C hasta la cuantificación y el control de calidad. Las alícuotas de los lisados se ensayaron para el ensayo de SPA para asegurar la consistencia de un lote a otro, y a través

del análisis de SDS-PAGE después de la purificación usando Resina Ni-NTA (Qiagen) y se ajustaron para la concentración de proteína y el nivel de expresión antes de su uso en ensayos de detección.

Preparación de Reactivos de Evaluación

Soluciónde [^{3}H] 24,25 Epoxicolesterol (EC): Para una placa de 384 receptáculos (o de 400 receptáculos), 21 ul de [^{3}H] EC (actividad específica 76,5 Ci/mmol, 3,2 mCi/ml) se agregó a 4,4 ml de 2x tampón de SPA para proporcionar una concentración final de 200 nM. Para cada placa de 384 recepáculos adicional, se agregaron 19,1 ul de [^{3}H] EC a 4,0 ml de tampón 2 x SPA. La concentración final de [3H] EC en el receptáculo fue: 50 nM. El LXRalfa lisado (preparado como anteriormente) se dilyó con tampón de dilución de proteína lisada Se prepararon 1400 ul de LXRalfa lisado diluido por cada placa de 384 receptáculos (o de 200 receptáculos) y 1120 ul de LXRalfa lisado diluido para cada placa de 384 receptáculos adicional. El LXRalfa lisado (preparado como anteriormente) se diluyó con tampón de dilución de proteína lisada. Se prepararon 1400 ul de LXRbeta lisado diluido por cada placa de 384 receptáculos (o 200 receptáculos) y 1120 ul de LXRbeta lisado diluido por cada placa de 384 receptáculos adicional. Solución de cuentas de SPA: Para cada placa de 384 receptáculos (o 400

receptáculos), 3,75 ml de 2 x tampón de SPA con EDTA, 2,225 ml de H_2O y 1,5 ml de cuentas de SPA marcado con His Ysi (vórtice mucho antes de la recolección) se mezclaron juntos. Para cada placa de 384 receptáculos adicional, un adicional de 3,5 ml de 2 x tampón de SPA con EDTA, 2,1 ml de H_2O y 1,4 ml de cuentas de SPA marcado con His Ysi se mezclaron juntos. .

Procedimiento:

Las diluciones apropiadas de cada compuesto se preparon y se colocaron con una pipeta en los receptáculos apropiados de una placa de varios receptáculos. Se agregaron 9,1 ul de [3H] EC a cada receptáculo de las columnas 2-23 de la placa de varios receptáculos. Se agregaron 5 ul de LXRalfa lisado diluido a cada receptáculo de las columnas 2-23 en las filas impares de la placa de varios receptáculos. Se agregaron 5 ul de LXRbeta lisado diluido a cada recepáculo de las columnas 2-23 en las filas pares de la placa de varios receptáculos. Se agregaron 17,5 ul de la solución de cuentas de SPA a cada receptáculo de las columnas 2-23 de la placa de varios receptáculos.

Las placas se cubrieron con un sellador transparente y se colocaron en una incubadora a tempertura ambiente durante 1 hora. Después de la incubación las placas se analizaron usando un lector de placas luminiscente (MicroBeta, Wallac), usando el programa n ABASE 3H_384DPM. La instalación para n ABASE

3H_384DPM fue: Modo de Recuento: DPM; Tipo de Muestra: SPA, Modo ParaLux: fondo bajo; Tiempo de recuento: 30 segundos.

Los ensayos para LXRalfa y LXRbeta se realizaron en forma idéntica. Ki determinado representa el promedio de por lo menos dos sobrenadantes de respuesta a la dosis independientes. La afinidad a la unión para cada compuesto se puede determinar mediante dos análisis de regresión no lineales usando la fórmula de competencia de un sitio para determinar la IC50 donde:

$$Y = \text{Base} + \frac{(\text{Parte Superior} - \text{Base})}{(1+10^{X-\log IC50}}$$

El Ki se calcula usando la ecuación de Cheng y Prusoff donde:

Ki = IC50/(1+[Concentración del Ligando]/Kd del Ligando)

Para este ensayo, generalmente la concentración del ligando = 50 nM y el Kd de EC para el receptor es 200 nM como se determina mediante la unión de saturación.

Los compuestos de la nvención demostraron la capacidad de unirse a LXRalfa y/o LXRbeta cuando se usaron en este ensayo.

Ejemplo 33

Ensayo de Co-Transfección

Para medir la capacidad de los compuestos de activar o inhibir la actividad transcripcional de LXR en un ensayo basado en

células, se usó el ensayo de co-transfección. Se ha mostrado qu LXR funciona coo un heterodímero con RXR. Para el ensayo de co-transfección, plásmidos de expresión para LXR y RCXR se introducen a través mediante transfección transitoria en células de mamíferos junto con un plásmido indicador de luciferasa que contiene una copia de una secuencia de ADN que está unida por heterodímeros de LXR-RXR (LXRE; Willy, P. et al, 1995). El tratamiento de células transfectadas con un agonista de LXR aumenta la actividad transcripcional de LXR, que se mide mediante un aumento en la actividad de luciferasa. En forma similar, la actividad de los antagonistas de LXR se puede medir determinando la capacidad de un compuesto de inhibir en forma competitiva la actividad de un agonista de LXR.

Materiales Necesarios:

Plásmidos de expresión de co-transfección de células de riñón de Mono Verde Africano CV-1, que comprenden LXRalfa de longitud completa (pCMX-h, LXRbeta (pCMX-hLXRbeta), o RXRalfa (pCMX-RXR), plásmido indicador (LXREx1-Tk-Luciferasa) y control (vector de expresión de pCMX-Galactosidasa) (Willey et al, Gene & Development 9 1033-1045 (1995)). Reactivo de transfección tal como FuGENE6 (Roche). 1x Tampón de lisis de células (1% Triton X (JT Baker X200-07), 10$ glicerol (JT Baker M778-07), 5 mM Ditritreitol (Quantum Bioprobe DTT03;

agregar nuevo antes lisar), 1 mM EDTA (Etilenglicol-bis (B-Amino etil éter)-ácido N,N,N',N'-Tetra acético (Sigma E-4378), 25 mM Tricina (ICN 807420) pH 7,8) 1 x tampón de ensayo de luciferasa (ph a 7,8) (0,73 mM ATP, 22,3 mM Tricina, 0,11 mM EDTA, 33,3 mM DTT) 1 x Luciferrina/CoA (10 mM Luciferrina, 3,05 mM Coenzima A, 10 mM HEPES).

Preparación de reactivos de detección

Se prepararon células CV-1 24 hors antes del experimento colocando en placas en matraces T-175 o platillos de 500 cm^2 para lograr 70-80% de confluencia el día de la transfección. El número de células que se deben transfectar se determinó por el número de placas qu ese detectaron. Cada placa de 384 receptáculos requiere 1,92x106 células o 5000 células por receptáculo. El reactivo de transfección de ADN se preparó usando los ADN de plásmidos requeridos con un reactivo de trasnfección de lípidos catiónico FuGENE6 (Roche) siguiendo las instrucciones dadas con los reactivos. Se determinaro cantidades óptimas de ADN en forma empírica por cada línea de células y el tamaño de recipiente que se debe transfectar. Se agregaron 10-20 ml de medios en el reactivo de transfección de ADN y esta mezcla se agregó a las células después de aspirar los medios desde el matraz de T175 cm^2. Las células luego se

incubaron por lo menos durante 5 horas a 37°C para preparar la detección de células.

El reactivo de ensayo de luciferasa se preparó combnando antes del uso (por cada 10 ml): 10 ml 1x tampón de ensayo de luciferasa; 0,54 ml de 1x Luciferrina/CoA; 0,56 ml de 0,2 M sulfato de magnesio.

Procedimiento:

Las placas de ensayo se prepararon disponiendo 5 ul de compuesto por cada receptáculo de una placa de 384 receptáculos para alcanzar una concentración final del ocmpuesto de 10 uM y no más del 1% de DMSO. Los medios se removieron de las células de detección, las células se tripsinaron, se cosecharon células mediante centrifugación, se contaron y colocaron en placas a una dnesidad de aproximadamente 5000 células por receptáculo en la placa de ensayo de 384 receptáculos preparada anteriormente en un volumen de 45 ul. Las placas de ensayo que contienen ambos compuestos y las células de detección (50 ul de volumen total) se incubaron durante 20 hors a 37°C.

Después de la incubación con compuestos, los medios se removieron de las células y se agregó el tampón de liss (30 ul/receptáculo). Después de 30 minutos a temperatura ambiente,

se agregó el tampón de ensayo de luciferasa (30 ul/receptáculo) y las placas de ensayo se leyeron en un luminómetro (lector PE Biosystems Northstar con inyectores a bordo, o equivalente). Las placas se leyeron inmediatamente después de de agregar el tampón de ensayo de luciferasa.

El ensayo de co-transfección de LXR/LXRE se puede usar para establecer los valores de EC50/IC50 para la potencia y el porcentaje de actividad o la inhibición para eficacia. La eficacia define la actividad de un compuesto en relación con un control alto ((N-(3-((4-fluorofenil)-(naftalen-2-sulfonil)amino)propil-2,2-dimetilpropionamida)) o un bajo control (vehículo DMSO). Las curvas de respuesta a la dosis se generan a partir de una curva de 8 puntos con concentraciones que difieren en unidades de 1/2 DOG. Cada punto representa el promedio de 4 receptáculos de datos de una placa de 384 receptáculos.

Los datos de este ensayo se cargan a la siguiente ecuación, que se puede resolver desde el valor de EC50:

$$Y=\text{Base} + (\text{Parte Superior} - \text{Base})/(1+10^{//\log EC50-X)*\text{Pendiente de la colina}})$$

La EC50/IC50 se define entonces como la concentración a la cual un agonista o antagonista produce una respuesta que está a mitad de camino entre los valores de la parte superior (máximo) y la Base (referencia). Los valores de EC50/IC50

representados son el promedio de por lo menos 3 experimentos independientes. La determinación de la eficacia relativa o del % de control para un agonista es mediante la comparación con la respuesta máxima lograda por ((N-(3-((4-fluorofenil)-(naftalen-2-sulfonil)amino)propil-2,2-dimetilpropionamida) qu se mide individualmente en cada experimento de respuesta a la dosis.

Para el ensayo de antagonistas, se puede agregar un agonista de LXR a cada receptáculo de una placa de 384 receptáculos para producir una respuesta. El % de inhibición para cada antagonista es entonces una medición de la inhibición de la actividad del agonista. En este ejemplo, un 100% de inhibición indicaría que la actividad de una concentración específica del agonista de LXR se ha reducido a los niveles de referencia, definida como la actividad del ensayo en la presencia de DMSO solamente.

Los compuestos de la invención, cuando se ensayaron de esta manera, demostraron la capacidad de modular la actividad de LXRalfa y/o LXRbeta. Preferentemente, los compuestos activos modulan la actividad de LXR con una EC50 o IC50 de 10uM o menos. Más preferentemente, l EC50 o IC50 de los compuestos activos preferidos es 1 uM o menos.

Ejemplo 34

Estudios in vivo

Para evaluar la regulación directa de los genes blanco claves por los compuestos de la invención, se administra a animales una sola dosis oral del compuesto del ensayo y se recogen tejidos a diferentes puntos de tiempo. Se aplican dosis orales a ratones C57BL/6 machos (n=8) con vehículo o compuesto. En diferentes puntos de tiempo después de la dosis, se hace sangrar a los animales a través del seno retroorbital para la extracción de plasma. Luego se sacrifica a los animales y los tejidos, tales como el hígado y mucosa intestinal se extraen y se congelan para otro análisis. El plasma se analiza por los parámetros de lípidos, tales como los niveles de colesterol total, colesterol HDL y triglicéridos. Se extrae el ARN para los tejidos congelados y se puede analizar mediante PCR de tiempo real cuantitativa por la regulación de los genes blanco claves. Para identificar la especificidad de la regulación de genes blanco por subtipos de LXR, se usan ratones que carecen de LXR (LXRalfa+/- o LXRbeta+/-) y controles de tipo silvestre de C57BL/6 en el mismo protocolo.

Evaluación de Lípidosen plasma

Para comparar los efectos de los compuestos sobre el colesterol y los triglicéridos en plasma, se aplican dosis a

los animales con el compuesto durante una seman y se monitorean los niveles de lípidos en plasma durante todo el estudio. Se dosifica a ratones C57BL/6 machos (n=8), vía oral con vehículo o compuesto. Se extraen muestras de plasma el día 1 (para agrupar a los animales), el día 1, 3 y 7. Se recogen muestras tres horas después de la dosis diaria. El día 7 del estudio, después de la extracción del plasma, se sacrifica a los animales y se extraen tejidos, tales como hígado y mucosa intestinal y se congelan para otro análisis. El plasma se analiza por los parámetros de lípidos, tales como los niveles de colesterol, colesterol HDL y triglicéridos. Se extrae el ARN para los tejidos congelados y se puede analizar mediante PCR de tiempo real cuantitativa por la regulación de genes blanco claves. Para identificar la especificidad de la regulación de genes blanco por subtipos de LXR, se usan ratones que carecen de LXR (LXR alfa +/- o LXR beta +/-), y controles de tipo silvestre de C57BL/6 en el mismo protocolo.

Ejemplo 35

EC50 e IC50 Medidas para LXR para compuestos de la invención

Los compuestos de la invención, cuando se ensayaron como se describió en el Ejemplo 33, demostraron la capacidad de modular la actividad de LXR alfa y/o LXR beta. Las actividades de LXR para diferentes compuestos de la invencion se presentan

en la siguiente tabla; los compuestos con valores de EC50 o IC50 < 10 uM para por lo menos uno de LXR alfa y LXR beta se consideran activos. En la siguiente tabla, los datos de IC50 o EC50 están representados de la siguiente manera: A=<1 uM, B= 1-10 uM, y C= > 10 uM.

Cpd #	activity	44	B	100	B	142	A	186	A	379	A	443	A
		45	B	101	A	143	A	187	A	380	B	444	A
1	A	58	A	102	A	144	A	188	A	381	B	445	A
2	A	59	A	103	B	145	A	189	A	382	A	448	C
3	A	60	A	104	A	146	A	190	A	383	A	449	A
4	A	61	A	105	A	147	A	191	A	384	B	450	A
5	A	62	A	106	B	148	A	192	A	385	B	451	A
6	A	63	A	107	A	149	A	193	A	386	A	452	A
7	A	64	A	108	A	150	A	194	A	387	B	453	B
8	A	65	A	109	A	151	A	195	A	388	B	454	B
9	A	66	A	110	A	152	A	196	A	389	B	455	A
10	A	67	A	111	A	153	A	197	A	390	B	456	A
11	A	68	A	112	A	154	A	198	A	391	B	457	A
12	A	69	A	113	A	155	A	199	B	392	A	458	B
13	A	70	A	114	A	156	A	200	A	393	A	459	A
14	A	71	A	115	A	157	A	201	A	394	A	460	A
15	A	72	A	116	A	158	A	220	A	395	B	461	C
16	A	73	A	117	A	159	A	274	B	396	B	462	A
17	A	74	A	118	A	160	A	281	A	397	A	463	A
18	A	75	A	119	A	161	A	344	A	398	A	464	A
19	A	76	A	120	A	162	A	357	A	399	B	465	A
20	A	77	A	121	A	163	A	358	A	400	A	466	C
21	A	78	A	122	A	164	B	359	A	401	B	467	A
22	A	80	B	123	A	165	B	360	A	402	A	468	A
23	A	82	A	124	A	168	B	361	B	403	A	469	B
24	A	83	B	125	A	169	A	362	A	404	B	470	A
25	A	84	A	126	A	170	A	363	B	405	B	471	A
26	A	85	A	127	B	171	A	364	A	406	A	472	A
27	A	86	A	128	A	172	A	365	A	407	A	473	A
28	A	87	A	129	A	173	A	366	B	408	A	474	A
29	A	88	A	130	B	174	A	367	A	409	B	475	B
30	A	89	A	131	B	175	A	368	B	410	B	476	B
31	A	90	A	132	B	176	A	369	A	411	A	477	B
32	A	91	B	133	A	177	A	370	A	412	A	479	A
33	A	92	B	134	A	178	A	371	A	413	A	480	A
34	A	93	A	135	A	179	A	372	A	415	B	481	A
35	B	94	A	136	A	180	A	373	A	416	B	482	A
36	B	95	A	137	A	181	A	374	B	417	A		
37	C	96	A	138	A	182	A	375	A	418	A		
38	C	97	B	139	A	183	A	376	A	419	B		
41	B	98	A	140	A	184	A	377	B	420	B		
42	A	99	A	141	A	185	A	378	B	421	B		

Se entiende que los ejemplos y las realizaciones descritas aquí tienen sólo propósitos ilustrativos y que diferentes modificaciones o cambios a la luz de ellas les serán sugeridos a los expertos en el arte y se los debe incorporar dentro del alcance de esta solicitud de patente y del alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes y solicitudes de patentes citadas en la presente se incorporan como referencia en su totalidad con todos los fines.

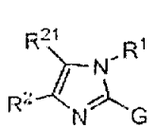
Todas las patentes estadounidenses, publicciones de solicitudes de patentes estadounidense, solicitudes de patentes estadounidenses, patentes extranjeras, publicaciones de patentes extranjeras y publicaciones que no son patentes citadas en esta memoria descriptiva y/o enumeradas en la Planilla de Datos de la Solicitud de Patente se incorporan en la presente como referencia en su totalidad.

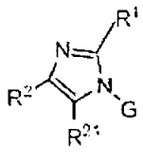
A partir de lo antedicho, se apreciará que, aunque se han descrito realizaciones específicas de la invención con propósitos ilustrativos, se pueden hacer diferentes modificaciones sin apartarse del espíritu y alcance de la invención. Por consiguiente, la invención no está limitada excepto por las reivindicaciones adjuntas. Esta invención también comprende todas las combinaciones de aspectos alternativos de la invención indicados aquí. Se entiende que

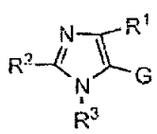
todas y cada una de las realizaciones de la presente invención se pueden tomar en conjunto con cualquier otra realización para describir realizaciones adicionales de la presente invención. Además, cualquier elemento de una realización se puede combinar con todos y cada uno de los elementos de cualquiera de las realizaciones adicionales descritas.

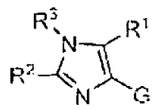
REIVINDICACIONES

1. Un compuesto de acuerdo con una de las siguientes fórmulas:


IIa


IIb


IIc


IId

O una sal farmacéuticamente aceptable, isómero, o profármaco de él, en donde:

(A) R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$ o $-L^6-L^5-L^6-$, en donde:

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), cicloalquilo (de C_3-C_6) o haloalquilo (de C_1-C_6); y

Cada L^6 es independientemente $-CS-$, $-CO-$, $-SO_2-$, $-O-$, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, o $-C(=NN(R^{11})_2)-$, -arilo-, -cicloalquilo de C_3-C_8-, -heteroarilo-, o -heterociclilo-,

En donde el arilo, cicloalquilo, heteroarilo, o heterociclilo se sustituye optativamente con uno o más R^{14};

O cada L^6 se selecciona independientemente de alidilo de C_2-C_6,

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$,

-CO-, $-CO_2-$, -OC(=O)-, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})$; y

R^5 es arilo, heterociclilo, heteroarilo, cicloalquilo (de C_3-C_6), -C o -B-C-, en donde

B es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8-; y

C es halógeno, -alquilo de C_1-C_6, -haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, o $-N(R^{11})_2$,

En donde R^5 se sustituye optativmente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalqulo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, arilalcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquiloCOOR^{11}, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SON(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, -

$CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 y R^{21} son $-L^3-R^7$, en donde

Cada L^3 es independientemente un enlace o $-(CH_2)_m-V^1-(CH_2)_n-$, en donde

n es 0-6; y

V^1 es $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-OCO-$, $-CO-$, $-CS-$, $-CONR^{10}-$, $-C(=N-R^{11})-$, $-C(=N-OR^{11})-$, $-C[=N-N(R^{11})_2]$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, cicloalquilo de C_3-C_6 o ciclohaloalquilo de C_3-C_6;

O cada L^3 es independientemente alidilo de C_2-C_6,

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$,$-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-CON(R^{10})-$, $-CO-$, $-CO-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$; y

Cada R^7 es independientemente hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z-, -Y-Z-, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$,

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, haloarilo, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, $C(R^{11})=C(R^{11})-COOH$, arilo, heteroarilo, heterociclilo, heterocicliloxi, heteroariloxi, -Z', -Y'-Z', o -X'-Y'-Z', en donde

X' es -O-;

Y' es $-[C(R^{15})_2]_m$ o cicloalquilo de C_3-C_8; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})$, $-N(R^{11})C(=O)R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-OR^{11}$, $-N(R^{11})C(=O)-R^{11}$, o $-N(R^{11})S(O=)_2R^{11}$,

En donde cada R^{7a} se sustituye optativamente con uno o más R^8,

En donde cada R^8 es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, haloalquilo de C_1-$C_6(OR^{11})$, alquilo de C_0-C_6OR^{11}, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6COR^{11}, alquilo de C_0-C_6COOR^{11}, o alquilo de C_0-$C_6SO_2R^{11}$,

Siempre que R^2 y R^{21} no sean simultáneamente hidrógeno,

R^3 es $-L-R^6$, en donde

L es un enlace, $-X^3-(CH_2)_n-X^3-$, $-(CH_2)_m-X^3-(CH_2)_n-$ o $-(CH_2)_{1+w}-Y^3-(CH_2)_w-$, en donde

n es 0-6; cada w es independientemente 0-5; y

cada X^3 es independientemente un enlace, $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C\equiv C$, $-CO-$, $-CS-$, $-CONR^{10}-$, $-C(=N)(R^{11})-$, $-C(=N-OR^{11})-$, $-[=N-N(R^{11})_2]$, $-CO_2-$, $-SO_2-$, o $-SO_2N(R^{10})-$; y

Y^3 es $-O-$, $-S-$, $-NR^7-$, $-N(R^{10})CO-$, $N(R^{10})CO_2-$, $-OCO-$, $-OC(=O)N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-N(R^{10})SO_2-$, o $-NR^{10}CSNR^{10}-$;

o L es una cadena de alidilo en donde la cadena de alidilo está optativamente interrumpida por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO-$, o $-SO_2N(R^{10})$; y

R^6 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, arilo, cicloalquilo de C_3-C_8, heteroarilo, heterociclilo, $-CN$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2-$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})N(OR^{11})$, en donde el arilo, heteroarilo, cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{6a}, en donde

cada R^{6a} es independientemente $-Z''$, $-Y''-Z''$, o $-X''-Y''-Z''$, en donde

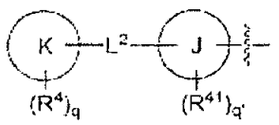
X'' es $-O-$;

Y" es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, heterociclilo, arilo o heteroarilo, en donde

El arilo, heteroarilo, cicloalquilo, o heterociclilo optativamente se sustituye con por lo menos un grupo que es cada uno independientemente Z";

Z" es -H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)n(R^{11})_2$, $-N(R^{11})_2$, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, $-OC(=O)-OR^{11}$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$; y

G es un grupo de la fórmula



, en donde

J es arilo, heteroarilo, o está ausente;

K es arilo, heteroarilo, o está ausente;

Siempre que

(i) si K está ausente, entonces q es 1 y R^4 está unido a L^2; y cada R^4 y R^{41} es independientemente halógeno, oxo, nitro, $CR^{11}=CR^{11}COOR^{11}$, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCN(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, -

$NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, $-SOR^{11}$, o $-SR^{11}$,

En donde cada R^4 se sustituye optativamente con uno o más R^{4a},

En donde cada R^{4a} es independientemente halógeno, ariloxi, analquiloxi, ariloxialquilo, alcoxiarilo de C_1-C_6, aril alquilcarboxi de C_0-C_6, -G', -E'-G', o -D'-E'-G', en donde

D' es -O-;

E' es $-[C(R^{15})]_m-$ o cicloalquilo de C_3-C_8; y

G' es -H, halógeno, $-COR^{11}$, $-COOR^{11}$, -C≡N, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace o $-[C(R^{15})_2]_m-V^2-[C(R^{15})_2]_n-$, en donde

V^2 es independientemente $-C(R^{11})_m$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $-SO_2-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, -CS-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, cicloalquilo de C_3-C_8, o ciclohaloalquilo de C_3-C_6,

o V^2 es alidilo de C_{2-6},

en donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2O-$, $-C(R^{11})NR^{11}$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$;

o V^2 es arilo, heteroarilo, o heterociclilo, cada uno de los cuales se sustituye optativamente con uno o más R^9, en donde

cada R^9 es independientemente halógeno, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alquiloxi de C_1-C_6, alquilo de C_0-C_6COOR^{11};

cada m es 0, 1, 2, 3, 4, 5 o 6;

q es 0, 1, 2, 3, 4, o 5;

siempre que q sea 0 si y sólo si K no es fenilo; y

q' es 0, 1, 2, 3, o 4,

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-, -haloalquilo de C_1-C_6, $-N(R^{12})_2$, arilo, alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, haloalquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C=O(OR^{13})$; alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, aluqilo de C_0-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{0-6},

arilalquilcarboxi de C_{0-6}, alquilo de C_0-$C_6N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-;

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, alquilo de C_1-$C_6CON(R^{11})_2$, alquilo de C_0-$C_6CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}; y

(B) siempre que

(i) cuando L^2 es un enlace, tanto J como K no están ausentes;

(ii) si el compuesto definido por la fórmula IIa, entonces

a. si J es fenilo y K es tienilo, furilo o tiazoilo y q es 0, entonces R^1 no es 4-(NH_2SO_2)fenilo, 4-(NH_2SO_2)-3-fluorofenilo-, y

b. si R^5 es piridilo o fenilo optativamente sustituido con uno o más R^{5a} y L^1 es un enlace, entonces G no es p-(NH_2SO_2)fenilo o p-(CH_3SO_2)fenilo-;

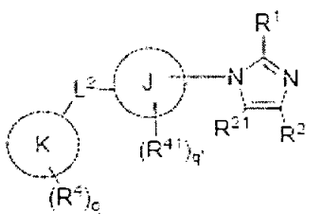
(iii) si el compuesto se define con la fórmula IIc o IId, entonces G no es p-(NH_2SO_2)fenilo o p-(CH_3SO_2)fenilo;

(iv) el compuesto no es 1-(bifenil-4-il)-2,5-difenil-1H-imidazol.

2. El compuesto de acuerdo con la reivindicación 1, en donde L^1 es un enlace.

3. El compuesto de acuerdo con la reivindicación 2, en donde R^5 es arilo optativamente sustituido con un o más R^{5a}.

4. El compuesto de acuerdo con la reivindicación 3, de la fórmula



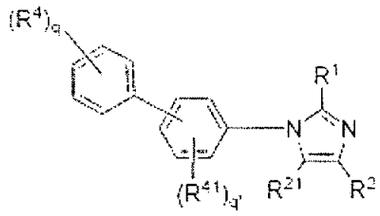
O una sal farmacéuticamente aceptable, isómero o profármaco de él, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

5. El compuesto de acuerdo con la reivindicación 4, en donde L^2 es un enlace.

6. El compuesto de acuerdo con la reivindicación 4, en donde por lo menos uno de J y K es fenilo.

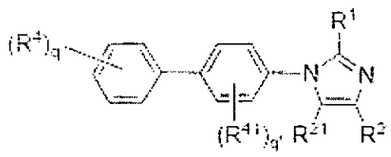
7. El compuesto de acuerdo con la reivindicación 6, en donde J y K son ambos fenilo.

8. El compuesto de acuerdo con la reivindicación 7, de la fórmula



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

9. El compuesto de acuerdo con la reivindicación 8, de la fórmula:



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él, en donde R^{21} es -H, halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

10. El compuesto de acuerdo con la reivindicación 9, en donde cada R^4 es independientemente halógeno, $-G^1$, $-E-G^1$ o $D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m$,

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, o $-SO_2N(R^{11})_2$.

11. El compuesto de acuerdo con reivindicación 10, en donde cada R^{41} es independientemente halógeno, $-G^2$ o $-E-G^2$, en donde
E es $-[C(R^{15})_2]_m$,
en donde cada R^{15} es independientemente hidrógeno o halógeno y G^2 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

12. El compuesto de acuerdo con la reivindicación 9, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, hterociclilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m$, y
G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

13. El compuesto de acuerdo con la reivindicación 12, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m-$, en donde
Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

14. El compuesto de acuerdo con la reivindicación 9, en donde R^2 es $-L^3-R^7$, en donde

L^5 es un enlace y

R^7 es hidrógeno, halógeno, arilo, heteroarilo, heterociclilo, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$.

15. El compuesto de acuerdo con la reivindicación 14, en donde R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

16. El compuesto de acuerdo con la reivindicación 11, en donde cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$ en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-OR^{11}$ o $-SO_2R^{11}$.

17. El compuesto de acuerdo con la reivindicación 13, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})$.

18. El compuesto de acuerdo con la reivindicación 15, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

19. El compuesto de acuerdo con la reivindicación 16, en donde:

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

20. El compuesto de acuerdo con la reivindicación 9, en donde R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_8, OR^{11}, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $C\equiv N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $NR^{11}COR^{11}$ o $N(R^{11})_2$.

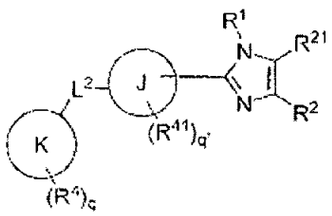
21. El compuesto de acuerdo con la reivindicación 9, en donde R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

22. El compuesto de acuerdo con la reivindicación 17, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalquilode C_1-C_6.

23. El compuesto de acuerdo con la reivindicación 18, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalqulo de C_1-C_6.

24. El compuesto de acuerdo con la reivindicación 19, en donde cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

25. El compuesto de acuerdo con la reivindicación 3, de la fórmula



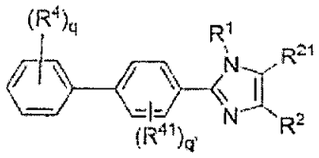
O una sal farmacéuticamente aceptable, un isómero o un profármaco de él, en donde R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

26. El compuesto de acuerdo con la reivindicación 25, en donde K es fenilo o piridilo.

27. El compuesto de acuerdo con la reivindicación 25, en donde J es fenilo.

28. El compuesto de acuerdo con la reivindicación 27, en donde K es fenilo.

29. El compuesto de acuerdo con la reivindicación 28, de la fórmula



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

30. El compuesto de acuerdo con la reivindicación 29, en donde R^{5a} es independientemente halógeno, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_8, OR^{11}, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $NR^{11}COR^{11}$ o $N(R^{11})_2$.

31. El compuesto de acuerdo con la reivindicación 30, en donde R^{5a} es independientemente halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

32. El compuesto de acuerdo con la reivindicación 29, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace, y

R^7 es hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6;

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, -

$C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$ o $-OC(=O)-N(R^{11})_2$.

33. El compuesto de acuerdo con la reivindicación 32, en donde R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde
Y es $-[C(R^{15})_2]_m$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,
En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y
Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

34. El compuesto de acuerdo con la reivindicación 29, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m-$, y
G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

35. El compuesto de acuerdo con la reivindicación 34, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m-$, en donde
Cada R^{11} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

36. El compuesto de acuerdo con la reivindicación 31,

R^2 es $-L^3$ es un enlace, y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

37. El compuesto de acuerdo con la reivindicación 33, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$ en donde

Cada R^{15} es es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

38. El compuesto de acuerdo con la reivindicación 36, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, $-G^1$, o $-E-G^1$, en donde

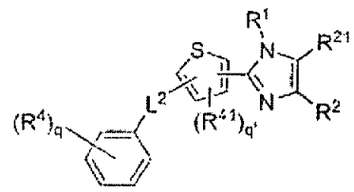
E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es -H, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

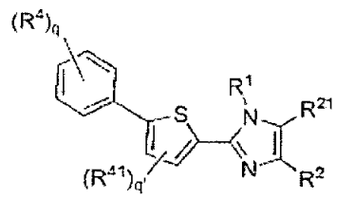
39. El compuesto de acuerdo con la reivindicación 25, en donde J es tienilo.

40. El compuesto de acuerdo con la reivindicación 39, de la fórmula



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

41. El compuesto de acuerdo con la reivindicación 40, de la fórmula



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

42. El compuesto de acuerdo con la reivindicación 41, en donde cada R^{5a} es independientemente halógeno, alquilo de C_{1-6},

haloalquilo de C_{1-6}, cicloalquilo de C_{3-6}, OR^{11}, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $NR^{11}COR^{11}$, o $N(R^{11})_2$.

43. El compuesto de acuerdo con la reivindicación 42, en donde R^{5a} es independientemente halógeno, alquilo de C_{1-6} o haloalquilo de C_{1-6}.

44. El compuesto de acuerdo con la reivindicación 41, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_1-C_6) o alquenilo de C_2-C_6;

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^1)$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$.

45. El compuesto de acuerdo con la reivindicación 44, en donde R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente -H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})$, o $-C(=S)N(R^{11})_2$.

46. El compuesto de acuerdo con la reivindicación 41, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})]_m-$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

47. El compuesto de acuerdo con la reivindicación 46, en donde

R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

Ees $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, en donde

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

48. El compuesto de acuerdo con la reivindicación 43,

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, $-Z$ o $-Y-Z$, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

49. El compuesto de acuerdo con la reivindicación 45, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, en donde E es $-[C(R^{15})_2]_m-$, en donde Cada R^{15} es independientemente hidrógeno o halógeno; y G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

50. El compuesto de acuerdo con la reivindicación 48, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m$, en donde
Cada R^{15} es independientemente hidrógeno o halógeno y G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

51. El compuesto de acuerdo con la reivindicación 39, en donde K es piridinilo.

52. El compuesto de acuerdo con la reivindicación 2, en donde R^1 es heteroarilo optativamente sustituido con uno o más R^{5a}.

53. El compuesto de acuerdo con la reivindicación 52, en donde R^1 es tienilo, furilo, pirrolilo, piridinilo, pirimidinilo, pirazidinilo, pirazolilo, quinolinilo, o isoquinolinilo, la

totalidad de los cuales se sustituyen optativamente con uno o más R^{5a}.

54. El compuesto de acuerdo con la reivindicación 53, en donde por lo menos uno de J y K es fenilo.

55. El compuesto de acuerdo con la reivindicación 54, en donde J y K son ambos fenilo.

56. El compuesto de acuerdo con la reivindicación 55, en donde L^2 es un enlace.

57. El compuesto de acuerdo con la reivindicación 56, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

58. El compuesto de acuerdo con la reivindicación 56, en donde Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^2$ o $E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$ en donde

Cada R^1 es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

59. El compuesto de acuerdo con la reivindicación 56, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $E-G^1$, en donde

E es $-[C(R^{15})_2]_m$,

En donde cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

60. El compuesto de acuerdo con la reivindicación 1, en donde

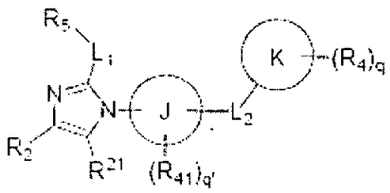
L_1 es $-[C(R^{15})_2]_{m'}-$ o cicloalquilo de C_3-C_8, en donde

m' es cualquiera de 1 a 3, y

cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6) o haloalquilo (de C_1-C_6); y

R^{21} es hidrógeno, halógeno, nitro, ciano, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

61. El compuesto de acuerdo con la reivindicación 60, de la fórmula



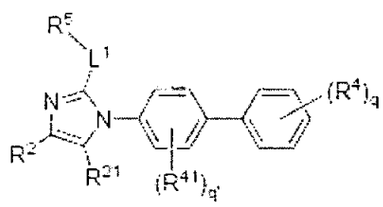
O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

62. El compuesto de acuerdo con la reivindicación 61, en donde al menos uno de J o K es fenilo.

63. El compuesto de acuerdo con a reivindicación 62, en donde J y K son ambos fenilo.

64. El compuesto de acuerdo con la reivindicación 63, en donde L_2 es un enlace.

65. El compuesto de acuerdo con la reivindicación 64, de la fórmula



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

66. El compuesto de acuerdo con la reivindicación 65, en donde

Cada R^{15} es independientemente -H o alquilo (de C_1-C_2),

m' es 1 o 2 y

R^5 es fenilo optativamente sustituido con uno o más R^{5a}.

67. El compuesto de acuerdo con la reivindicación 66, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

68. El compuesto de acuerdo con la reivindicación 66, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$ en donde

E es $-[C(R^{15})_2]_m-$, en donde R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

69. El compuesto de acuerdo con la reivindicación 66, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$ en donde

E es $-[C(R^{15})_2]_m-$,

en donde cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

70. El compuesto de acuerdo con la reivindicación 65, en donde

R^{15} es -H

m es 1, 2 o 3 y

R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}.

71. El compuesto de acuerdo con la reivindicación 70, en donde

R^2 es $-L^3-R^7$ en donde

L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})$.

72. El compuesto de acuerdo con la reivindicación 70, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

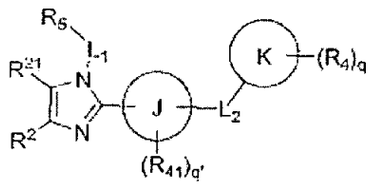
cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

73. El compuesto de acuerdo con la reivindicación 70, en donde
Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m-$,
en donde cada R^{15} es independientemente hidrógeno o halógeno y
G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

74. El compuesto de acuerdo con la reivindicación 1, en donde
R^1 es $-L^3-R^5$, en donde
L^1 es un enlace, $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8, y
R^5 es fenilo o piridilo, cada uno optativamente sustituido con uno o dos R^{5a}, en donde
Cada R^{5a} es independientemente -halógeno, alcoxi de C_1-C_6, alquilo de C_1-C_6, o haloalquilo de C_1-C_6, halógeno, $-C(O)N(R^{11})_2$ o $-COOR^{11}$;
L^2 es un enlace;
J es fenilo, piridilo o tienilo;
K es fenilo o pridilo;
Cada R^{41} es halógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6; y
Cada R^4 es halógeno, $-[C(R^{15})_2]_m-OH$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, $-C(O)N(R^{11})_2$, $-COOR^{11}$, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

75. El compuesto de acuerdo con la reivindicación 60, de la fórmula



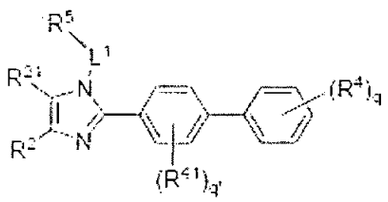
O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

76. El compuesto de acuerdo con la reivindicación 75, en donde al menos uno de J o K es fenilo.

77. El compuesto de acuerdo con a reivindicación 76, en donde J y K son ambos fenilo.

78. El compuesto de acuerdo con la reivindicación 77, en donde L_2 es un enlace.

79. El compuesto de acuerdo con la reivindicación 78, de la fórmula



O una sal farmacéuticamente aceptable, un isómero o un profármaco de él.

80. El compuesto de acuerdo con lar reivindicación 79, en donde:

Cada R^{15} es independientemente -H o alquilo (de C_1-C_2);

m' es 1 o 2; y

R^5 es fenilo optativamente sustituido con uno o más R^{5a}.

81. El compuesto de acuerdo con la reivindicación 79, en donde R^2 es $-L^3-R^7$, en donde

L^3 es un enlace,

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno o alquilo (de C_1-C_6); y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

82. El compuesto de acuerdo con la reivindicación 80, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

83. El compuesto de acuerdo con la reivindicación 80, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

84. El compuesto de acuerdo con la reivindicación 79, en donde

R^{15} es -H;

m es 1, 2 o 3; y

R^5 es heterociclilo optativamente sustituido con uno o más R^{5a}.

85. El compuesto de acuerdo con la reivindicación 84, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

86. El compuesto de acuerdo con la reivindicación 84, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

87. El compuesto de acuerdo con la reivindicación 84, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

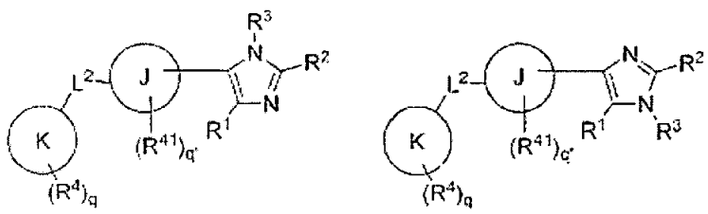
E es $-[C(R^{11})_2]_m-$

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

88. El compuesto de acuerdo con la reivindicación 1, que es una de las especies enumeradas en la Tabla 1.

89. El compuesto de acuerdo con la reivindicación 3, una de las fórmulas



O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde R^3 es hidrógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

90. El compuesto de acuerdo con la reivindicación 89, en donde
J es arilo;
K es arilo; y
L^2 es un enlace.

91. El compuesto de acuerdo con la reivindicación 90, en donde
J es fenilo; y
K es fenilo.

92. El compuesto de acuerdo con la reivindicación 91, en donde R^1 es fenilo optativamente sustituido con uno o más R^{5a}.

93. El compuesto de acuerdo con la reivindicación 92, en donde
Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde
E es $-[C(R^{15})_2]_m-$; y
G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

94. El compuesto de acuerdo con la reivindicación 92, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

95. El compuesto de acuerdo con la reivindicación 92, en donde

R es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C); y

Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

96. El compuesto de acuerdo on la reivindicación 92, en donde

Cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, o haloalquilo de C_1-C_6.

97. El compuesto de acuerdo con la reivindicación 89, en donde

J es heteroarilo,

K es arilo; y

L^2 es un enlace.

98. El compuesto de acuerdo con la reivindicación 97, en donde

J es tienilo, pirrolilo, furanilo, piridilo, piridinilo, o pirarinilo; y

K es fenilo.

99. El compuesto de acuerdo con la reivindicación 98, en donde R^1 es fenilo optativamente sustituido con uno o más R^{5a}.

100. El compuesto de acuerdo con la reivindicación 99, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $SO_2N(R^{11})_2$ o $-SR^{11}$.

101. El compuesto de acuerdo con la reivindicación 99, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno o

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

102. El compuesto de acuerdo con la reivindicación 99, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace, y

R^7 es hidrógeno, halógeno, -Z, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$, cicloalquilo de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

103. El compuesto de acuerdo con la reivindicación 99, en donde

Cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6 o haloalquilo de C_1-C_6.

104. El compuesto de acuerdo con la reivindicación 89, en donde

J es heteroarilo,

K es heteroarilo y

L^2 es un enlace.

105. El compuesto de acuerdo con la reivindicación 94, en donde

J es tienilo, pirrolilo, furanilo, piridilo, pirimidilo, o pirazinilo, y

K es piridilo, pirimidilo, o pirazinilo.

106. El compuesto de acuerdo con la reivindicación 95, en donde

R^1 es fenilo optativamente sustituido con uno o más R^{5a}.

107. El compuesto de acuerdo con la reivindicación 96, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo,, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$ y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

108. El compuesto de acuerdo con reivindicación 96, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

109. El compuesto de acuerdo con la reivindicación 96, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$, cicloalquilo (de C_3-C_6) o alquenilo de C_1-C_6,

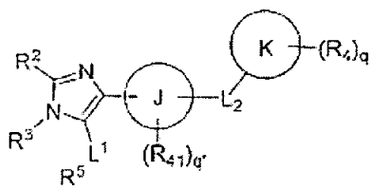
En donde cada R^{15} es independientemente H, halógeno o alquilo (de C_1-C_6) y

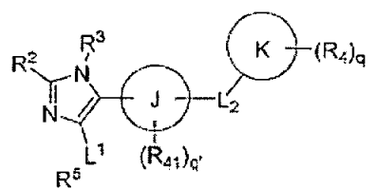
Z es H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

110. El compuesto de acuerdo con la reivindicación 96, en donde

Cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6 o haloalquilo de C_1-C_6.

111. El compuesto de acuerdo con la reivindicación 60, de una de las fórmulas





O una sal farmacéuticamente aceptable, un isómero o un profármaco de él, en donde R^3 es hidrógeno, alquilo de C_1-C_6 o haloalquilo de C_1-C_6.

112. El compuesto de acuerdo con la reivindicación 111, en donde

J es arilo;

K es arilo; y

L^2 es un enlace.

113. El compuesto de acuerdo con la reivindicación 112, en donde

J es fenilo; y

K es fenilo.

114. El compuesto de acuerdo con la reivindicación 113, en donde

Cada R^{15} es independientemente -H o alquilo (de C_1-C_2);

m' es 1 o 2; y

R^5 es fenilo optativamente sustituido con uno o más R^{5a}.

115. El compuesto de acuerdo con la reivindicación 114, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$ y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

116. El compuesto de acuerdo con la reivindicación 114, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{11})_2]_m$,

En donde cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

117. El compuesto de acuerdo con la reivindicación 114, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo (de C_3-C_6), o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6), y

Z es -E, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

118. El compuesto de acuerdo con la reivindicación 114, en donde

Cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C6 o haloalquilode C_1-C_6.

119. El compuesto de acuerdo con la reivindicación 113, en donde

R^{15} es -H;

m es 1, 2 o 3; y

R^5 es heterociclilo optativamente sustituido con uno o má R^{5a}.

120. El compuesto de acuerdo con la reivindicación 119, en donde

Cada R^4 es independientemente halogeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-N(R^{11})_2$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$ o $-SR^{11}$.

121. El compuesto de acuerdo con la reivindicación 119, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

122. El compuesto de acuerdo con la reivindicación 119, en donde

R^2 es $-L^3-R^7$ en donde

L^3 es un enlace y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, cicloalquilo(de C_3-C_6) o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

123. El compuesto de acuerdo con la reivindicación 119, en donde

Cada R^{5a} es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6 o haloalquilo de C_1-C_6.

124. El compuesto de acuerdo con la reivindicación 119, en donde

Cada R^{15} es independientemente -H o alquilo (de C_1-C_2),

m' es 1 o 2; y

R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}.

125. El compuesto de acuerdo con la reivindicación 124, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hirógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$ o alquenilo de C_2-C_6,

En donde cada R^{15} es es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$, o $-C(=S)N(R^{11})_2$.

126. El compuesto de acuerdo con la reivindicación 124, en donde

Cada R^4es independientmenete halógeno, arilo, heteroarilo, heterociclilo, $-G^1$, o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

127. El compuesto de acuerdo con la reivindicación 124, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno, y

G^1 es alquilo de C_1-C_6, haloalquilode C_1-C_6 o halógeno.

128. El compeusto de acuerdo con la reivindicación 79, en donde

Cada R^{15} es independientmeente -H o alquilo (de C_1-C_2);

m' es 1 o 2; y

R^5 es heteroarilo optativamente sutituido con uno o más R^{5a}.

129. El compeusto de acuerdo con la reivindicación 128, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno, halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$ o alquenilo de C_2-C_6,

En donde cada R^{15} es independientemente H, halógeno o alquilo (de C_1-C_6); y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$) o $-C(=S)N(R^{11})_2$.

130. El compuesto de acuerdo con la reivindicación 128, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m$, en donde

Cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$ o $-SO_2R^{11}$.

131. El compuesto de acuerdo con la reivindicación 128, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es alquilo de C_1-C_6, haloalquilo de C_1-C_6, o halógeno.

132. El compuesto de acuerdo con la reivindicación 113, en donde

Cada R^{15} es independientemente -H o alquilo (de C_1-C_2);

m' es 1 o 2; y

R^5 es heteroarilo optativamente sustituido con uno o más R^{5a}.

133. El compuesto de acuerdo con la reivindicación 132, en donde

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace; y

R^7 es hidrógeno halógeno, -Z o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m$ o alquenilo de C_2-C_6,

En ddonde cada R^{15} es independientemente H, halógeno, o alquilo (de C_1-C_6) y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{11})_2$, $-C(=N-OH)R^{11}$ o $-C(=S)N(R^{11})_2$.

134. El compuesto de acuerdo con la reivindicación 132, en donde

Cada R^4 es independientemente halógeno, arilo, heteroarilo, heterociclilo, $-G^1$ o $-E-G^1$, endonde

E es $-[C(R^{15})_2]_m$, en donde

Cada R^{15} es inedependientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, halógeno, $-OR^{11}$, o $-SO_2R^{11}$.

135. El compuesto de acuerdo con la reivindicación 132, en donde

Cada R^{41} es independientemente halógeno, $-G^1$ o $-E-G^1$, en donde

E es $-[C(R^{15})_2]_m-$,

En donde cada R^{15} es independientemente hidrógeno o halógeno; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6 o halógeno.

136. El compeusto de acuerdo con la reivindicación 1, en donde

R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$ o $-L^6-L^5-L^6-$, en donde:

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

m es 0, 1, 2, 3 o 4; y

Cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

L^6 es $-CO-$, $-SO_2-$, $-O-$, $-CON(R^{11})-$, -cicloalquilo de C_3-C_8-, o -heterociclilo-,

En donde el cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{14}; y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C-, en donde

B es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_6-; y

C es halógeno, -alquilo de C_1-C_6, o -haloalquilo de C_1-C_6,

En donde R^5 se sustituye optativmente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6,

(cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, arilalcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquiloCOOR^{11}, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

R^7 es halógeno, arilo, heteroarilo, heterociclilo, -Z-, o -Y-Z, en donde

Y es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, o $-C(=O)N(R^{11})(OR^{11})$,

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, -Z', -Y'-Z', o -X'-Y'-Z', en donde

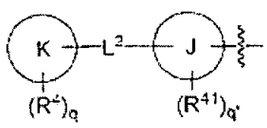
X' es -O-;

Y' es $-[C(R^{15})_2]_m$ o cicloalquilo de C_3-C_6; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, o $-N(R^{11})S(O=)_2R^{11}$,

R^{21} y R^3 son cada uno independientemente hidrógeno, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6, y

G es un grupo de la fórmula



, en donde

J es arilo o heteroarilo;

K es arilo o heteroarilo;

cada R^4 y R^{41} es independientemente halógeno, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_6; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace,

q es 1, 2, o 3; y

q' es 0, 1, 2, o 3,

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SO_2R^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-, -haloalquilo de C_1-C_6, $-N(R^{12})_2$, arilo, alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, alquilo de C_0-$C_6N(R^{13})_2$, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C=O(OR^{13})$; alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_0-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{0-6}, arilalquilcarboxi de C_{0-6}, alquilo de C_0-$C_6N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-

C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-;

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, alquilo de C_1-$C_6CON(R^{11})_2$, alquilo de C_0-$C_6CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

137. El compuesto de acuerdo con la reivindicación 1, en donde R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, cicloalquilo de C_3-C_8 o L^5, en donde:

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

m es 0, 1, 2, o 3; y

Cada R^{15} es independientemente hidrógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C-, en donde

B es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8-; y

C es -alquilo de C_1-C_6, o -haloalquilo de C_1-C_6,

En donde R^5 se sustituye optativmente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, arilalcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, cicloalquilo de C_3-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N,

$C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquiloCOOR^{11}, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SON(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 es $-L^3-R^7$, en donde

L^3 es un enlace y

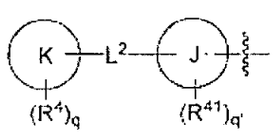
R^7 es -Z-, o -Y-Z-, en donde

Y es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$,

R^{21} y R^3 son cada uno independientemente hidrógeno, halógeno, alquilo de C_1-C_6, o haloalquilo de C_1-C_6, y

G es un grupo de la fórmula



, en donde

J es arilo o heteroarilo;

K es arilo o heteroarilo;

cada R^4 y R^{41} es independientemente halógeno, heteroarilo, heterociclilo, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es $-O-$;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace,

q es 1, 2, o 3; y

q' es 0, 1, 2, o 3,

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SOR^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-, -haloalquilo de C_1-C_6, $-N(R^{12})_2$, arilo, alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, OR^{13}, $N(R^{13})_2$, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C=O(OR^{13})$; alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, alquilo de C_0-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi,

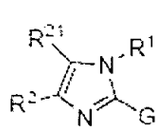
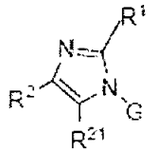
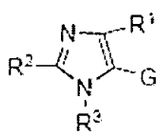
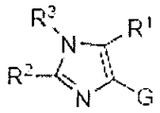
ariloxialquilo, alcoxiarilo de C_{0-6}, arilalquilcarboxi de C_{0-6}, alquilo de C_0-$C_6N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-;

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, alquilo de C_1-$C_6CON(R^{11})_2$, alquilo de C_0-$C_6CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

138. El compuesto de acuerdo con la reivindicación 1, que es una de las especies enumeradas en la Tabla 1.

139. Un compuesto de las fórmulas:

O una sal farmacéuticamente aceptable, un isómero, o un profármaco de él, en donde

R^1 es $-L^1-R^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$ o $-L^6-L^5-L^6-$, en donde:

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno, halógeno, alquilo (de C_1-C_6), o haloalquilo (de C_1-C_6); y

Cada L^6 es independientemente -CS-, -CO-, $-SO_2$-, -O-, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, o $-C(=NN(R^{11})_2)-$, -arilo-, -cicloalquilo de C_3-C_8-, -heteroarilo-, o -heterociclilo-,

En donde el arilo, cicloalquilo, heteroarilo, o heterociclilo se sustituye optativamente con uno o más R^{14};

O cada L^6 es independientemente alidilo de C_2-C_6,

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, -SO-, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})$; y

R^5 es arilo, heterociclilo, heteroarilo, -C o -B-C-, en donde B es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8-; y

C es halógeno, -alquilo de C_1-C_6, -haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, o $-N(R^{11})_2$,

En donde R^5 se sustituye optativmente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalqulo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6,

(cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, arilalcoxi de C_{1-6}, alquilo de C_1-C_6, haloalquilo de C_1-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, C≡N, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0-6}SO_2R^{11}$, alquiloCOOR^{11}, alcoxiarilo de C_{0-6}, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SON(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, -C≡N, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 y R^{21} son $-L^3-R^7$, en donde

Cada L^3 es independientemente un enlace o $-(CH_2)_m-V^1-(CH_2)_n-$, en donde

n es 0-6; y

V^1 es $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $-NR^{11}-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, -OCO-, -CO-, -CS-, $-CONR^{10}-$, $-C(=N-R^{11})-$, $-C(=N-OR^{11})-$, $-C[=N-N(R^{11})_2]$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, cicloalquilo de C_3-C_6 o ciclohaloalquilo de C_3-C_6;

O cada L^3 es independientemente alidilo de C_2-C_6,

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-NR^{11}-$, $-CON(R^{10})-$, $-CO-$, $-CO-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$; y

Cada R^7 es independientemente hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z-, -Y-Z-, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N-OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, o $-OC(=O)-N(R^{11})_2$,

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, haloarilo, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, $C(R^{11})=C(R^{11})-COOH$, arilo, heteroarilo, heterociclilo, heterocicliloxi, heteroariloxi, -Z', -Y'-Z', o -X'-Y'-Z', en donde

X' es -O-;

Y' es $-[C(R^{15})_2]_m$ o cicloalquilo de C_3-C_8; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})$, $-N(R^{11})C(=O)R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, -

$C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-OR^{11}$, $-N(R^{11})C(=O)-R^{11}$, o $-N(R^{11})S(O=)_2R^{11}$,

En donde cada R^{7a} se sustituye optativamente con uno o más R^8,

En donde cada R^8 es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, haloalquilo de C_1-$C_6(OR^{11})$, alquilo de C_0-C_6OR^{11}, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6COR^{11}, alquilo de C_0-C_6COOR^{11}, o alquilo de C_0-$C_6SO_2R^{11}$,

Siempre que R^2 y R^{21} no sean simultáneamente hidrógeno,

R^3 es $-L-R^6$, en donde

L es un enlace, $-X^3-(CH_2)_n-X^3-$, $-(CH_2)_m-X^3-(CH_2)_n-$ o $-(CH_2)_{1+w}-Y^3-(CH_2)_w-$, en donde

n es 0-6; cada w es independientemente 0-5; y

cada X^3 es independientemente un enlace, $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C\equiv C$, $-CO-$, $-CS-$, $-CONR^{10}-$, $-C(=N)(R^{11})-$, $-C(=N-OR^{11})-$, $-[=N-N(R^{11})_2]$, $-CO_2-$, $-SO_2-$, o $-SO_2N(R^{10})-$; y

Y^3 es $-O-$, $-S-$, $-NR^7-$, $-N(R^{10})CO-$, $N(R^{10})CO_2-$, $-OCO-$, $-OC(=O)N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-N(R^{10})SO_2-$, o $-NR^{10}CSNR^{10}-$;

o L es una cadena de alidilo en donde la cadena de alidilo está optativamente interrumpida por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO-$, o $-SO_2N(R^{10})$; y

R^6 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, arilo, cicloalquilo de C_3-C_8, heteroarilo, heterociclilo, -CN, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)N(R^{11})_2$-, -$N(R^{11})_2$, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$C(=O)N(R^{11})N(OR^{11})$, en donde el arilo, heteroarilo, cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{6a}, en donde

cada R^{6a} es independientemente -Z", -Y"-Z", o -X"-Y"-Z", en donde

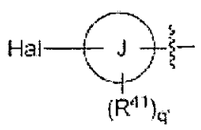
X" es -O-;

Y" es -$[C(R^{15})_2]_m$-, alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, heterociclilo, arilo o heteroarilo, en donde

El arilo, heteroarilo, cicloalquilo, o heterociclilo optativamente se sustituye con por lo menos un grupo que es cada uno independientemente Z";

Z" es -H, -CN, halógeno, -OR^{11}, -$C(=O)R^{11}$, -$C(=O)n(R^{11})_2$, -$N(R^{11})_2$, -N_3, -SO_2R^{11}, -$S(=O)_2N(R^{11})_2$, -$C(=O)N(R^{11})N(R^{11})_2$, -$N(R^{11})C(=O)N(R^{11})_2$, -$OC(=O)$-$OR^{11}$, -$C(=O)N(R^{11})(OR^{11})$, -$OC(=O)$-$R^{11}$, -$OC(=O)$-$N(R^{11})_2$, o -$N(R^{11})COOR^{11}$; y

G es un grupo de la fórmula



, en donde

Hal es halógeno;

J es arilo o heteroarilo;

cada R^{41} es independientemente halógeno, nitro, $CR^{11}=CR^{11}COOR^{11}$, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, $-E-G^1$, o $-D-E-G^1$, en donde

D es -O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, $-C\equiv N$, $-OR^{11}$, $-OCN(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, $-SOR^{11}$, o $-SR^{11}$,

En donde cada R^4 se sustituye optativamente con uno o más R^{4a},

En donde cada R^{4a} es independientemente halógeno, ariloxi, analquiloxi, ariloxialquilo, alcoxiarilo de C_1-C_6, aril alquilcarboxi de C_0-C_6, -G', -E'-G', o -D'-E'-G', en donde

D' es -O-;

E' es $-[C(R^{15})]_m-$ o cicloalquilo de C_3-C_8; y

G' es -H, halógeno, $-COR^{11}$, $-COOR^{11}$, $-C\equiv N$, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

cada m es 0, 1, 2, 3, 4, 5 o 6;

q' es 0, 1, 2, 3, o4

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SOR^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-

C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-, -haloalquilo de C_1-C_6, $-N(R^{12})_2$, arilo, alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, haloalquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)$C=O(OR^{13})$; alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, aluqilo de C_0-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de C_{0-6}, arilalquilcarboxi de C_{0-6}, alquilo de C_0-$C_6N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, o -Oalquilo de $C_{0-6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-;

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, alquilo de C_1-$C_6CON(R^{11})_2$, alquilo de C_0-$C_6CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}.

140. El compuesto de acuerdo con la reivindicación 139, que es una de las especies enumeradas en la Tabla 2.

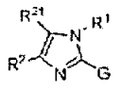
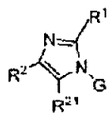
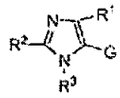
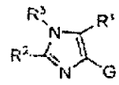
141. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1 o un derivado farmacéuticamente aceptable de él en un portador farmacéuticamente aceptable.

142. Un método para tratar, prevenir, inhibir o mejorar los síntomas de una enfermedad o trastorno que está modulado o afectado de otro modo por la actividad de un receptor nuclear o en el cual está implicada la activadad de un receptor nuclear, que comprende administrar a un sujeto que lo necesita, una cantidad terapéuticamente aceptable de un compuesto de acuerdo con la parte (A) de la reivindicación 1.

143. El método de acuerdo con la reivindicación 142, en donde la enfermedad o el trastorno es hipercolesterolemia, hiperlipoproteinemia, hipertrigliceridemia, lipodistrofia, hiperglucemia, diabetes mellitus, dislipidemia, aterosclerosis, enfermedad de cálculos biliares, acné común, condiciones de la piel acneiforme, diabetes, enfermedad de Parkinson, cáncer, enfermedad de Alzheimer, inflamación, trastornos inmunológicos, trastornos de los lípidos, obesidad, condiciones caracterizadas por una función de la barrera epidérmica perturbada, condiciones de diferenciación interrumpida, o exceso de la proliferación de la epidermis o de la membrana mucosa, trastornos cardiovasculares.

144. Un método para modular la actividad de los receptores nucleares, que comprende poner en contacto al receptor nuclear con un compuesto de acuerdo con la parte (A) de la reivindicación 1.

RESUMEN

 (IIa)  (IIb)  (IIc)  (IId)

Compuestos de la invención, tales como compuestos de las fórmulas IIa, IIb, IIc o IId y sales farmacéuticamente aceptables, isómeros o profármacos de ellos, son útiles como inhibidores de la actividad de los receptores X del hígado, en donde R^1, R^2, R^{21}, R^3 y G se definen en la presente. También se revelan composiciones farmacéuticas que contienen los compuestos y métodos de uso de los compuestos.

Industria y Comercio
SUPERINTENDENCIA

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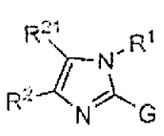
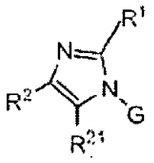
Reivindicación(es):

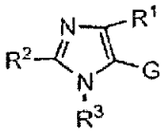
1. Un compuesto de acuerdo con una de las siguientes fórmulas:



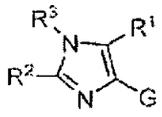
IIa



IIb



IIc



IId

O una sal farmacéuticamente aceptable, isómero, o profármaco de él, en donde:

(A) R^1 es $-L^1-L^5$, en donde

L^1 es un enlace, L^5, L^6, $-L^5-L^6-L^5-$ o $-L^6-L^5-L^6-$, en donde:

(A) R^1 es $-L^1-L^5$, en donde

Cada L^5 es independientemente $-[C(R^{15})_2]_m-$, en donde

Cada R^{15} es independientemente hidrógeno, alquilo (de C_1-C_6), cicloalquilo (de C_3-C_6) o haloalquilo (de C_1-C_6); y

Cada L^6 es independientemente $-CS-$, $-CO-$, $-SO_2-$, $-O-$, $-CON(R^{11})-$, $-CONR^{11}N(R^{11})-$, $-C(=NR^{11})-$, $-C(=NOR^{11})-$, o $-C(=NN(R^{11})_2)-$, -arilo-, -cicloalquilo de C_3-C_8-, -heteroarilo-, o -heterociclilo-,

En donde el arilo, cicloalquilo, heteroarilo, o heterociclilo se sustituye optativamente con uno o más R^{14};

O cada L^6 se selecciona independientemente de alidilo de C_2-C_6,

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, $-C\equiv C-$, $-O-$, $-S-$, $N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CO-$, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})$; y

R^5 es arilo, heterociclilo, heteroarilo, cicloalquilo (de C_3-C_6), -C o -B-C-, en donde

B es $-[C(R^{15})_2]_m-$, o cicloalquilo de C_3-C_8-; y

C es halógeno, -alquilo de C_1-C_6, -haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-SR^{11}$, $-SO_2N(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C\equiv N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, o $-N(R^{11})_2$,

En donde R^5 se sustituye optativmente con uno o más R^{5a}, en donde

Cada R^{5a} es independientemente halógeno, nitro, heteroarilo, heterociclilo, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalqulo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6, arilo, arilalquilo, ariloxi, ariloxiarilo, arilalcoxi de $C_{1\text{-}6}$, alquilo de C_1-C_6, haloalquilo de C_1-C_6, SO_2R^{11}, OR^{11}, SR^{11}, N_3, SO_2R^{11}, COR^{11}, $SO_2N(R^{11})_2$, $SO_2NR^{11}COR^{11}$, $C{\equiv}N$, $C(O)OR^{11}$, $CON(R^{11})_2$, $CON(R^{11})OR^{11}$, $OCON(R^{11})_2$, $NR^{11}COR^{11}$, $NR^{11}CON(R^{11})_2$, $NR^{11}COOR^{11}$, o $N(R^{11})_2$, en donde

Cada R^{5a} se sustituye optativamente con uno o más grupos que son independientemente -halógeno, alquilo de C_1-C_6, ariloxi alquilo de $C_{0\text{-}6}SO_2R^{11}$, alquiloCOOR^{11}, alcoxiarilo de $C_{0\text{-}6}$, haloalquilo de C_1-C_6, $-SO_2R^{11}$, $-OR^{11}$, $-SR^{11}$, $-N_3$, $-SO_2R^{11}$, $-COR^{11}$, $-SON(R^{11})_2$, $-SO_2NR^{11}COR^{11}$, $-C{\equiv}N$, $-C(O)OR^{11}$, $-CON(R^{11})_2$, $-CON(R^{11})OR^{11}$, $-OCON(R^{11})_2$, $-NR^{11}COR^{11}$, $-NR^{11}CON(R^{11})_2$, $-NR^{11}COOR^{11}$, o $-N(R^{11})_2$;

R^2 y R^{21} son $-L^3$-R^7, en donde

Cada L^3 es independientemente un enlace o $-(CH_2)_m$-V^1-$(CH_2)_n$-, en donde

n es 0-6; y

V^1 es $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, $-C{\equiv}C$-, -O-, -S-, $-NR^{11}$-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, -OCO-, -CO-, -CS-, $-CONR^{10}$-, $-C(=N\text{-}R^{11})$-, $-C(=N\text{-}OR^{11})$-, $-C[=N\text{-}N(R^{11})_2]$, $-CO_2$-, $-OC(=O)$-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, $-SO_2N(R^{10})$-, $-NR^{10}CONR^{10}$-, $-NR^{10}CSNR^{10}$-, cicloalquilo de C_3-C_6 o ciclohaloalquilo de C_3-C_6;

O cada L^3 es independientemente alidilo de C_2-C_6,

En donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, $-C{\equiv}C$-, -O-, -S-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, $-NR^{11}$-, $-CON(R^{10})$-, -CO-, -CO-, $-OC(=O)$-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO_2$-, o $-SO_2N(R^{10})$-; y

Cada R^7 es independientemente hidrógeno, halógeno, nitro, arilo, heteroarilo, heterociclilo, -Z-, -Y-Z-, o -X-Y-Z, en donde

X es -O-;

Y es $-[C(R^{15})_2]_m$-, alquenilo de C_2-C_6, o cicloalquilo de C_3-C_6; y

Z es -H, halógeno, $-OR^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})_2$, $-C(=N\text{-}OH)R^{11}$, $-C(=S)N(R^{11})_2$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)$-R^{11}, o $-OC(=O)$-$N(R^{11})_2$,

En donde R^7 se sustituye optativamente con uno o más R^{7a}, en donde

R^{7a} es halógeno, haloarilo, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, $C(R^{11})=C(R^{11})$-COOH, arilo, heteroarilo, heterociclilo, heterocicliloxi, heteroariloxi, -Z', -Y'-Z', o -X'-Y'-Z', en donde

X' es -O-;

Y' es $-[C(R^{15})_2]_m$ o cicloalquilo de C_3-C_8; y

Z' es -H, halógeno, $-OR^{11}$, $-SR^{11}$, $-S(=O)_2R^{11}$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$, $-N(R^{11})$, $-N(R^{11})C(=O)R^{11}$, $-S(=O)_2N(R^{11})C(=O)R^{11}$, -CN, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)$-R^{11}, $-OC(=O)$-OR^{11}, $-N(R^{11})C(=O)$-R^{11}, o $-N(R^{11})S(O=)_2R^{11}$,

En donde cada R^{7a} se sustituye optativamente con uno o más R^8,

En donde cada R^8 es independientemente halógeno, alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, haloalquilo de C_1-$C_6(OR^{11})$, alquilo de C_0-C_6OR^{11}, alquilo de C_0-$C_6CON(R^{11})_2$, alquilo de C_0-C_6COR^{11}, alquilo de C_0-C_6COOR^{11}, o alquilo de C_0-$C_6SO_2R^{11}$,

Siempre que R^2 y R^{21} no sean simultáneamente hidrógeno,

R^3 es $-L$-R^6, en donde

L es un enlace, $-X^3$-$(CH_2)_n$-X^3-, $-(CH_2)_m$-X^3-$(CH_2)_n$- o $-(CH_2)_{1+w}$-Y^3-$(CH_2)_w$-, en donde

n es 0-6; cada w es independientemente 0-5; y

cada X^3 es independientemente un enlace, $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C{\equiv}C$, -CO-, -CS-, $-CONR^{10}$-, $-C(=N)(R^{11})$-, $-C(=N\text{-}OR^{11})$-, $-[=N\text{-}N(R^{11})_2]$, $-CO_2$-, $-SO_2$-, o $-SO_2N(R^{10})$-; y

Y^3 es -O-, -S-, $-NR^7$-, $-N(R^{10})CO$-, $N(R^{10})CO_2$-, -OCO-, $-OC(=O)N(R^{10})$-, $-NR^{10}CONR^{10}$-, $-N(R^{10})SO_2$-, o $-NR^{10}CSNR^{10}$-;

o L es una cadena de alidilo en donde la cadena de alidilo está optativamente interrumpida por $-C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})_2C(R^{11})_2$-, $-C(R^{11})=C(R^{11})$-, $-C(R^{11})_2O$-, $-C(R^{11})_2NR^{11}$-, $-C{\equiv}C$-, -O-, -S-, $-N(R^{10})CO$-, $-N(R^{10})CO_2$-, $-CON(R^{10})$-, -CO-, $-CO_2$-, $-OC(=O)$-, $-OC(=O)N(R^{10})$-, $-SO_2$-, $-N(R^{10})SO$-, o $-SO_2N(R^{10})$; y

R^6 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, arilo, cicloalquilo de C_3-C_8, heteroarilo, heterociclilo, -CN, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{11})_2$-, $-N(R^{11})_2$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-C(=O)N(R^{11})N(OR^{11})$, en donde

el arilo, heteroarilo, cicloalquilo, o heterociclilo se sustituye optativamente con uno o más R^{6a}, en donde

cada R^{6a} es independientemente -Z", -Y"-Z", o -X"-Y"-Z", en donde

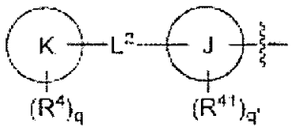
X" es –O-;

Y" es $-[C(R^{15})_2]_m-$, alquenilo de C_2-C_6, cicloalquilo de C_3-C_8, heterociclilo, arilo o heteroarilo, en donde

El arilo, heteroarilo, cicloalquilo, o heterociclilo optativamente se sustituye con por lo menos un grupo que es cada uno independientemente Z";

Z" es –H, -CN, halógeno, $-OR^{11}$, $-C(=O)R^{11}$, $-C(=O)n(R^{11})_2$, $-N(R^{11})_2$, $-N_3$, $-SO_2R^{11}$, $-S(=O)_2N(R^{11})_2$, $-C(=O)N(R^{11})N(R^{11})_2$, $-N(R^{11})C(=O)N(R^{11})_2$, $-OC(=O)-OR^{11}$, $-C(=O)N(R^{11})(OR^{11})$, $-OC(=O)-R^{11}$, $-OC(=O)-N(R^{11})_2$, o $-N(R^{11})COOR^{11}$; y

G es un grupo de la fórmula



, en donde

J es arilo, heteroarilo, o está ausente;

K es arilo, heteroarilo, o está ausente;

Siempre que

(i) si K está ausente, entonces q es 1 y R^4 está unido a L^2; y cada R^4 y R^{41} es independientemente halógeno, oxo, nitro, $CR^{11}=CR^{11}COOR^{11}$, ariloxi, aralquiloxi, ariloxialquilo, aril alquilcarboxi de C_0-C_6, arilo, heteroarilo, heterociclilo, heteroariloxi, heterocicliloxi, $-G^1$, -E-G^1, o –D-E-G^1, en donde

D es –O-;

E es $-[C(R^{15})_2]_m-$ o cicloalquilo de C_3-C_8; y

G^1 es alquilo de C_1-C_6, haloalquilo de C_1-C_6, $-COR^{11}$, $-COOR^{11}$, $-CON(R^{11})_2$, -C≡N, $-OR^{11}$, $-OCN(R^{11})_2$, $-OCOOR^{11}$, $-N_3$, $-NR^{11}COR^{11}$, $-NR^{11}SO_2R^{11}$, $-N(R^{11})_2$, $-NR^{11}COOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^{11}COR^{11}$, $-SO_2N(R^{11})_2$, $-SOR^{11}$, o $-SR^{11}$,

En donde cada R^4 se sustituye optativamente con uno o más R^{4a},

En donde cada R^{4a} es independientemente halógeno, ariloxi, analquiloxi, ariloxialquilo, alcoxiarilo de C_1-C_6, aril alquilcarboxi de C_0-C_6, -G', -E'-G', o –D'-E'-G', en donde

D' es –O-;

E' es $-[C(R^{15})]_m-$ o cicloalquilo de C_3-C_8; y

G' es –H, halógeno, $-COR^{11}$, $-COOR^{11}$, -C≡N, $-OR^{11}$, $-NR^{11}SO_2R^{11}$, $-SO_2R^{11}$, $-SO_2N(R^{11})_2$, o $-SR^{11}$,

L^2 es un enlace o $-[C(R^{15})_2]_m-V^2-[C(R^{15})_2]_n-$, en donde

V^2 es independientemente $-C(R^{11})_m$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $-SO_2-$, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, -CS-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-N(R^{10})SO_2-$, $-SO_2N(R^{10})-$, $-NR^{10}CONR^{10}-$, $-NR^{10}CSNR^{10}-$, cicloalquilo de C_3-C_8, o ciclohaloalquilo de C_3-C_6,

o V es alidilo de $C_{2\text{-}6}$,

en donde la cadena de alidilo está interrumpida optativamente por $-C(R^{11})_2-$, $-C(R^{11})_2C(R^{11})_2-$, $-C(R^{11})=C(R^{11})-$, $-C(R^{11})_2O-$, $-C(R^{11})_2O-$, $-C(R^{11})NR^{11}$, $-C(R^{11})_2NR^{11}-$, -C≡C-, -O-, -S-, $-N(R^{10})CO-$, $-N(R^{10})CO_2-$, $-CON(R^{10})-$, $-CON(R^{11})-$, $-CON(R^{11})O-$, -CO-, $-CO_2-$, $-OC(=O)-$, $-OC(=O)N(R^{10})-$, $-SO_2-$, $-N(R^{10})SO_2-$, o $-SO_2N(R^{10})-$;

o V^2 es arilo, heteroarilo, o heterociclilo, cada uno de los cuales se sustituye optativamente con uno o más R^9, en donde

cada R^9 es independientemente halógeno, haloalquilo de C_1-C_6, alquilo de C_1-C_6, alquiloxi de C_1-C_6, alquilo de C_0-C_6COOR^{11};

cada m es 0, 1, 2, 3, 4, 5 o 6;

q es 0, 1, 2, 3, 4, o 5; siempre que q sea 0 si y sólo si K no es fenilo; y

q' es 0, 1, 2, 3, o4

cada R^{10} es independientemente $-R^{11}$, $-C(=O)R^{11}$, $-CO_2R^{11}$, o $-SOR^{11}$;

cada R^{11} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-, -haloalquilo de C_1-C_6, $-N(R^{12})_2$, arilo, alquilo (de C_1-C_6)-arilo, heteroarilo, alquilo (de C_1-C_6)heteroarilo, heterociclilo, o alquilo (de C_1-C_6)-heterociclilo,

en donde cualquiera de R^{11} se sustituye optativamente con uno o más radicales de R^{12};

cada R^{12} es independientemente halógeno, haloalquilo de C_1-C_6, alcoxi de C_1-C_6, (alquilo de C_0-C_6)C=O(OR^{13}); alquilo de C_0-C_6OR^{13}, alquilo de C_0-C_6COR^{13}, alquilo de C_0-$C_6SO_2R^{13}$, alquilo de C_0-$C_6CON(R^{13})_2$, aluqilo de C_0-$C_6CONR^{13}OR^{13}$, alquilo de C_0-$C_6SO_2N(R^{13})_2$, alquilo de C_0-C_6SR^{13}, haloalquilo de C_0-C_6OR^{13}, ariloxi, aralquiloxi, ariloxialquilo, alcoxiarilo de $C_{0\text{-}6}$, arilalquilcarboxi de $C_{0\text{-}6}$, alquilo de C_0-$C_6N(R^{13})_2$, $-NR^{13}SO_2R^{13}$, o –Oalquilo de $C_{0\text{-}6}COOR^{13}$;

cada R^{13} es independientemente hidrógeno, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, cicloalquilo de C_3-C_8, (cicloalquilo de C_3-C_8)-alquilo de C_1-C_6, (cicloalquenilo de C_3-C_8)-alquilo de C_1-C_6, o (cicloalquilo de C_3-C_8)-alquenilo de C_2-C_6-;

cada R^{14} es independientemente alquilo de C_1-C_6, alcoxi de C_1-C_6, haloalquilo de C_1-C_6, alquilo de C_1-$C_6CON(R^{11})_2$, alquilo de C_0-$C_6CONR^{11}OR^{11}$, alquilo de C_0-C_6OR^{11}, o alquilo de C_0-C_6COOR^{11}; y

(B) siempre que

(i) cuando L^2 es un enlace, tanto J como K no están ausentes;

(ii) si el compuesto definido por la fórmula IIa, entonces

a. si J es fenilo y K es tienilo, furilo o tiazoilo y q es 0, entonces R^1 no es 4-(NH_2SO_2)fenilo, 4-(NH_2SO_2)-3-fluorofenilo-, y

b. si R^5 es piridilo o fenilo optativamente sustituido con uno o más R^{5a} y L^1 es un enlace, entonces G no es p-(NH_2SO_2)fenilo o p-(CH_3SO_2)fenilo-;

(iii) si el compuesto se define con la fórmula IIc o IId, entonces G no es p-(NH_2SO_2)fenilo o p-(CH_3SO_2)fenilo;

(iv) el compuesto no es 1-(bifenil-4-il)-2,5-difenil-1H-imidazol.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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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 [ ]

Edgar Nacimo

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