08-52929 QF

Organizacion y Digitalizacion CSA Ltda

CSA851033

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

# Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

**SOLICITUD**

# PATENTE DE INVENCIÓN

21. EXPEDIENTE No. 08-529129

54. TITULO: "COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO"

51. CLASIFICACIÓN INTERNACIONAL: A61K31/164 // A61K31/02
A61P3/06

71. SOLICITANTE: BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO: NUEVA JERSEY, ESTADOS UNIDOS DE AMÉRICA

74. APODERADO: ALVARO CORREA ORDOÑEZ
T.P.No.20.281

P2008/000210

22. BOGOTA, D.C., MAYO 23, 2008

SS

# PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-052929- -00000-0000
Fecha: 2008-05-23 15:34:21 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 2074

## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
## PCT
## ENTRADA EN FASE NACIONAL

**(1) SOLICITUD DE :**

| | | | |
|---|---|---|---|
| [X] | Patente de Invención | [ ] | Patente de Modelo de Utilidad |
| [X] | Capítulo I. | [ ] | Capítulo II. |

**(2) SOLICITANTE (71)**

Nombre: BRISTOL-MYERS SQUIBB COMPANY
Dirección: Route 206 and Province Line Road, Princeton, Nueva Jersey 08543-4000, Estados Unidos de América
Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América
Lugar de Constitución: Delaware, Estados Unidos de América
Teléfono: Fax:
E-Mail

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

**(3) REPRESENTANTE O APODERADO**

Nombre: ALVARO CORREA ORDOÑEZ
Dirección: Avenida 82 No.10-62 Piso 6
Teléfono: 634 1500 Fax: 376 2211
E-Mail: office.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 de Usaquén TP 20.281

**(4) INVENTOR (ES)**

Nombre: SALVATI, Mark E.; FINLAY, Heather; CHEN, Bang-chi; HARIKRISHNAN, Lalgudi S.; JIANG, Ji; JOHNSON, James A.; KAMAU, Muthoni G.; LAWRENCE, Michael R.; LI, Jianqing; LLOYD, John; MILLER, Michael Matthew; PI, Zulan; QIAO, Jennifer X; RAMPULLA, Richard; WANG, Tammy C.; WANG, Yufeng; YANG, Wu y ROBERGE, Jacques Y.

Dirección: c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543, Estados Unidos; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos y c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, Estados Unidos de América, respectivamente.

(72) Nacionalidad o Domicilio: Domicilio Estados Unidos de América

**(5) PCT (85)**

Solicitud Internacional No. PCT/US2006/060958 Fecha 16-NOV-06
Publicación Internacional No. WO/2007/062308 Fecha 31-MAY-07

**(6) Título (54)** COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO A61K31/164 // A61K31/02 // A61P3/06

**(7) Clasificación Internacional (51)** C07C 211/29, C07C 215/08, C07C 217/58, C07C 229/36, C07C 229/38, C07C 233/09, C07C 233/13, C07C 233/18, C07C 233/56, C07C 233/60, C07C 233/66, C07C 233/73, C07C 233/78, C07C 235/20, C07C 235/34

**(8) Prioridad** SI [X] NO [ ]

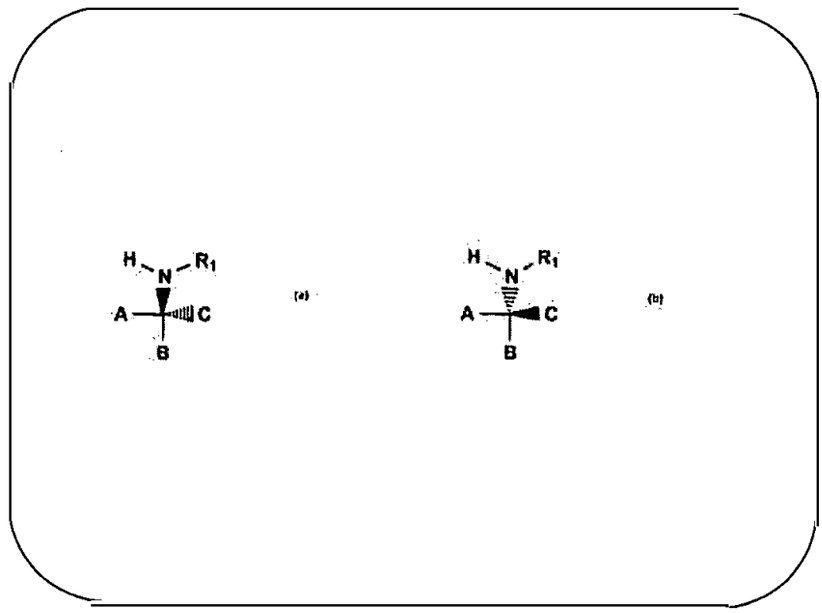
| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| US | 23-NOV-05 | 60/739,374 |
| US | 13-NOV-06 | 11/558,979 |

**(9) Comprobante de pago No.** 08-23086 **Fecha** 17-MAR-08

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [X] 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 indigenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos, Reporte de búsqueda internacional y opinión escrita y notificación de presentación de docuemtno de prioridad.

(11) **FIGURA CARATERISTICA**




(12) Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 26.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

RECIBO DE PAGO

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

2008 / 006

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 23,086
FECHA : MARZO 17 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-052929- -00000-0000
Fecha: 2008-05-23 15:34:21 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 2074

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| BAKER & MCKENZIE | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 116634 | 14/03/2008 | 52,393,300.00 |

***** 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. _____

POD-4002

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

## PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

---

## APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

---

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

---

JAIME A. GARAVITO B

COMO NOTARIO ÚNICO DEL CÍRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

2 MAY 2008

BOGOTÁ, D.C. - COLOMBIA
PAULMA NAVARRO DE BAUTISTA
NOTARIA ÚNICA (E)

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

*Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de* Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

*[Aparece sello realzado]*

---

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de ENERO 11 de 1983
MINISTERIO DE JUSTICIA

DESPACHO ONCE DE ESTE CIRCULO NOTARIAL DE BOGOTÁ D.C. HACE CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
22 MAY 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (E.P.)

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

22 MAY 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

X

BAKER & MCKENZIE

Baker, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

## POWER OF ATTORNEY

The undersigned,

**BRISTOL–MYERS SQUIBB COMPANY**

domiciled in

**Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America**

declares that it hereby grants to

**ALVARO CORREA-ORDOÑEZ and/or**
**OLGA GEORGETTE OTERO and/or**
**RICARDO METKE and/or**
**JUAN PABLO CONCHA**

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

**Signature of the person issuing the Power**

Anastasia P. Winslow
Senior Patent Counsel

## PODER DE ABOGADO

La abajo firmada,

**BRISTOL–MYERS SQUIBB COMPANY**

domiciliada en

**Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América**

declara por el presente que otorga a

**ALVARO CORREA-ORDOÑEZ y/o**
**OLGA GEORGETTE OTERO y/o**
**RICARDO METKE y/o**
**JUAN PABLO CONCHA**

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

**Firma de la persona que firma el Poder**



## NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

**CERTIFIES**

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
**Address, city, state, country**
**set his hand on the foregoing document.**

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
**Position of the person issuing the Power**
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
**Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America**
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
**(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)**
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
Sally B. Hansen

**SALLY B. HANSEN**
**Notary Public of New Jersey**
**My Commission Expires June 6, 2010**

## CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

**DA FE**

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
**Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América**
está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

22 MAY 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 May 2007 (31.05.2007)

PCT

(10) International Publication Number
WO 2007/062308 A3

(51) International Patent Classification:
*C07C 211/29* (2006.01) *C07C 233/56* (2006.01)
*C07C 215/08* (2006.01) *C07C 233/60* (2006.01)
*C07C 217/58* (2006.01) *C07C 233/66* (2006.01)
*C07C 229/36* (2006.01) *C07C 233/73* (2006.01)
*C07C 229/38* (2006.01) *C07C 233/78* (2006.01)
*C07C 233/09* (2006.01) *C07C 235/20* (2006.01)
*C07C 233/13* (2006.01) *C07C 235/34* (2006.01)
*C07C 233/18* (2006.01)

(21) International Application Number:
PCT/US2006/060958

(22) International Filing Date:
16 November 2006 (16.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/739,374 23 November 2005 (23.11.2005) US
11/558,979 13 November 2006 (13.11.2006) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

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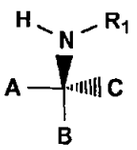
(74) Agents: **BOGIE, Terence J.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

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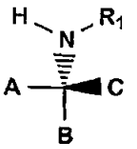
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*[Continued on next page]*

(54) Title: HOMO- AND HETEROCYCLIC COMPOUNDS SUITABLE AS CETP INHIBITORS




(a)




(b)

(57) Abstract: Compounds of formula (Ia) and (Ib) wherein A, B, C and $R_1$ are described herein. The compounds (Ia) and (Ib) are useful as CETP inhibitors.

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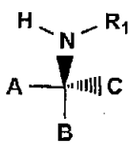
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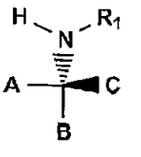
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*[Continued on next page]*

(54) Title: HETEROCYCLIC CETP INHIBITORS




(a)




(b)

(57) Abstract: Compounds of formula (Ia) and (Ib) wherein A, B, C and $R_1$ are described herein.

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# HETEROCYCLIC CETP INHIBITORS

## FIELD OF THE INVENTION

**[0001]** This present invention provides for cholesteryl ester transfer protein (CETP) inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein (HDL)-cholesterol and to lower certain other plasma lipid levels, such as low density lipoprotein (LDL)-cholesterol and triglycerides and accordingly to treat diseases which are affected by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in certain mammals (i.e., those which have CETP in their plasma), including humans.

## BACKGROUND OF THE INVENTION

**[0002]** Atherosclerosis and its associated coronary artery disease (CAD) is the leading cause of mortality in the industrialized world. Despite attempts to modify secondary risk factors (smoking, obesity, lack of exercise) and treatment of dyslipidemia with dietary modification and drug therapy, coronary heart disease (CHD) remains the most common cause of death in the U.S., where cardiovascular disease accounts for 44% of all deaths, with 53% of these associated with atherosclerotic coronary heart disease.

**[0003]** Risk for development of atherosclerosis has been shown to be strongly correlated with certain plasma lipid levels. While elevated LDL-C may be the most recognized form of dyslipidemia, it is by no means the only significant lipid associated contributor to CHD. Low HDL-C is also a known risk factor for CHD (Gordon, D J. et al., "High-density Lipoprotein Cholesterol and Cardiovascular Disease", Circulation, (1989), 79:8-15).

**[0004]** High LDL-cholesterol and triglyceride levels are positively correlated, while high levels of HDL-cholesterol are negatively correlated with the risk for developing cardiovascular diseases. Thus, dyslipidemia is not a unitary risk profile for CHD but may be comprised of one or more lipid aberrations.

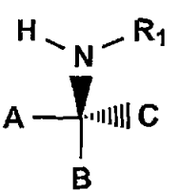
[0005] Among the many factors controlling plasma levels of these disease dependent principles, cholesteryl ester transfer protein (CETP) activity affects all three. The role of this 70,000 dalton plasma glycoprotein found in a number of animal species, including humans, is to transfer cholesteryl ester and triglyceride between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD.

[0006] No wholly satisfactory HDL-elevating therapies exist. Niacin can significantly increase HDL, but has serious toleration issues which reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-C only modestly (about.10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent which can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

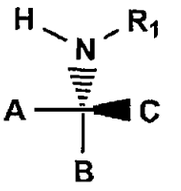
[0007] Thus, although there are a variety of anti-atherosclerosis therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

## SUMMARY OF THE INVENTION

[0008] In accordance with the present invention, heterocyclic compounds and related compounds are provided that have the general structures:




Ia and




Ib

wherein A, B, C and $R_1$ are defined below.

[0009] By use of a respective effective amount of at least one compound described herein, provided are methods of treating, preventing or slowing the progression of a disease requiring cholesteryl ester transfer protein inhibition, or inhibiting the cholesteryl ester transfer protein.

**[0010]** Also provided are pharmaceutical compositions comprising a therapeutically effective amount of at least one compound described herein and a pharmaceutically acceptable vehicle or carrier thereof. Such compositions can further comprise one or more additional therapeutic agents.

## DEFINITIONS

**[0011]** The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, or 1 to 8 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, or any subset of the foregoing. The term "substituted alkyl" refers to alkyl groups substituted with one or more groups (such as by groups described above in the definition of $R^{10}$), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

**[0012]** The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, or 2 to 4 carbon atoms, and at least one double carbon to carbon bond (either cis or trans), such as ethenyl. The term "substituted alkenyl" refers to alkenyl groups substituted with one or more groups (such as by groups described above in the definition of $R^{10}$), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

**[0013]** The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, or 2 to 4 carbon atoms, and at least one triple carbon to carbon bond, such as ethynyl. The term "substituted alkynyl" refers to alkynyl groups substituted with one or more groups (such as by groups described

above in the definition of $R^{10}$), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

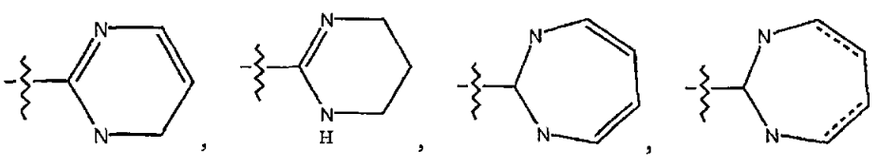
**[0014]** The term "aryl" refers to aromatic homocyclic (i.e., hydrocarbon) mono-, bi- or tricyclic ring-containing groups such as having 6 to 12 members such as phenyl, naphthyl and biphenyl. Phenyl is an example of an aryl group. The term "substituted aryl" refers to aryl groups substituted with one or more groups (such as by groups described above in the definition of $R^{10}$), such as selected from alkyl, substituted alkyl, alkenyl (optionally substituted), aryl (optionally substituted), heterocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl, (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing, where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

**[0015]** The term "cycloalkyl" refers to mono-, bi- or tri homocyclic ring groups of 3 to 15 carbon atoms which are, respectively, fully saturated and partially unsaturated. The rings of multi-ring cycloalkyl groups may be either fused, bridged and/or joined through one or more spiro unions. The term "substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more groups (such as by groups described above in the definition of $R^{10}$), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

**[0016]** The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

**[0017]** The terms "heterocycle", "heterocyclic", "heterocyclic group" or "heterocyclyl" refer to fully saturated or partially or completely unsaturated, including aromatic ("heteroaryl") or nonaromatic cyclic groups (for example, 3 to 13 ring member monocyclic, 7 to 17 ring member bicyclic, or 10 to 20 ring member tricyclic ring systems, such as, in certain embodiments, a monocyclic or bicyclic ring containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. The rings of multi-ring heterocycles may be either fused, bridged and/or joined through one or more spiro unions.

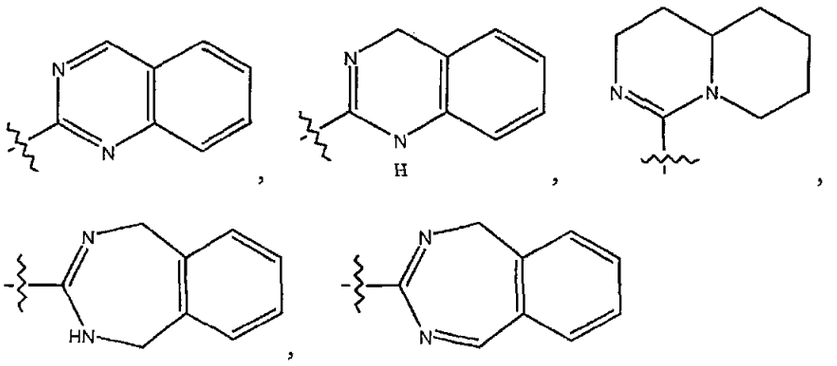
**[0018]** Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrahydropyranyl, tetrazoyl, triazolyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl,



and the like.

**[0019]** Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofuranyl, dihydrobenzofuranyl, chromonyl, coumarinyl, benzodioxolyl, dihydrobenzodioxolyl, benzodioxinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl),

dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl, azabicycloalkyls (such as 6-azabicyclo[3.2.1]octane), azaspiroalkyls (such as 1,4 dioxa-8-azaspiro[4.5]decane), imidazopyridinyl (such as imidazo[1,5-a]pyridin-3-yl), triazolopyridinyl (such as 1,2,4-triazolo[4,3-a]pyridin-3-yl), and hexahydroimidazopyridinyl (such as 1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-3-yl),



and the like.

**[0020]** Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

**[0021]** The terms "substituted heterocycle", "substituted heterocyclic", "substituted heterocyclic group" and "substituted heterocyclyl" refer to heterocycle, heterocyclic and heterocyclo groups substituted with one or more groups (such as by groups described above in the definition of $R^{10}$), such as selected from alkyl, substituted alkyl, alkenyl, oxo, aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amido, amino, substituted amino, lactam, urea, urethane, sulfonyl, , or any subset of the foregoing, where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

**[0022]** Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

[0023] The compounds of formulas Ia and Ib form salts or solvates which are also within the scope of this invention. Reference to a compound of the formula Ia or Ib herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula Ia or Ib contains both a basic moiety and an acidic moiety, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula Ia and Ib may be formed, for example, by reacting a compound of formula Ia or Ib with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0024] The compounds of formula Ia and Ib which contain a basic moiety may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[0025] The compounds of formula Ia and Ib which contain an acidic moiety may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium

salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like.

**[0026]** Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

**[0027]** Any compound that can be converted in vivo to provide the bioactive agent (i.e., a compound of formula Ia or Ib) is a prodrug within the scope and spirit of the invention.

**[0028]** The term "prodrugs" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula Ia and Ib with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, and the like.

**[0029]** Various forms of prodrugs are well known in the art and are described in:

a) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31 (Academic Press, 1996);

b) *Design of Prodrugs*, edited by H. Bundgaard (Elsevier, 1985);

c) *A Textbook of Drug Design and Development*, P. Krogsgaard–Larson and H. Bundgaard, eds., Ch. 5, pp. 113-191 (Harwood Academic Publishers, 1991); and

d) *Hydrolysis in Drug and Prodrug Metabolism*, Bernard Testa and Joachim M. Mayer, (Wiley-VCH, 2003).

Said references are incorporated herein by reference.

**[0030]** In addition, compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an

amount by weight equal to or greater than 99% formula Ia or Ib compound ("substantially pure" compound Ia or Ib), which may be used or formulated as described herein. Such "substantially pure" compounds of formula Ia and Ib are also contemplated herein as part of the present invention.

**[0031]** To the extent that compounds of the formula Ia and Ib, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of the present invention.

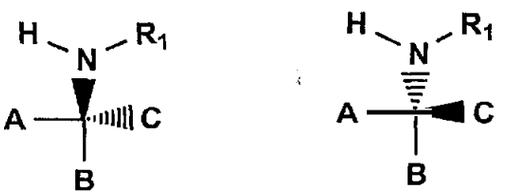
**[0032]** All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers.

**[0033]** The terms "including", "such as", "for example" and the like are intended to refer to exemplary embodiments and not to limit the scope of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

**[0034]** It will be understood that any given exemplary embodiment can be combined with one or more additional exemplary embodiments.

**[0035]** In accordance with the present invention, compounds of formula Ia and Ib are provided




Ia or Ib

or stereoisomers or prodrugs or pharmaceutically acceptable salt forms thereof, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally

substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) =O, 17) $-S(O)_pR_6$, 18) $-SO_2NHR_6$, 19) $-COOR_6$, 20) $-NHC(CN)NHR_6$, 21) $-CONR_6R_6$, 22) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 23) ($C_2$-$C_6$)-alkenyl, which may be optionally substituted with one or more $R_{20}$'s, 24) $-OCOR_6$, 25) $-OCOOR_6$, 26) $-OCONR_6R_6$, or 27) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, 20) $-CONR_6R_6$; and 21) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(b) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-

alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$, 20) –$CONR_6R_6$; and 21) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

C is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, 17) –$NHC(CN)NHR_6$; and 18) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl; and 15) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, 17) –$NHC(CN)NHR_6$; and 18) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(d) heterocyclo, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) –$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, 17) –$NHC(CN)NHR_6$; and 18) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is H, –$C(O)R_3$, -$C(O)NR_2R_3$, -$C(O)OR_4$, -$SO_2R_5$, -$C(S)NHR_7$, -$CR_8R_8R_8$, or -$C(S)R_3$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$,

4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$; and 20) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, 19) –$S(O)_pR_6$, 20) –$SO_2NHR_6$, 21) –$COOR_6$, 22) –$NHC(CN)NHR_6$; and 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CO(C_1$-$C_6$)-alkyl, 16) -COOH, 17) -$CO_2(C_1$-$C_6$)-alkyl, 18) -$CONR_6R_6$,

19) ($C_2$-$C_6$)-alkenyl, 20) ($C_2$-$C_6$)-alkynyl; and 21) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$; and 20) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18)

($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, 19) –$S(O)_pR_6$, 20) –$SO_2NHR_6$, 21) –$COOR_6$, 22) –$NHC(CN)NHR_6$; and 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_4$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl,

15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) ($C_2$-$C_6$)-alkenyl; or

(e) ($C_2$-$C_6$)-alkynyl;

$R_5$ is arylalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl,

which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, 24) –$NHC(CN)NHR_{36}$; and 25) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-

alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s,

4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –NHC(CN)$NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_7$ is aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, 23) –NHC(CN)$NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_8$ can independently be:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be

optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, 18) –$S(O)_pR_{26}$, 19) –$SO_2NHR_{26}$, 20) –$COOR_{26}$, 21) –$NHC(CN)NHR_{26}$; and 22) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, 23) –$NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl,

19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(e) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) $-CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(f) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) $-CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; (b) $-[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s; (c) $-[(C=O)O_r]_s(C_2-C_8)$-alkenyl, wherein the alkenyl may be optionally substituted with one or more $R_{20}$'s; (d) $-[(C=O)O_r]_s(C_1-C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s; (e) heterocyclyl optionally substituted with one or more $R_{20}$'s; (f) $-CONR_{26}R_{26}$; (g) $-(C_2-C_6)$-alkynyl; (h) $-COR_{26}$; (i) $-S(O)_pR_{26}$; (j) $-SO_2NHR_{26}$; (k) $-COOR_{26}$; (l) $-NHC(CN)NHR_{26}$; or m) $-[(C=O)O_r]_s$cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1-C_6)$alkyl; (o) $(C_2-C_6)$-alkenyl; (p) =O; (q) $-(C_2-C_6)$-alkynyl; (r) $-COR_{26}$; (s) $-S(O)_pR_{26}$; (t) $-SO_2NHR_{26}$; (u) $-COOR_{26}$; (v) $-NHC(CN)NHR_{26}$; (w) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (x) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (y) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1-C_6)$alkyl; (o) $-CONR_{26}R_{26}$;

(p) ($C_2$-$C_6$)-alkenyl; (q) =O; (r) ($C_2$-$C_6$)-alkynyl; (s) cycloalkyl; (t) cycloalkylalkyl; (u) $-COR_{26}$; (v) $-S(O)_pR_{26}$; (w) $-SO_2NHR_{26}$; (x) $-COOR_{26}$; or (y) $-NHC(CN)NHR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$; and 23) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, 24) $-NHC(CN)NHR_{36}$; and 25) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4)

-$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –NHC(CN)$NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –NHC(CN)$NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more

$R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, $-[(C=O)O_r]_s$aryl, $-[(C=O)O_r]_s$alkenyl, $-[(C=O)O_r]_s$alkyl, heterocyclyl, $-CONR_{46}R_{46}$, alkynyl, $-COR_{36}$, $-S(O)_pR_{36}$, $-SO_2NHR_{36}$, $-COOR_{36}$, $-C(CN)NHR_{36}$, or cycloalkyl, wherein the aryl, alkyl, alkenyl, cycloalkyl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

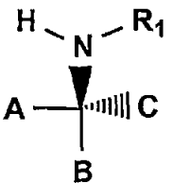
$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, $-NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, or $-NHC(CN)NHR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl;

r is 0 to 5;
s is 0 to 4; and
p is 1 or 2.

**[0036]** In one embodiment, compounds of the present invention are provided wherein the compounds are compounds of formula Ia



Ia

**[0037]** In another embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) –$S(O)_pR_6$, 18) –$SO_2NHR_6$, 19) –$COOR_6$, 20) –$NHC(CN)NHR_6$, 21) –$CONR_6R_6$, 22) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 23) ($C_2$-$C_6$)-alkenyl, which may be optionally substituted with one or more $R_{20}$'s, 24) –$OCOR_6$, 25) –$OCOOR_6$, or 26) -$OCONR_6R_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or

more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$; or

(b) heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$;

C is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, and 17) $-NHC(CN)NHR_6$;

(b) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl; or

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, and 17) –$NHC(CN)NHR_6$;

$R_1$ is H, –$C(O)R_3$, -$C(O)NR_2R_3$, -$C(O)OR_4$, -$SO_2R_5$, -$C(S)NHR_7$, -$CR_8R_8R_8$, or -$C(S)R_3$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, and 19) –$NHC(CN)NHR_6$;

(c) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl,

which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, 19) –$S(O)_pR_6$, 20) –$SO_2NHR_6$, 21) –$COOR_6$, and 22) –$NHC(CN)NHR_6$; or

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CO$($C_1$-$C_6$)-alkyl, 16) -COOH, 17) -$CO_2$($C_1$-$C_6$)-alkyl, 18) -$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkenyl, and 20) ($C_2$-$C_6$)-alkynyl;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl,

12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, and 19) –$NHC(CN)NHR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$; or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, 19) –$S(O)_pR_6$, 20) –$SO_2NHR_6$, 21) –$COOR_6$, and 22) –$NHC(CN)NHR_6$;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_4$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4)

($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(d) ($C_2$-$C_6$)-alkenyl; or

(e) ($C_2$-$C_6$)-alkynyl;

$R_5$ is arylalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl,

13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3)

($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl,

13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_7$ is aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

$R_8$ can independently be:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, 18) –$S(O)_pR_{26}$, 19) –$SO_2NHR_{26}$, 20) –$COOR_{26}$, and 21) –$NHC(CN)NHR_{26}$;

(c) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

(e) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$; or

(f) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O,

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18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; (b) –$[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s; (c) –$[(C=O)O_r]_s$($C_2$-$C_8$)-alkenyl, wherein the alkenyl may be optionally substituted with one or more $R_{20}$'s; (d) –$[(C=O)O_r]_s$($C_1$-$C_8$)alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s; (e) heterocyclyl optionally substituted with one or more $R_{20}$'s; (f) –$CONR_{26}R_{26}$; (g) -($C_2$-$C_6$)-alkynyl; (h) –$COR_{26}$; (i) –$S(O)_pR_{26}$; (j) –$SO_2NHR_{26}$; (k) –$COOR_{26}$; or (l) –$NHC(CN)NHR_{26}$;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{21}$'s; c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) =O; (q) -($C_2$-$C_6$)-alkynyl; (r) –$COR_{26}$; (s) –$S(O)_pR_{26}$; (t) –$SO_2NHR_{26}$; (u) –$COOR_{26}$; (v) –$NHC(CN)NHR_{26}$; (w) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (x) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (y) –$CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) –$CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) =O; (r) ($C_2$-$C_6$)-alkynyl; (s) cycloalkyl; (t) cycloalkylalkyl; (u) –$COR_{26}$; (v) –$S(O)_pR_{26}$; (w) –$SO_2NHR_{26}$; (x) –$COOR_{26}$; or (y) –$NHC(CN)NHR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3)

($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or

more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, $-[(C=O)O_r]_s$aryl, $-[(C=O)O_r]_s$alkenyl, $-[(C=O)O_r]_s$alkyl, heterocyclyl, $-CONR_{46}R_{46}$, alkynyl, $-COR_{36}$, $-S(O)_pR_{36}$, $-SO_2NHR_{36}$, $-COOR_{36}$, or $-C(CN)NHR_{36}$, wherein the aryl, alkyl, alkenyl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, $-NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, or $-NHC(CN)NHR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl;

r is 0 to 5;
s is 0 to 4; and
p is 1 or 2.

**[0038]** In yet another embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl,

which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) =O, 17) $-COOR_6$, 18) $-CONR_6R_6$, 19) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 20) ($C_2$-$C_6$)-alkenyl, which may be optionally substituted with one or more $R_{20}$'s, 21) $-OCOR_6$, 22) $-OCOOR_6$, or 23) $-OCONR_6R_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-COOR_6$, and 17) $-CONR_6R_6$; or

(b) a nitrogen containing heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$COOR_6$, and 17) –$CONR_6R_6$;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) -$OR_6$, 3) -$NR_9R_{10}$, 4) aryl, which may be optionally substituted with one or more $R_{20}$'s, 5) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 6) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 7) -$CONR_6R_6$, and 8) –$COOR_6$;

$R_1$ is –$C(O)R_3$, -$C(O)NR_2R_3$, -$C(O)OR_4$ or –$CH_2R_8$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, and 16) –$COOR_6$;

(c) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl,

15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, and 19) –$COOR_6$; or

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CO$($C_1$-$C_6$)-alkyl, 16) -COOH, 17) -$CO_2$($C_1$-$C_6$)-alkyl, 18) -$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkenyl, and 20) ($C_2$-$C_6$)-alkynyl;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro,

7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, and 19) –$COOR_6$;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_4$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; (b) $-[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s; (c) $-[(C=O)O_r]_s(C_1\text{-}C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s; or (d) heterocyclyl optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1\text{-}C_6)$-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) $(C_1\text{-}C_6)$-alkylthio; (e) cyano, (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1\text{-}C_6)$alkyl; (o) $(C_2\text{-}C_6)$-alkenyl; (p) $-(C_2\text{-}C_6)$-alkynyl; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1\text{-}C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1\text{-}C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1\text{-}C_6)$alkyl; (o) $-CONR_{26}R_{26}$; (p) $(C_2\text{-}C_6)$-alkenyl; (q) $(C_2\text{-}C_6)$-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) $-COR_{26}$; or (u) $-COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14)

heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) – $SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) – $SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, $-[(C=O)O_r]_s$aryl, $-[(C=O)O_r]_s$alkyl, or heterocyclyl, wherein the aryl, alkyl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, $-NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$ or $-COOR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, heteroaryl or heterocyclyl, other than heteroaryl;

r is 0 to 3;
s is 0 to 2; and
p is 1 or 2.

**[0039]** In still yet another embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro,

7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) –$COOR_6$, 18) –$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 20) –$OCOR_6$, 21) –$OCOOR_6$, or 22) -$OCONR_6R_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COOR_6$, and 16) –$CONR_6R_6$; or

(b) a 6- to 10-membered nitrogen containing heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s,

13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COOR_6$, and 16) –$CONR_6R_6$;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) -$OR_6$, 3) -$NR_9R_{10}$, 4) aryl, which may be optionally substituted with one or more $R_{20}$'s, 5) a nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 6) -$CONR_6R_6$, and 7) –$COOR_6$;

$R_1$ is –$C(O)R_3$, -$C(O)NR_2R_3$ or –$CH_2R_8$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, and 16) –$COOR_6$; or

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl,

15) -CO($C_1$-$C_6$)-alkyl, 16) -COOH, 17) -$CO_2$($C_1$-$C_6$)-alkyl, 18) -$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkenyl, and 20) ($C_2$-$C_6$)-alkynyl;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$,

4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, and 19) –$COOR_6$;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl,

which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$,

4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl,

15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen, (b) –$[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s, or (c) –$[(C=O)O_r]_s$($C_1$-$C_8$)alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may

be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) -($C_2$-$C_6$)-alkynyl; (q) –$COR_{26}$; (r) –$COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) –$CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) –$CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) ($C_2$-$C_6$)-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) –$COR_{26}$; or (u) –$COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl,

which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$; or

(f) hydrogen;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, –$[(C=O)O_r]_s$aryl, or –$[(C=O)O_r]_s$alkyl, wherein the aryl or alkyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, -$NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl,

haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$ or $-COOR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl or heteroaryl;

r is 0 to 2;
s is 0 to 1; and
p is 1 or 2.

**[0040]** In one embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1\text{-}C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1\text{-}C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo$(C_1\text{-}C_6)$alkyl, 15) $-COR_6$, 16) =O, 17) $-COOR_6$, 18) $(C_2\text{-}C_6)$-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 19) $-OCOR_6$, and 20) $-OCOOR_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1\text{-}C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1\text{-}C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with

one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, and 15) $-COOR_6$; or

(b) a 6-membered nitrogen containing heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, and 15) $-COOR_6$;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) phenyl, which may be optionally substituted with one or more $R_{20}$'s, or 3) a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is $-C(O)R_3$, $-C(O)NR_2R_3$ or $-CH_2R_8$;

$R_2$ is:

(a) H; or

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, and 16) –$COOR_6$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –NHC(CN)$NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –NHC(CN)$NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may

be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen, or (b) $-[(C=O)O_r]_s(C_1-C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1-C_6)$alkyl; (o) $(C_2-C_6)$-alkenyl; (p) $-(C_2-C_6)$-alkynyl; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1-C_6)$alkyl; (o) $-CONR_{26}R_{26}$; (p) $(C_2-C_6)$-alkenyl; (q) $(C_2-C_6)$-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) $-COR_{26}$; or (u) $-COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) $(C_1-C_6)$-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo$(C_1-C_6)$alkyl,

13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4)

-$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_{29}$ and $R_{30}$ are independently hydrogen or –$[(C=O)O_r]_s$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, $-NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, $–CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $–COR_{49}$, or $–COOR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, or heteroaryl;

r is 0 to 2;

s is 0 to 1; and

p is 1 or 2.

**[0041]** In another embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo$(C_1$-$C_6)$alkyl, 15) $–COR_6$, 16) =O, 17) $(C_2$-$C_6)$-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, and 18) $–OCOR_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) phenyl, which may be optionally substituted with one or more $R_{20}$'s, or 2) a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is –C(O)$R_3$, -C(O)N$HR_3$ or –$CH_2R_8$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be

optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl,

which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or

more $R_{20}$'s, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) $-CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) $-COR_{26}$, and 20) $-COOR_{26}$;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; or (b) $-[(C=O)O_r]_s(C_1$-$C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) -($C_2$-$C_6$)-alkynyl; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) $-OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) $-CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) ($C_2$-$C_6$)-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) $-COR_{26}$; or (u) $-COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –NHC(CN)$NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –NHC(CN)$NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14)

heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_{29}$ and $R_{30}$ are independently hydrogen or $-[(C=O)O_r]_s$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl or cycloalkylalkyl;

r is 0 to 2;
s is 0 to 1; and
p is 1 or 2.

**[0042]** In yet another embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, and 17) –$OCOR_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted

with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl;

C is methyl, which is substituted with one or more substituents selected from the group consisting of: 1) phenyl, which may be optionally substituted with one or more $R_{20}$'s, or 2) a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is $-C(O)R_3$, $-C(O)NHR_3$ or $-CH_2R_8$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) $-CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) $-COR_6$, and 16) $-COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or

more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$SO_2NHR_{36}$, 20) –$COOR_{36}$, and 21) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$SO_2NHR_{36}$, 22) –$COOR_{36}$, and 23) –$NHC(CN)NHR_{36}$;

(c) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11)

heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$; or

(d) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl,

which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; or (b) $-[(C=O)O_r]_s(C_1\text{-}C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1\text{-}C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1\text{-}C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1\text{-}C_6)$alkyl; (o) $(C_2\text{-}C_6)$-alkenyl; (p) $-(C_2\text{-}C_6)$-alkynyl; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1\text{-}C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1\text{-}C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1\text{-}C_6)$alkyl; (o) $-CONR_{26}R_{26}$; (p) $(C_2\text{-}C_6)$-alkenyl; (q) $(C_2\text{-}C_6)$-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) $-COR_{26}$; or (u) $-COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) $(C_1\text{-}C_6)$-alkyl, 4) $-OR_{36}$, 5) $(C_1\text{-}C_6)$-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo$(C_1\text{-}C_6)$alkyl, 13) $(C_2\text{-}C_6)$-alkenyl, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) $(C_2\text{-}C_6)$-alkynyl, 18) $-COR_{36}$, 19) $-SO_2NHR_{36}$, 20) $-COOR_{36}$, and 21) $-NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$SO_2NHR_{36}$, 22) –$COOR_{36}$, and 23) –$NHC(CN)NHR_{36}$;

(c) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$; or

(d) hydrogen;

$R_{29}$ and $R_{30}$ are independently hydrogen or –$[(C=O)O_r]_s$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl or heteroaryl, wherein the alkyl, aryl or heteroaryl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, or cycloalkylalkyl;

r is 0 to 2; and

s is 0 to 1.

**[0043]** In still yet another embodiment, compounds of the present invention are provided wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, and 15) –$COR_6$;

B is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl;

C is methyl, which is substituted with a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is $-C(O)R_3$, $-C(O)NHR_3$ or $-CH_2R_8$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 10) halo($C_1$-$C_6$)alkyl, 11) ($C_2$-$C_6$)-alkenyl, 12) ($C_2$-$C_6$)-alkynyl, 13) $-COR_6$, and 14) $-COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_6$, and 17) $-COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_6$, and 17) $-COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_6$, and 17) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_6$, and 17) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) -COOH, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_{36}$, and 16) –$COOR_{36}$; or

(b) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 10) halo($C_1$-$C_6$)alkyl, 11) ($C_2$-$C_6$)-alkenyl, 12) ($C_2$-$C_6$)-alkynyl, 13) –$COR_{26}$, and 14) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_{26}$, and 17) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_{26}$, and 17) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be

optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_{26}$, and 17) $-COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_{26}$, and 17) $-COOR_{26}$;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) $-OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) aryl, which may be optionally substituted with one or more $R_{21}$'s; (h) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (i) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (k) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (m) halo($C_1$-$C_6$)alkyl; (n) ($C_2$-$C_6$)-alkenyl; (o) -($C_2$-$C_6$)-alkynyl; (p) $-COR_{26}$; (q) $-COOR_{26}$; (r) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (s) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) $-OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) aryl; (h) arylalkyl; (i) heteroaryl; (j) heteroarylalkyl; (k) heterocyclyl; (l)

heterocyclylalkyl; (m) halo($C_1$-$C_6$)alkyl; (n) ($C_2$-$C_6$)-alkenyl; (o) ($C_2$-$C_6$)-alkynyl; (p) cycloalkyl; (q) cycloalkylalkyl; (r) –$COR_{26}$; or (s) –$COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) aryl, which may be optionally substituted with one or more $R_{40}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) -COOH, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_{36}$, or 16) –$COOR_{36}$; or

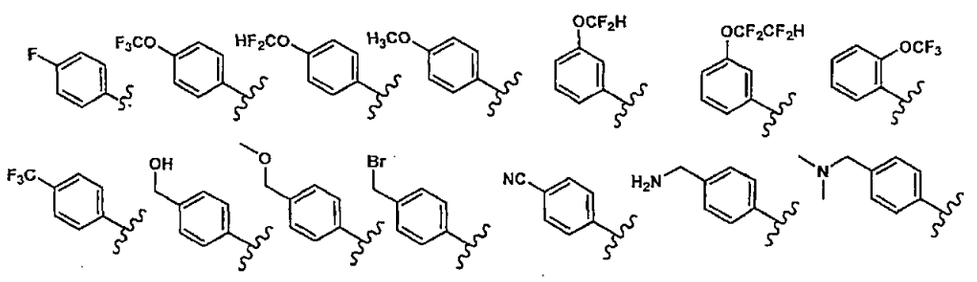
(b) hydrogen;

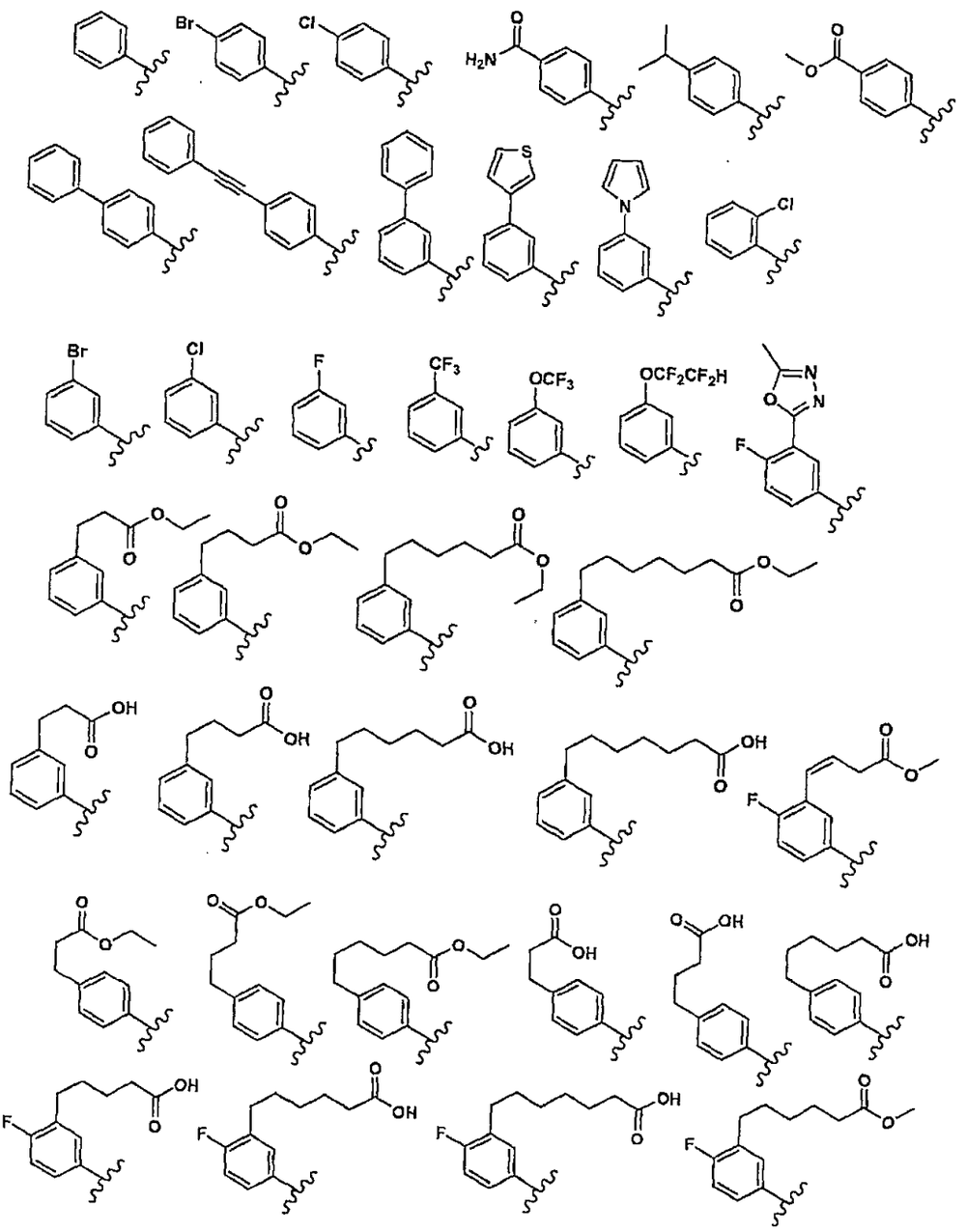
$R_{36}$, at each occurrence, is independently alkyl, aryl or heteroaryl, wherein the alkyl, aryl or heteroaryl may be optionally substituted with one or more $R_{40}$'s; and

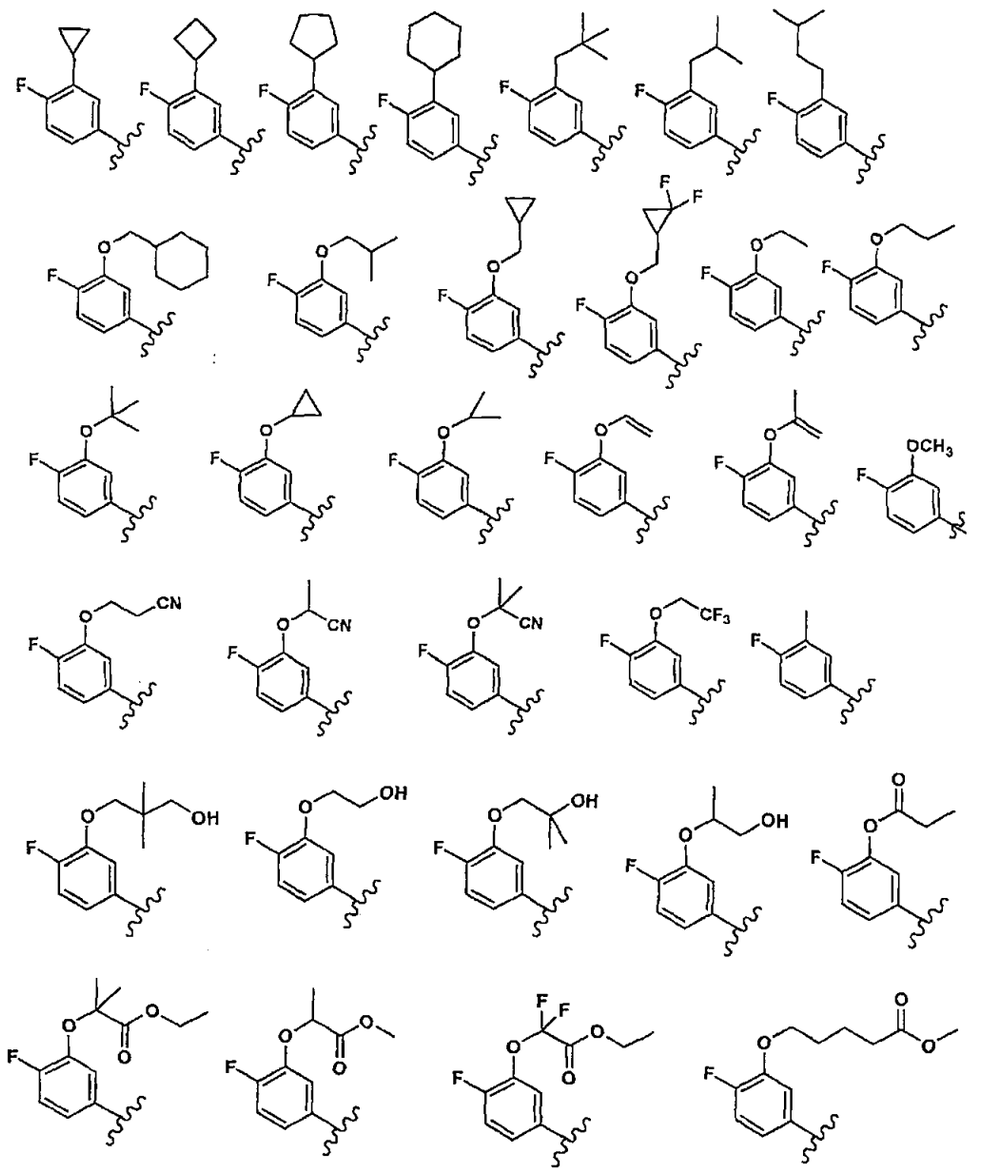
$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, alkenyl, arylalkyloxy, alkynyl, cycloalkyl or cycloalkylalkyl.

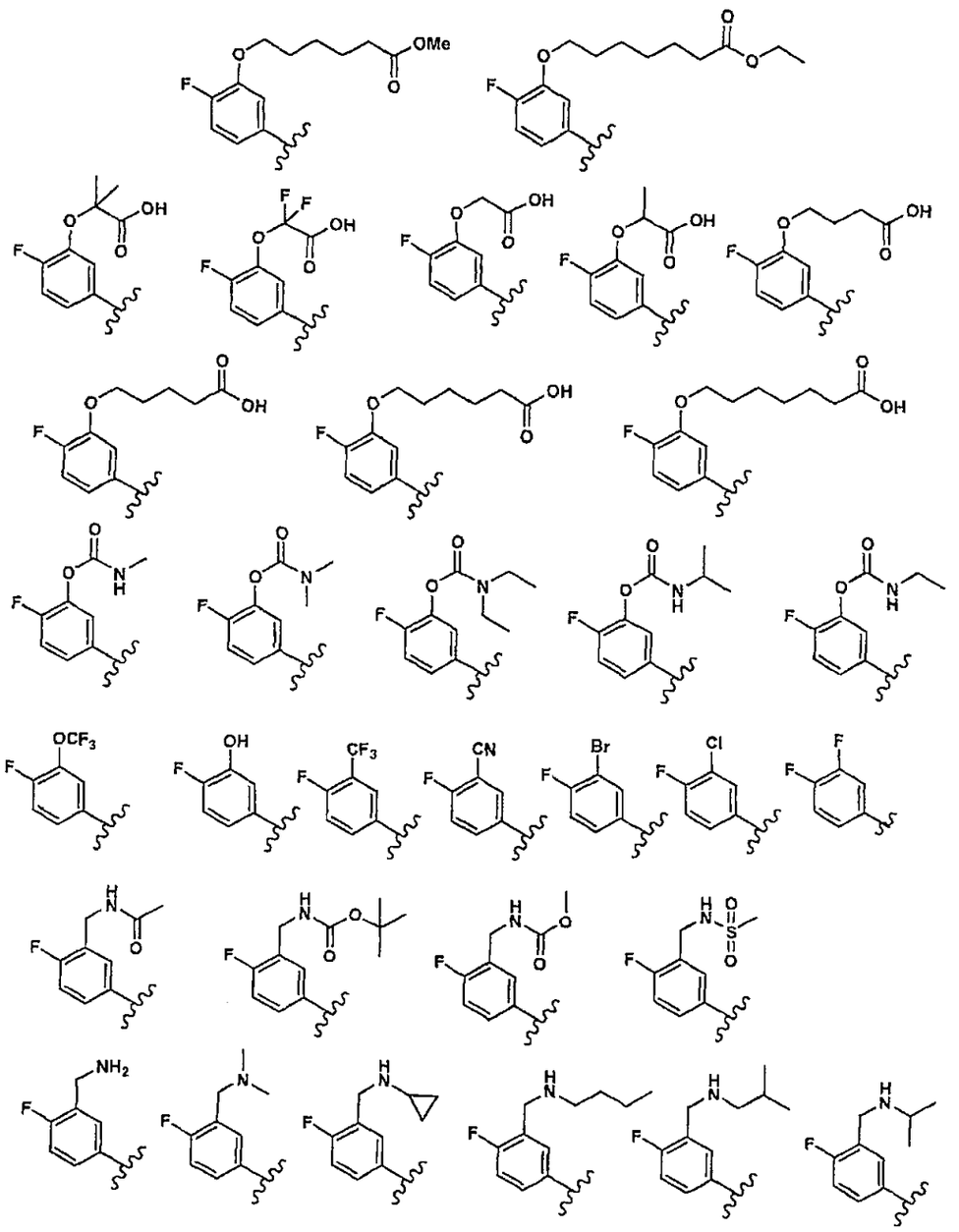
**[0044]** Also in accordance with the present invention, compounds of the present invention are those wherein:

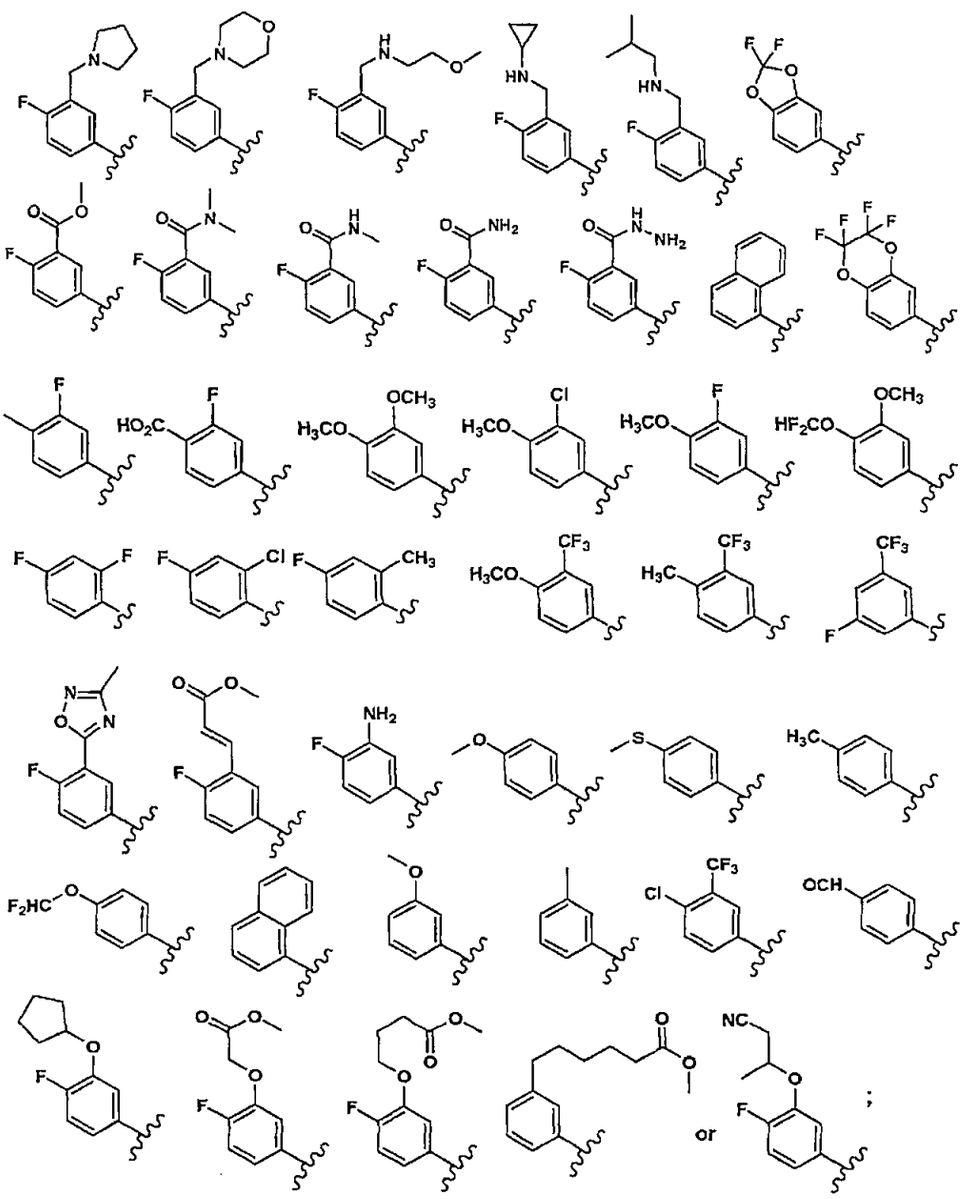
A is:





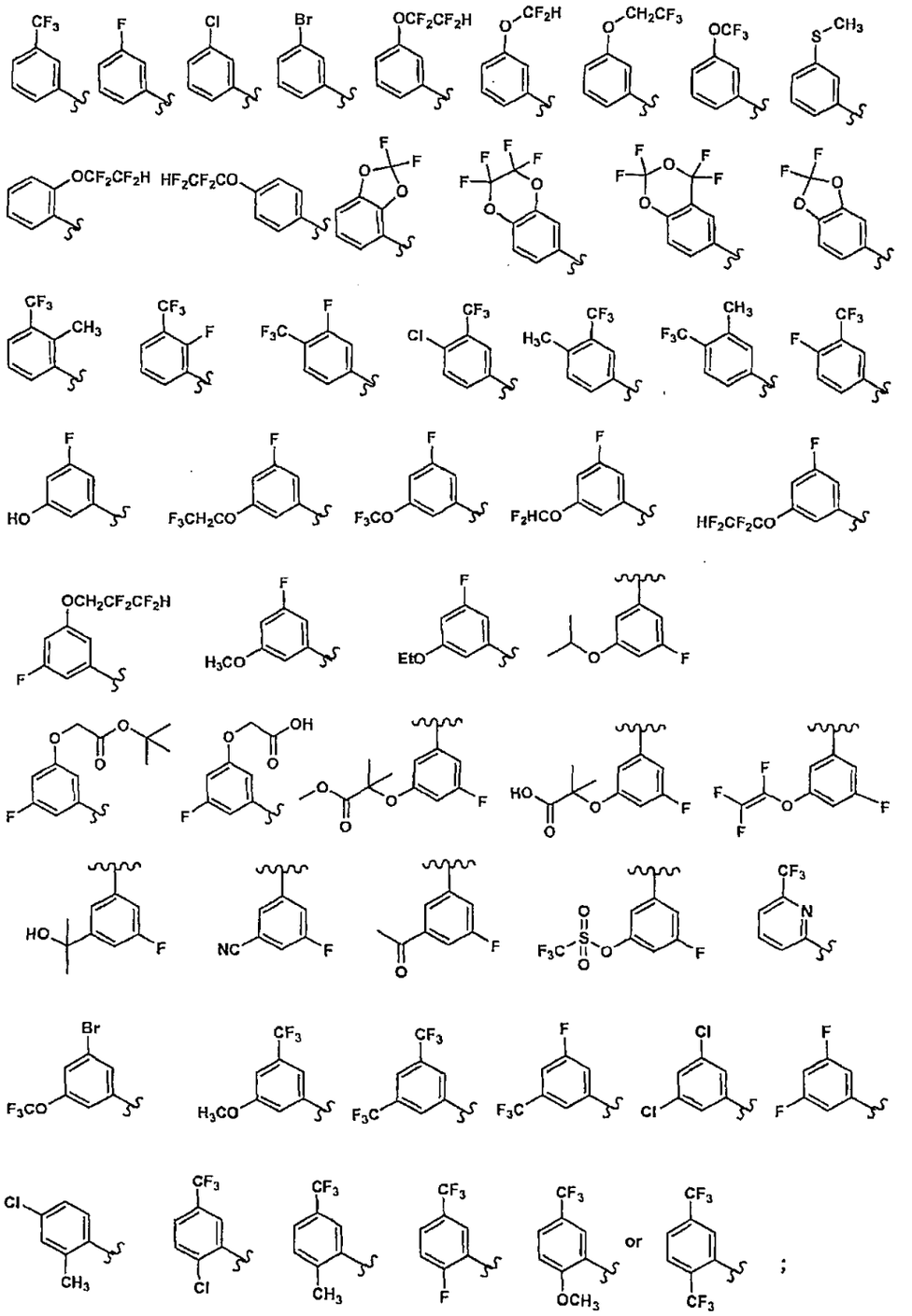






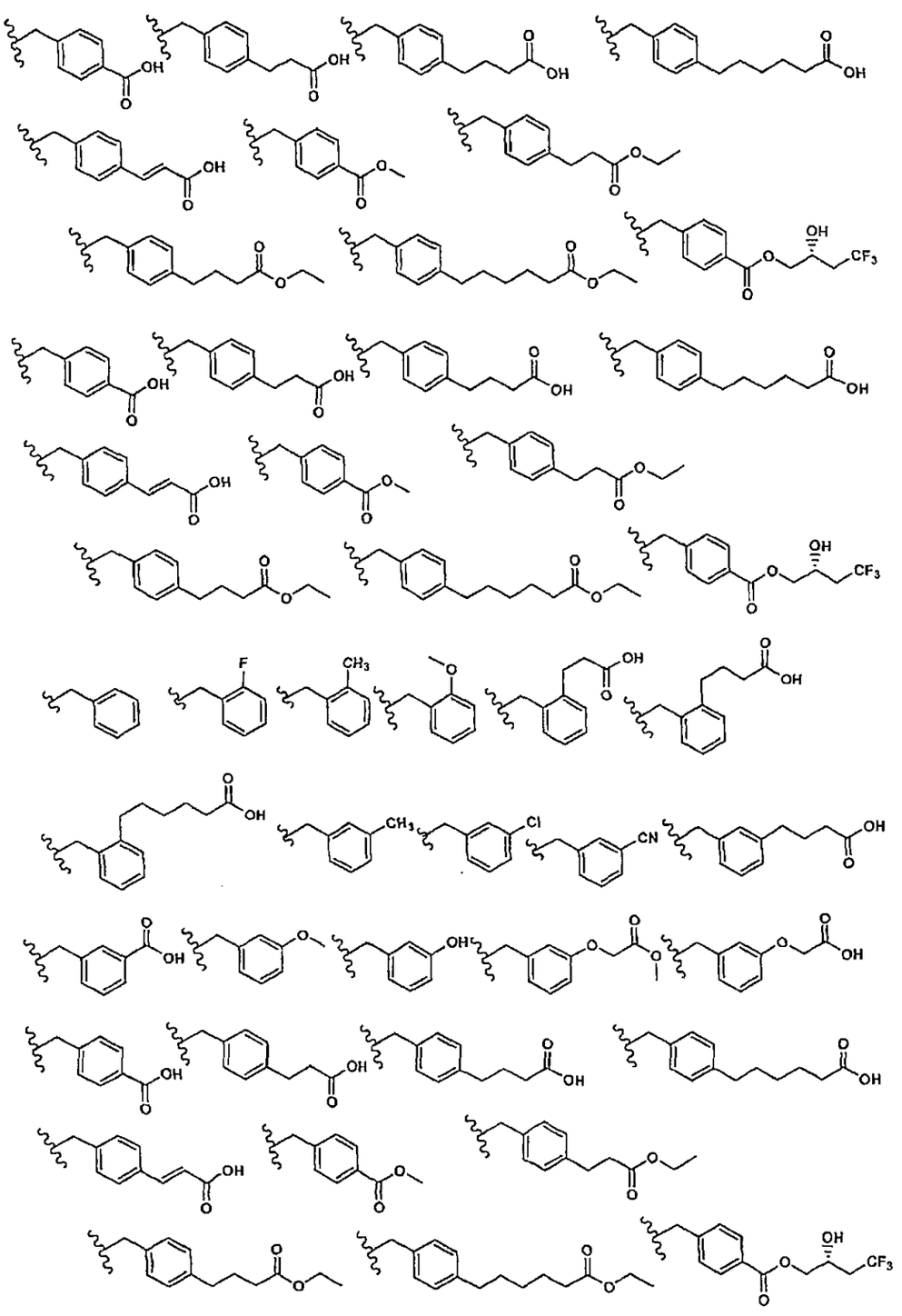
or ;

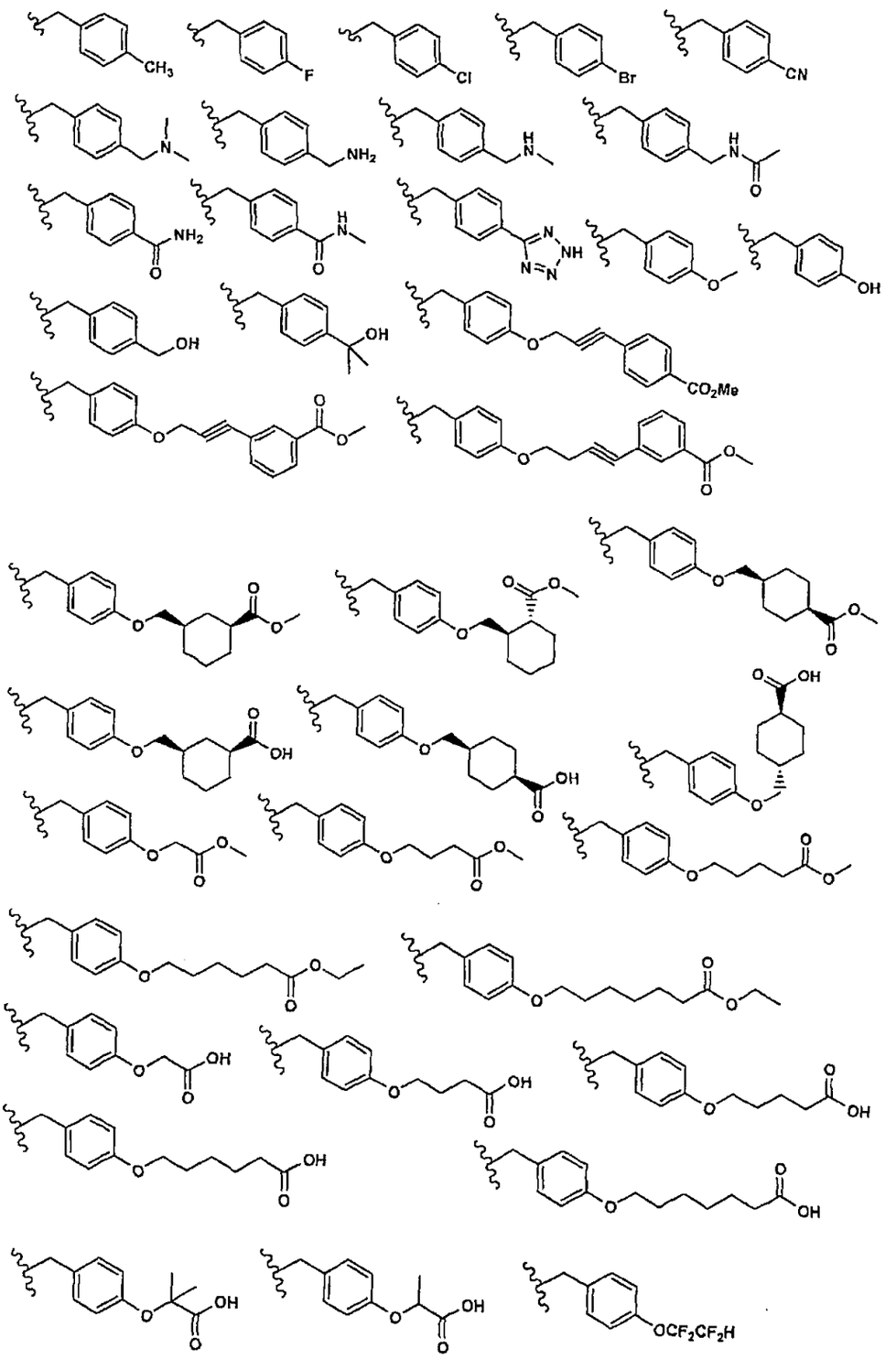
B is:

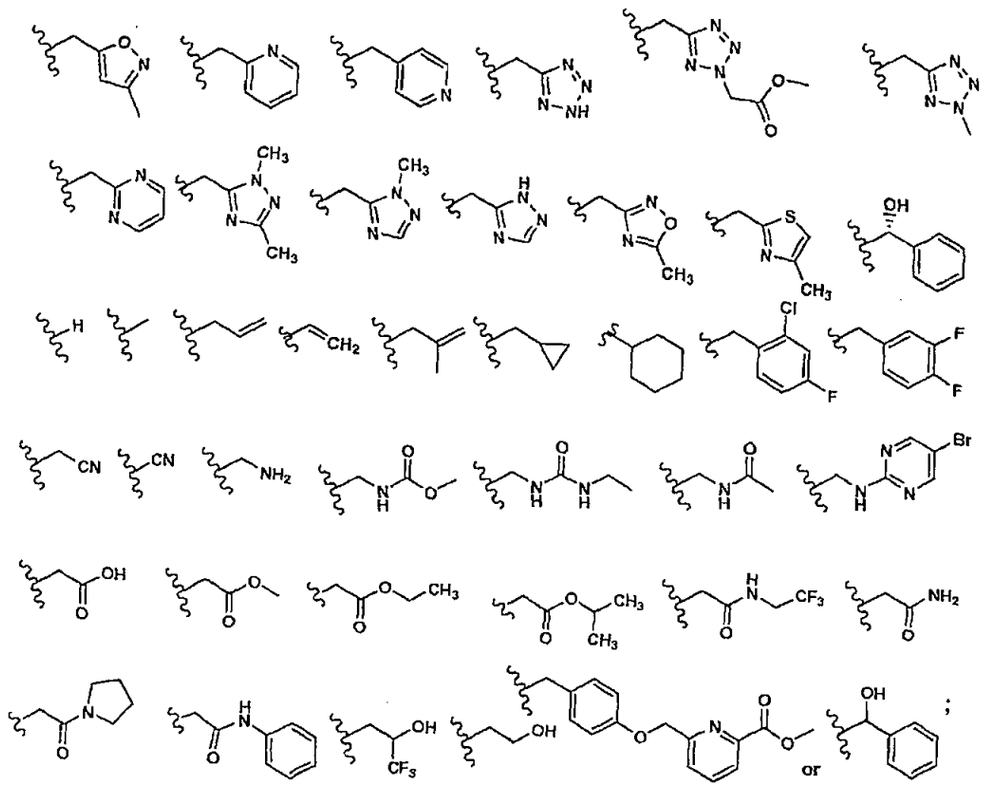


;

C is:

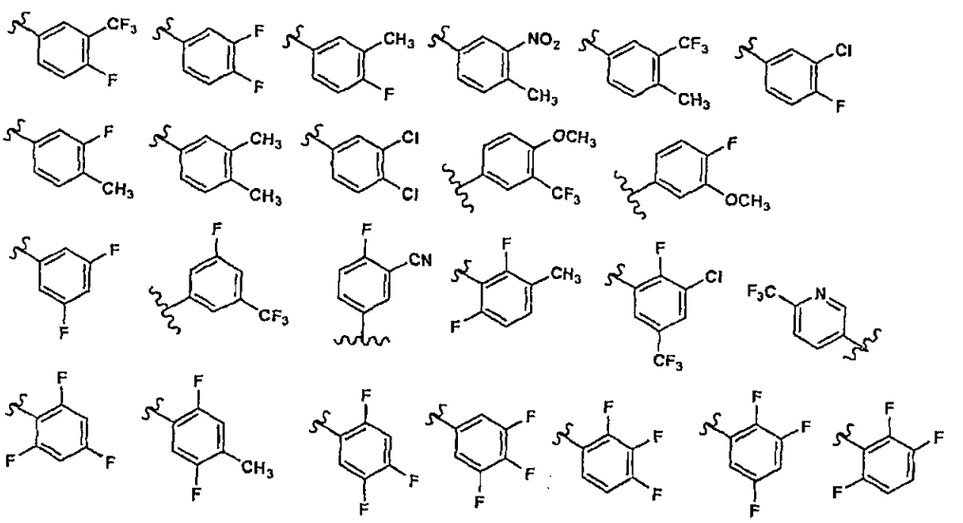


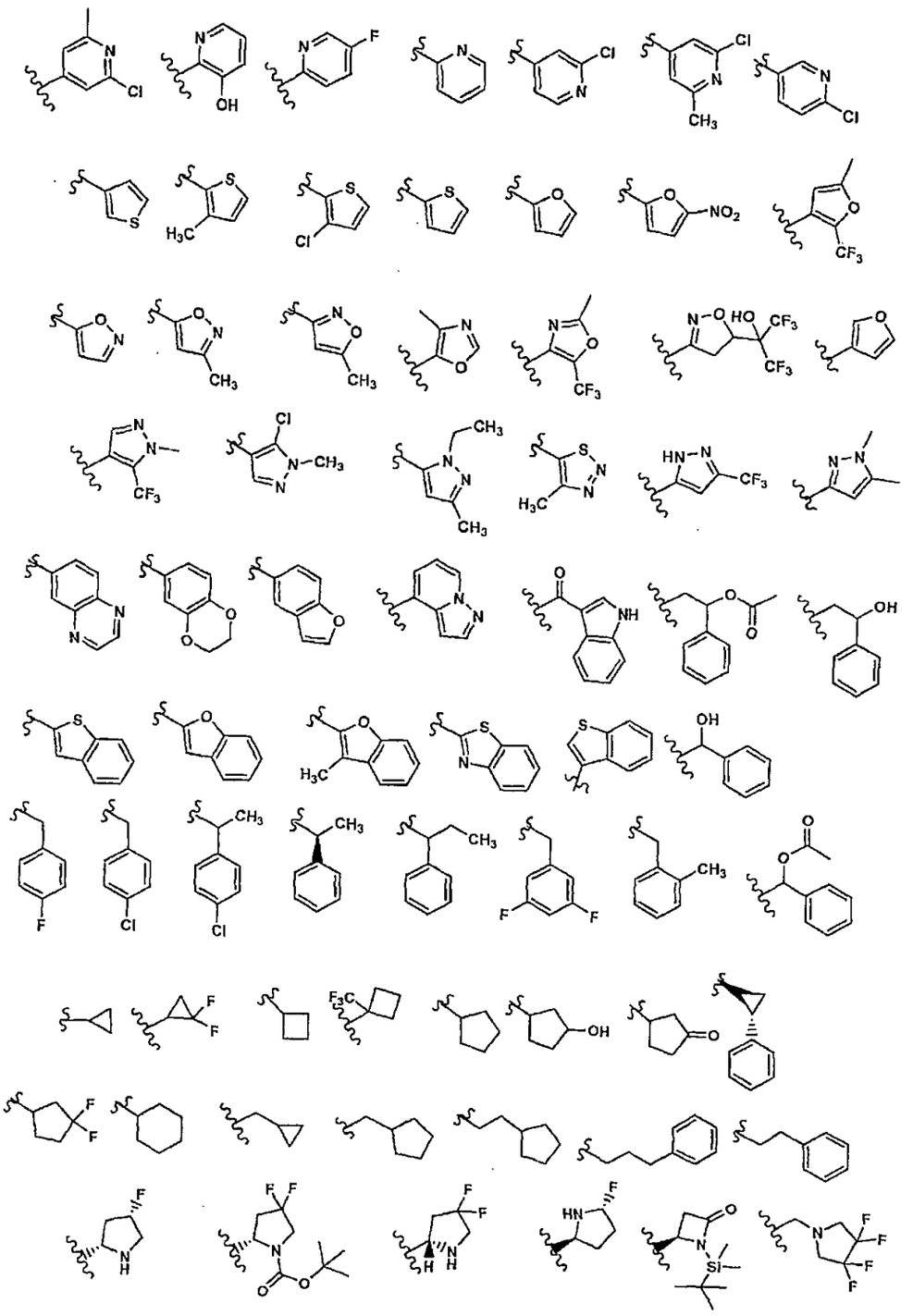


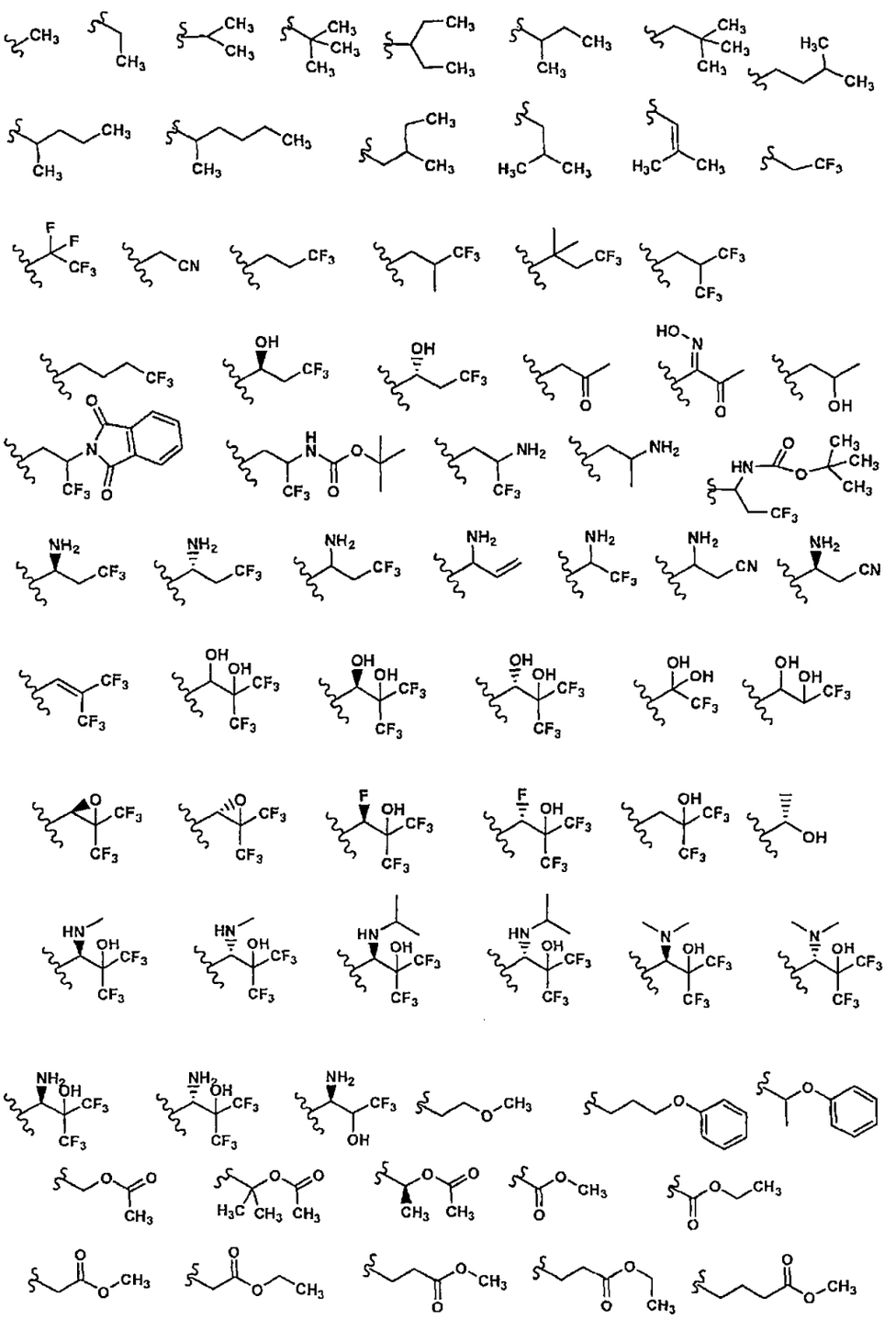


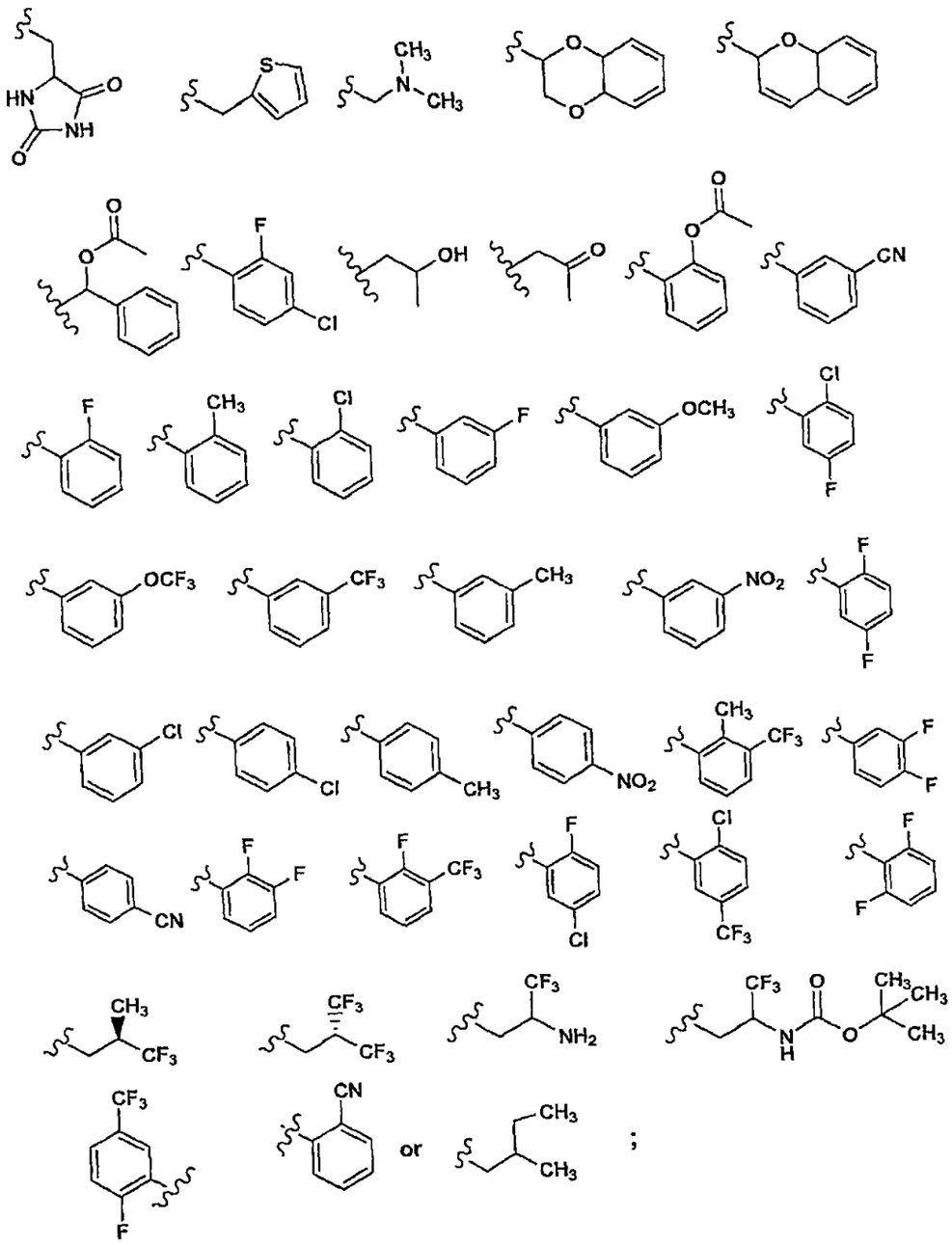
$R_1$ is:

(a) $-C(O)R_3$, wherein $R_3$:

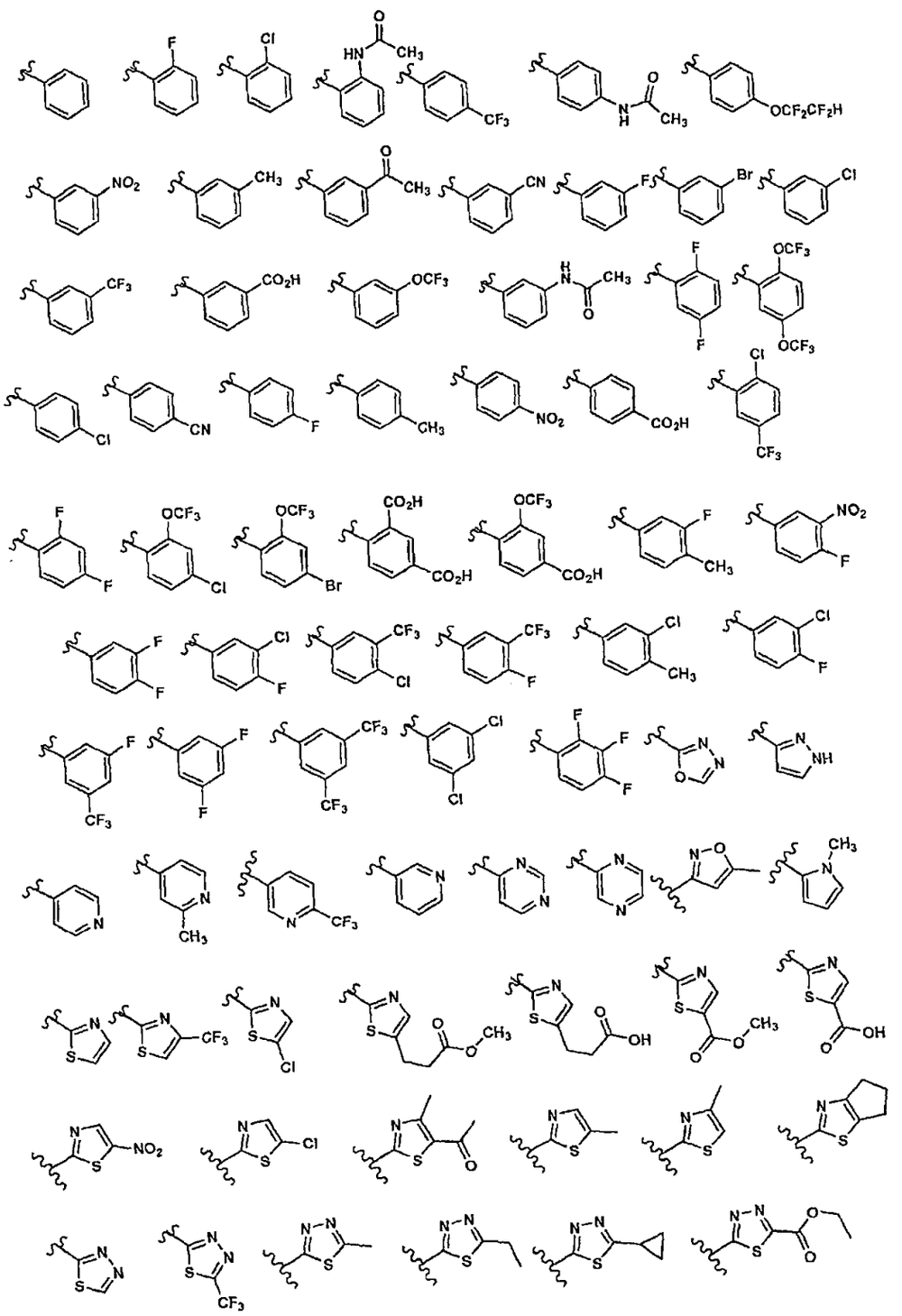


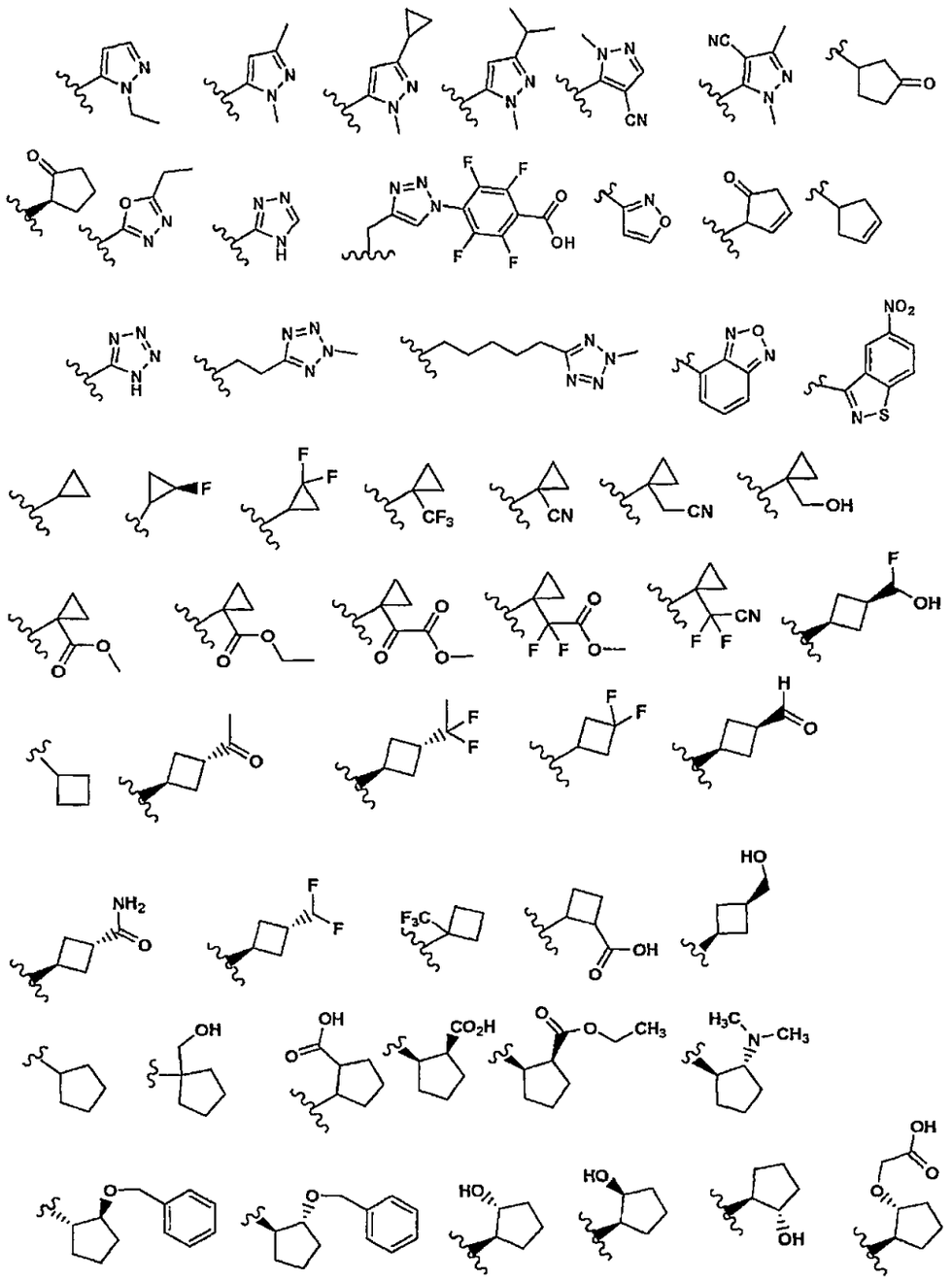


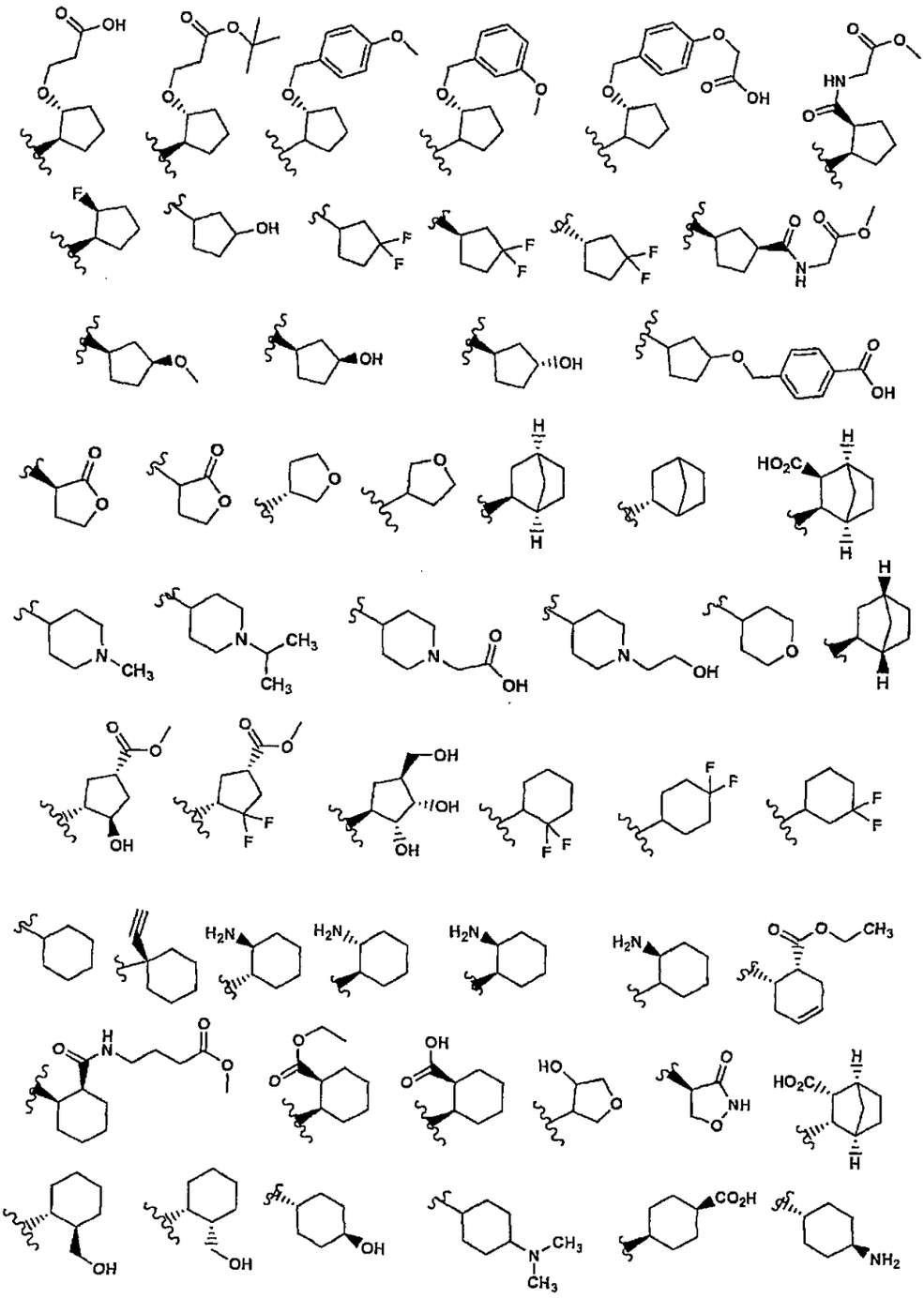


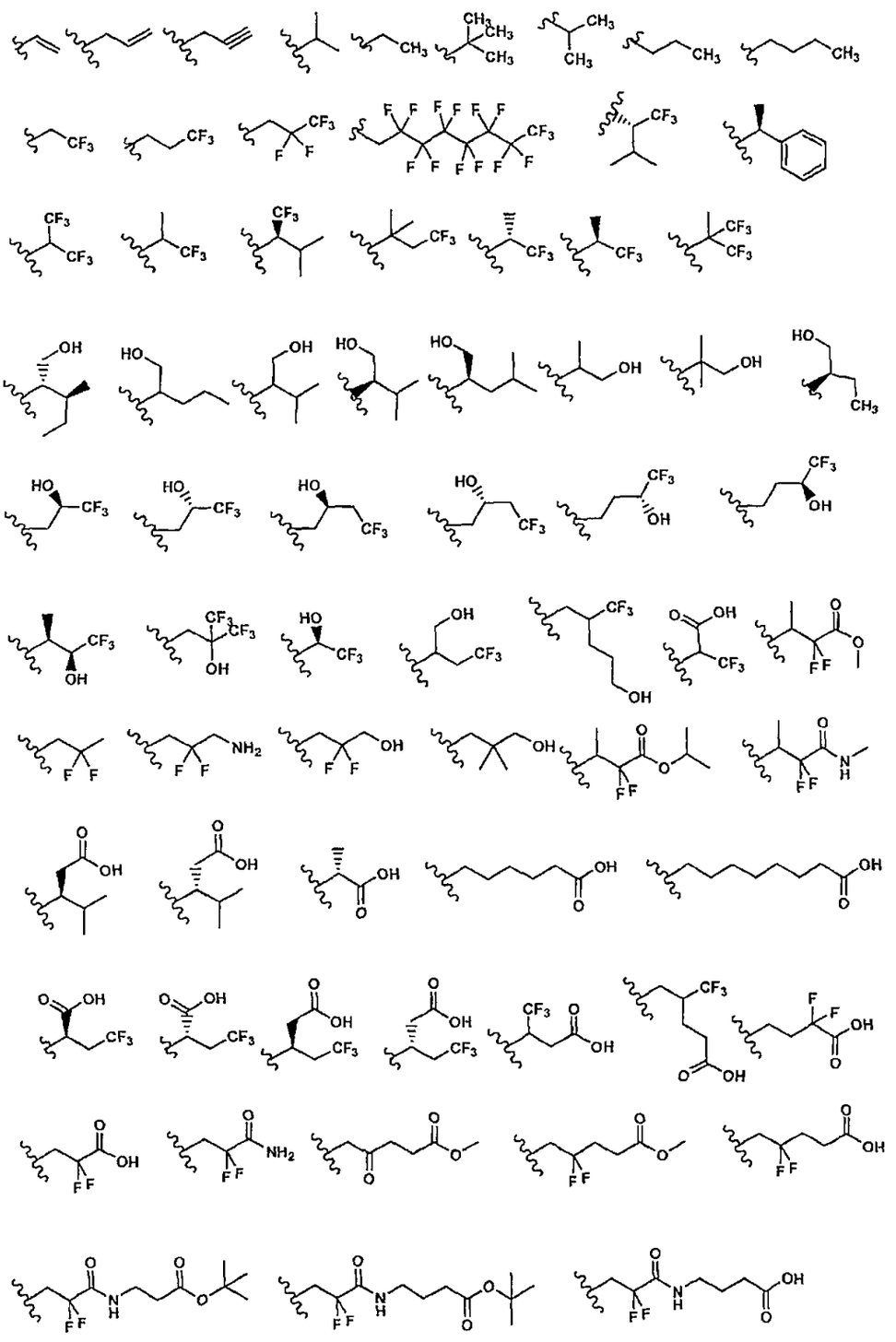


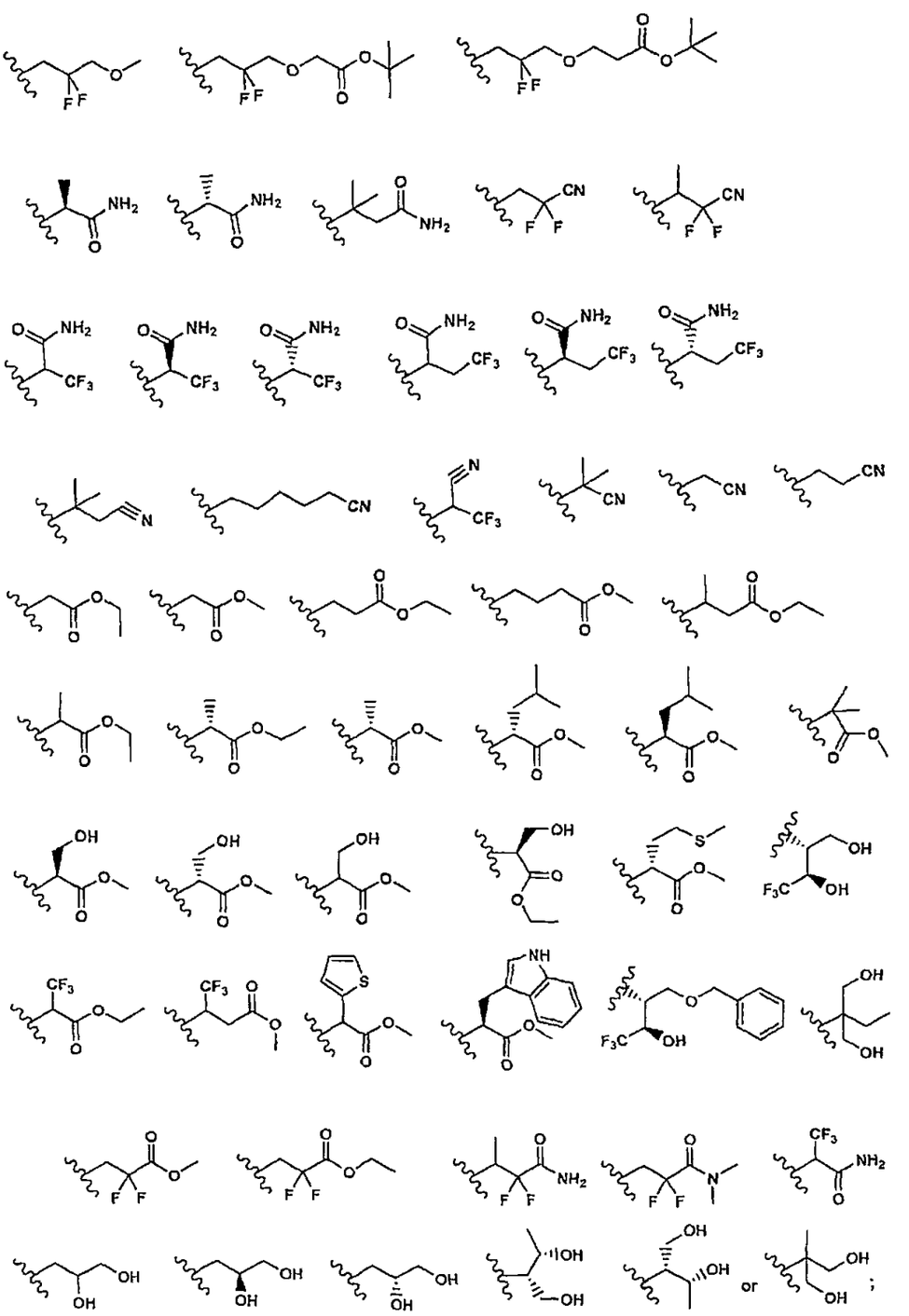
(b) -C(O)NHR$_3$, wherein the R$_3$ is:



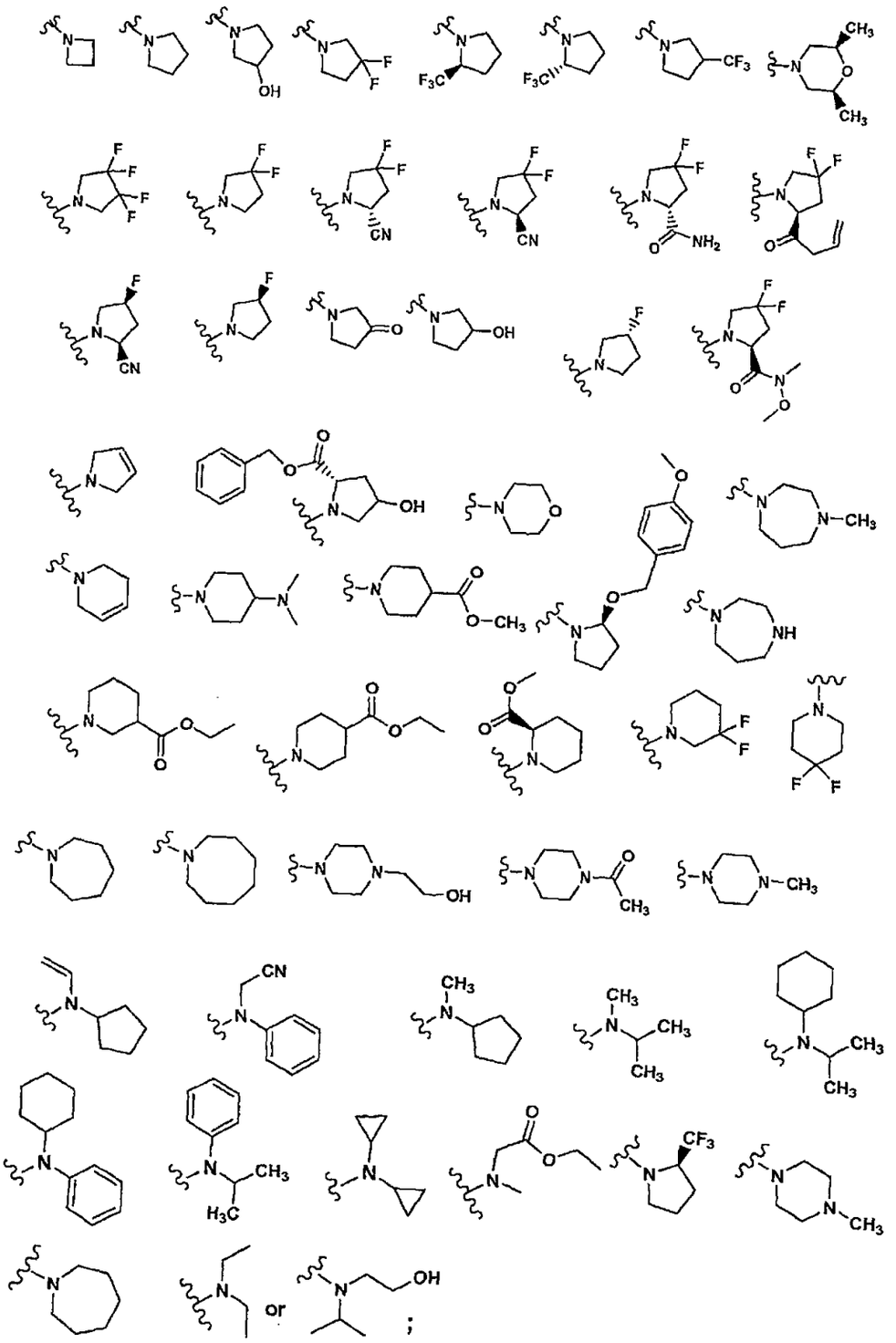




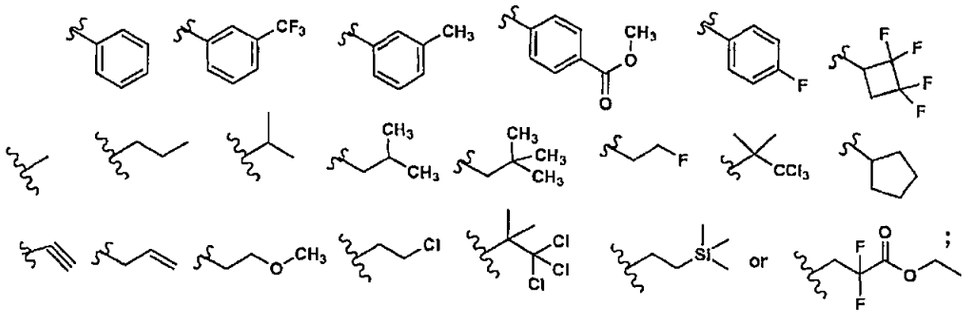




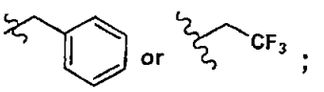
(c) -C(O)$NR_2R_3$, wherein the $NR_2R_3$ is:



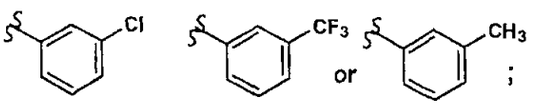
(d) -C(O)$OR_4$ wherein the $R_4$ is:



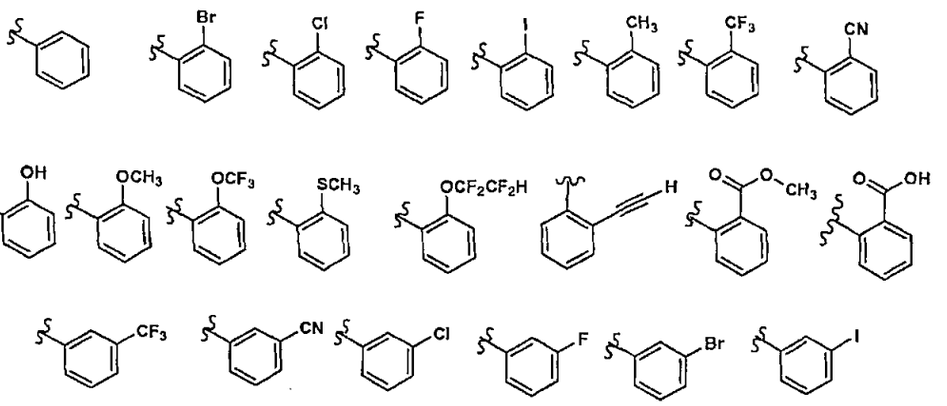
(e) $-SO_2R_5$ wherein the $R_5$ is:

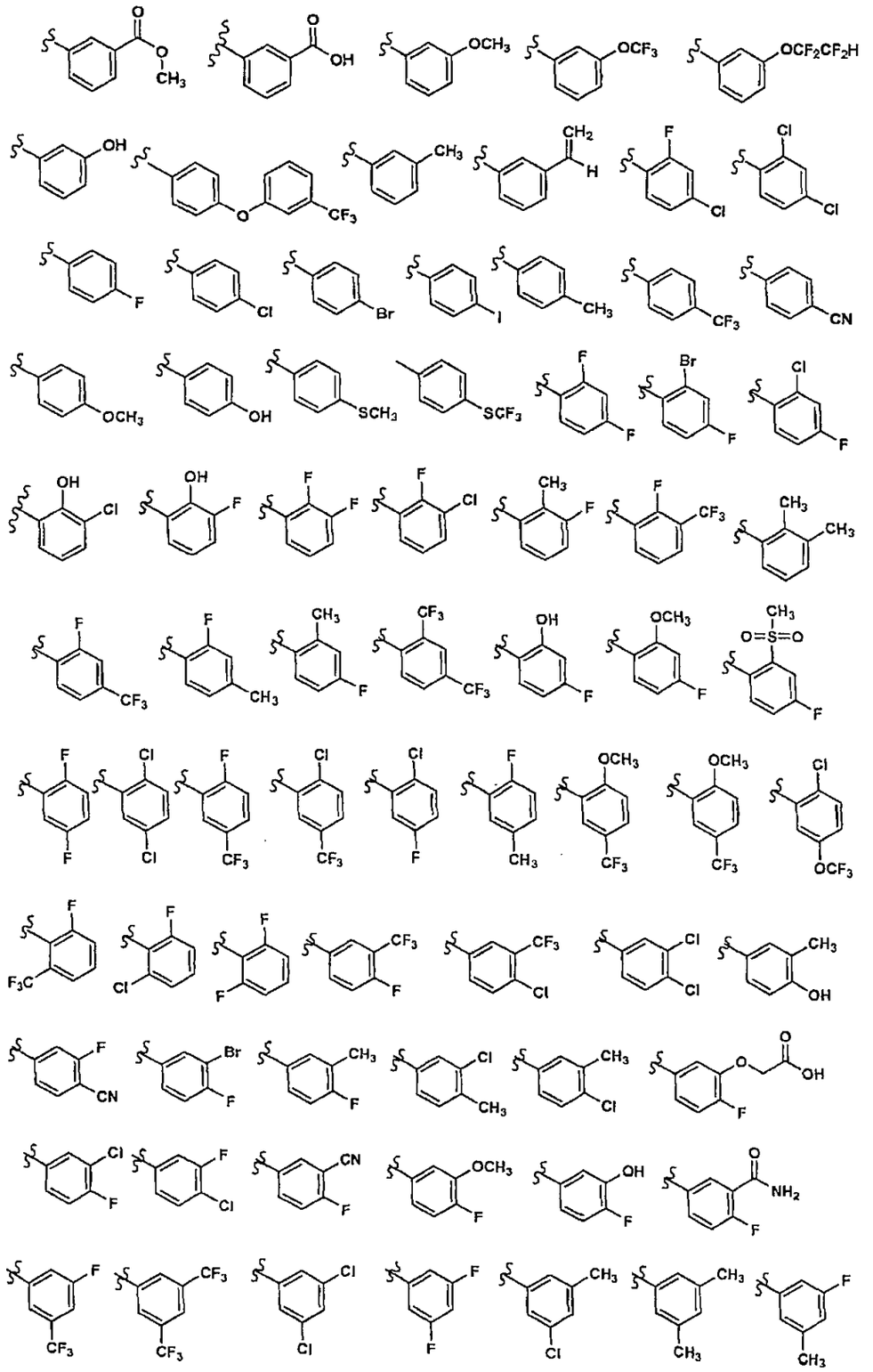


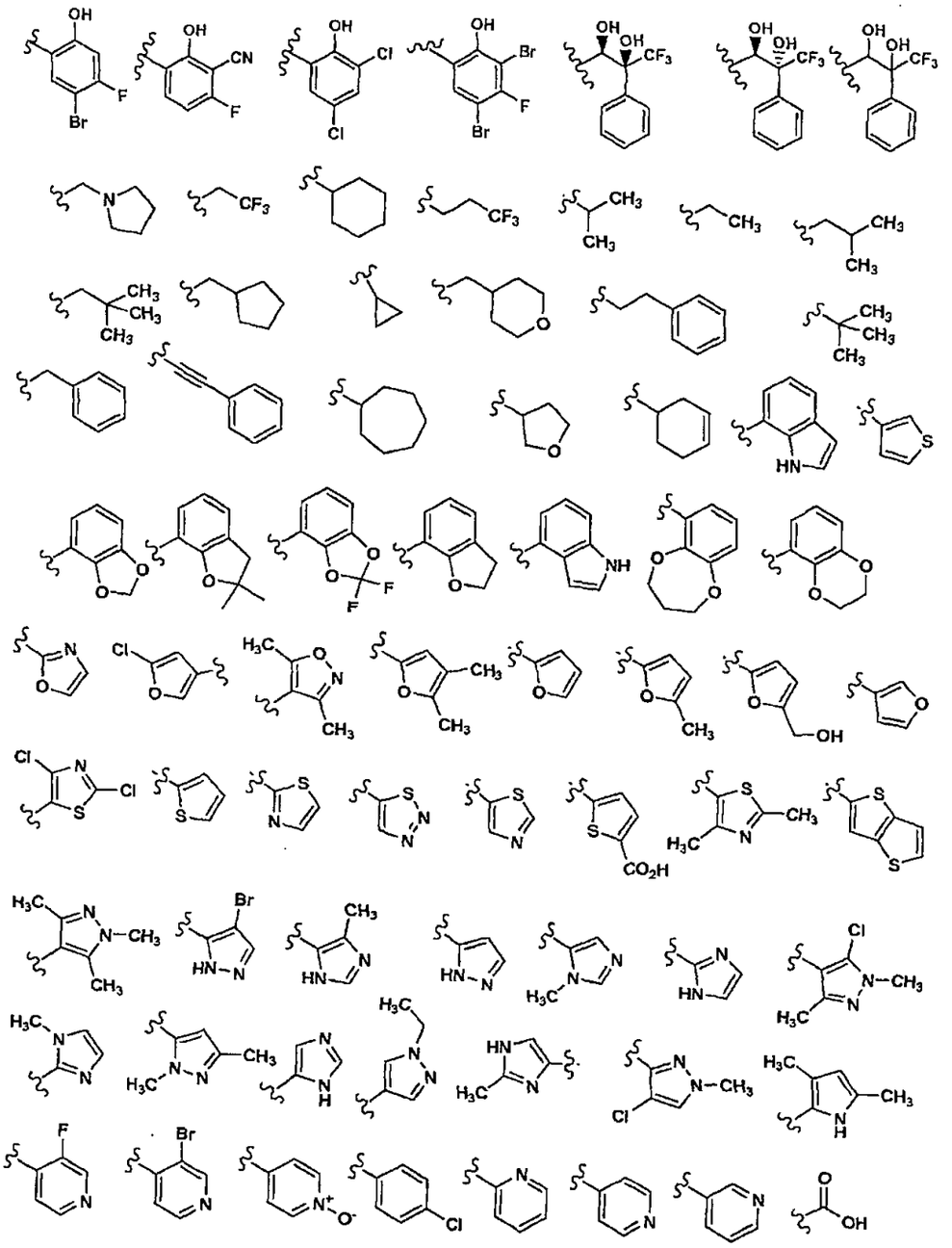
(f) -CSNH$R_7$ wherein the $R_7$ is:

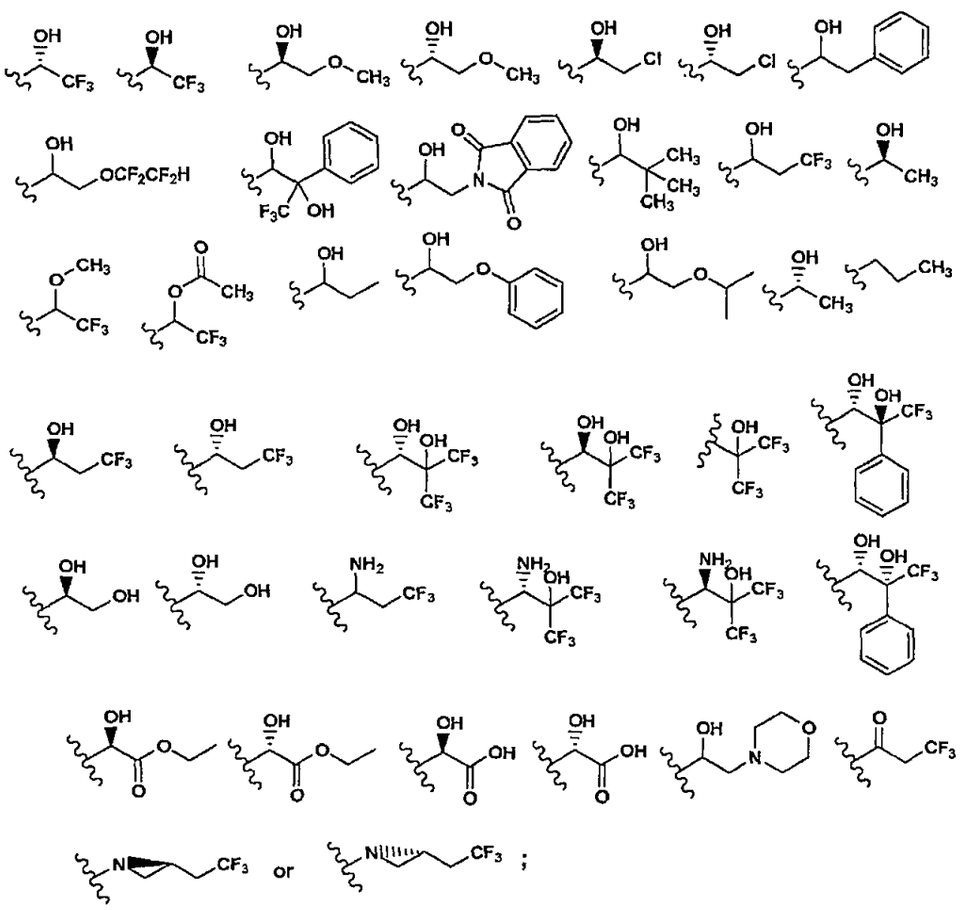


(g) $-CH_2R_8$ wherein the $R_8$ is:

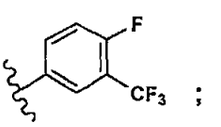




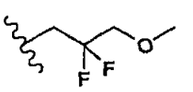




(h) -C(S)$R_3$ wherein the $R_3$ is:

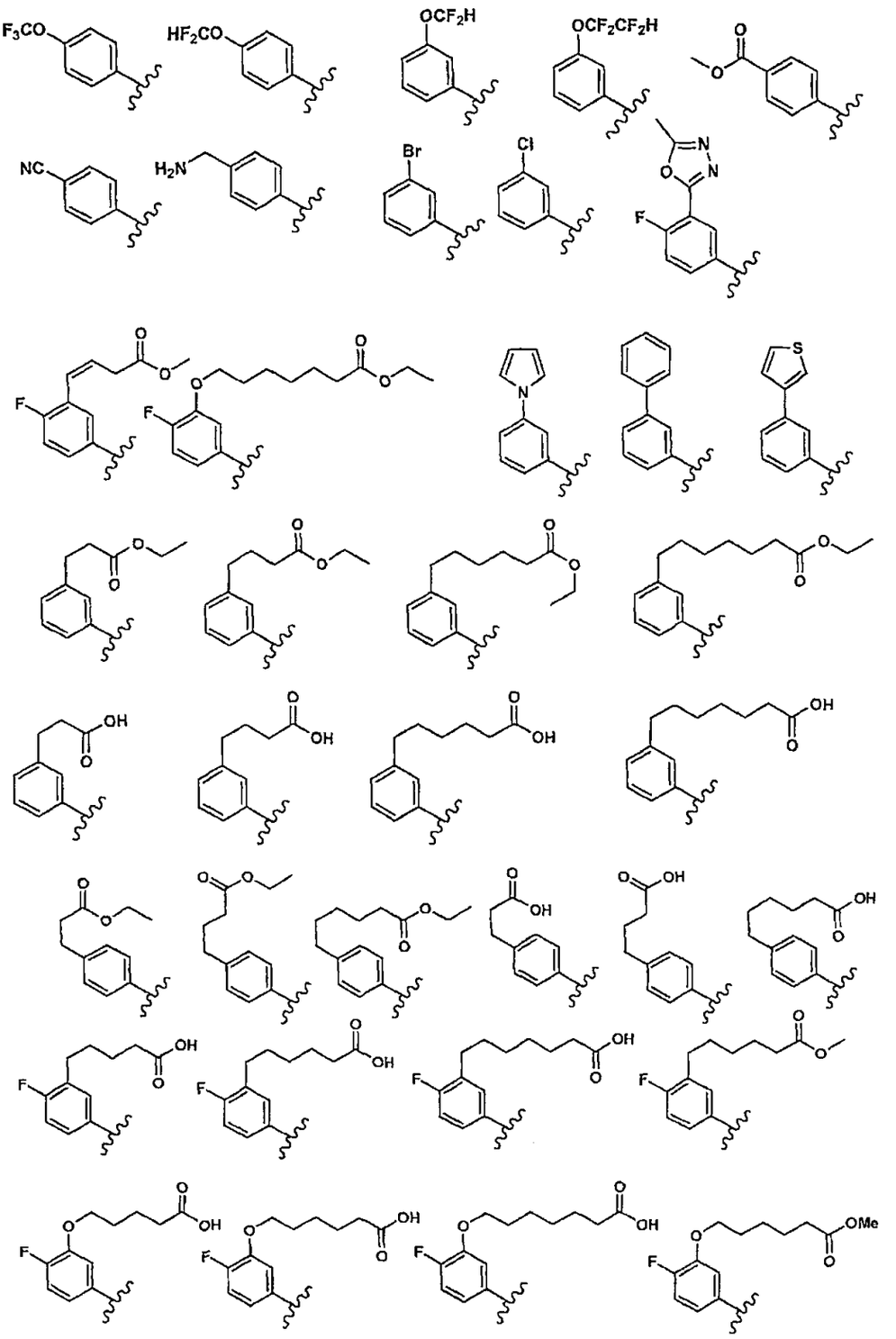


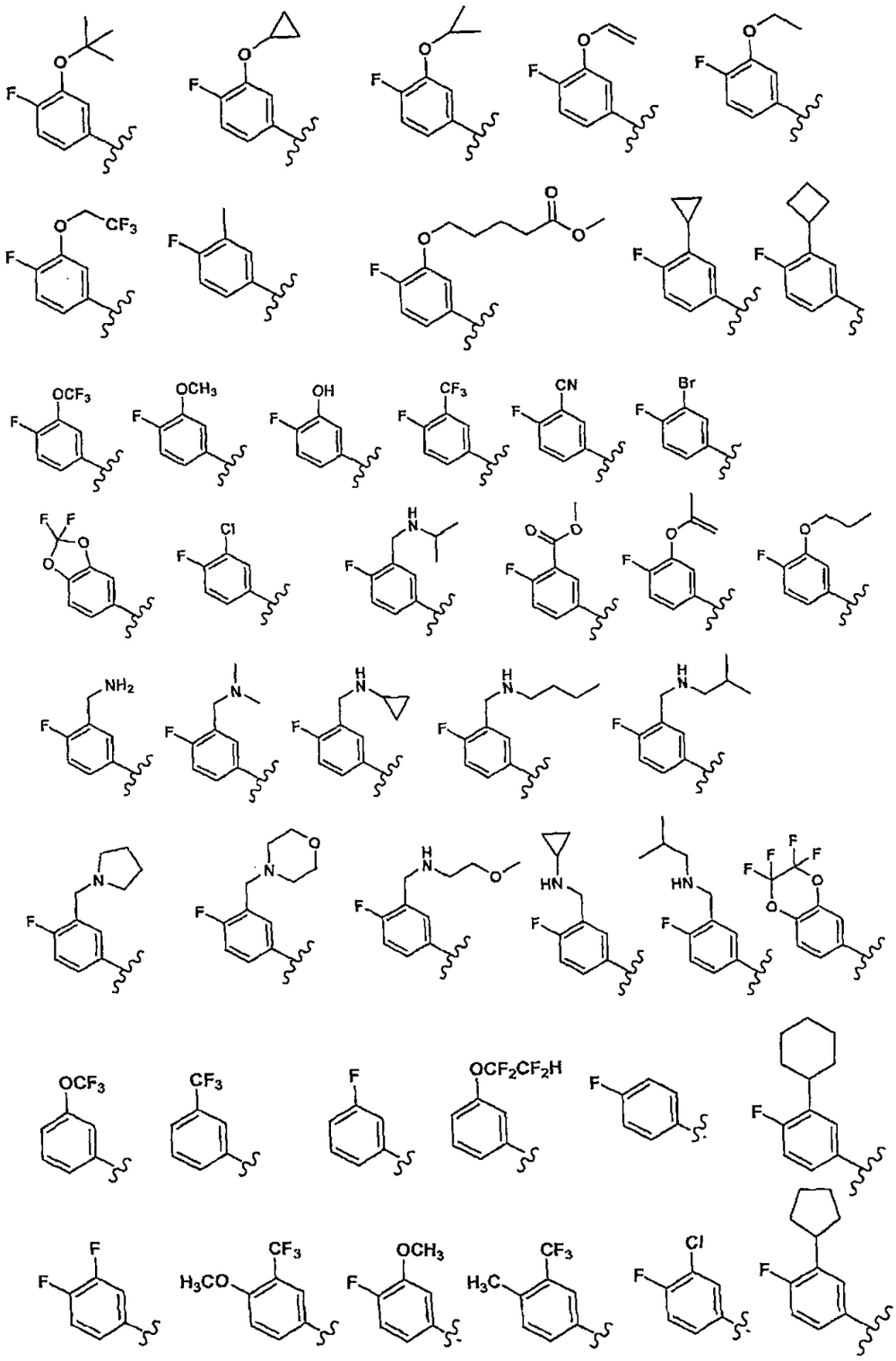
(i) –C(=N$R_3$)Oalkyl wherein the $R_3$ is:

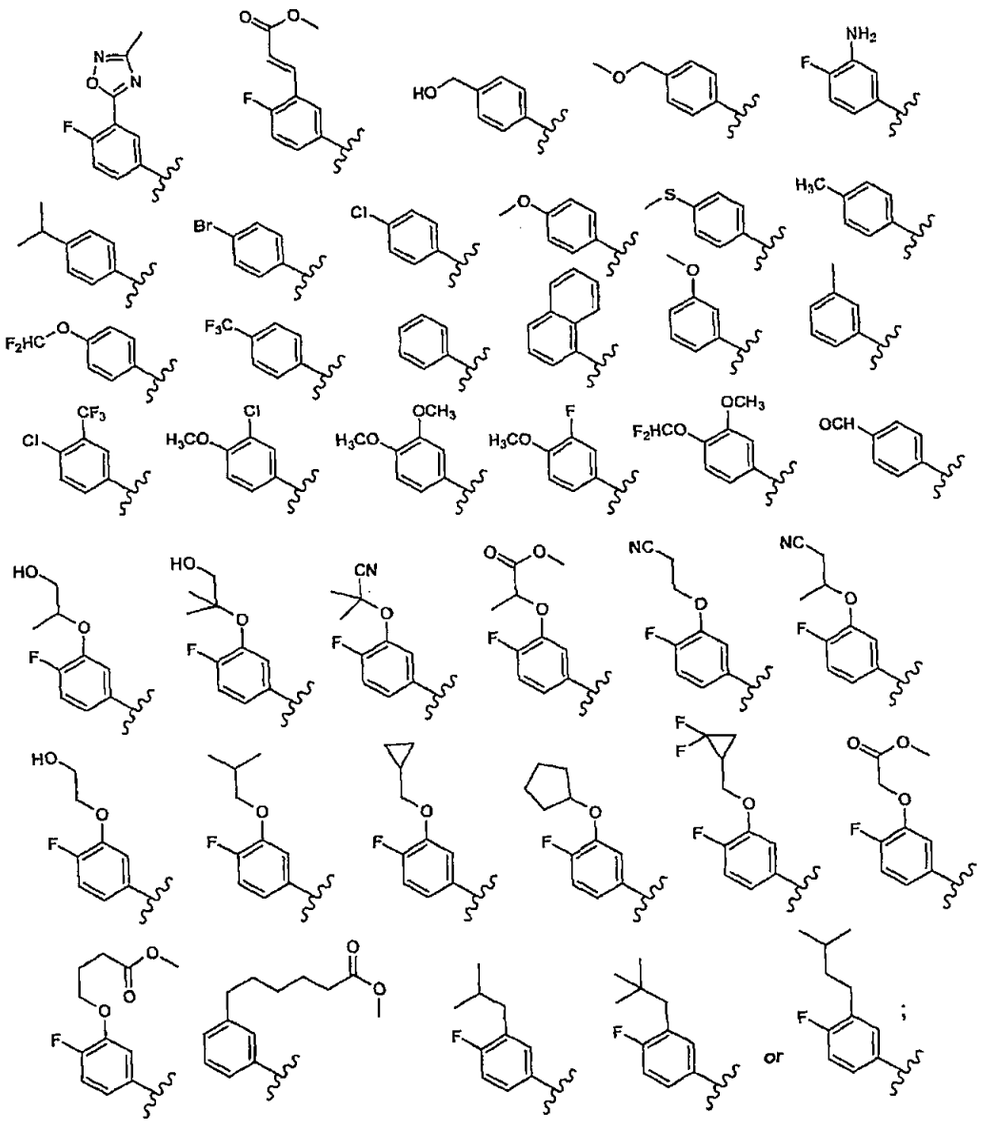


[0045] Also in accordance with the present invention, compounds of the present invention are those wherein:

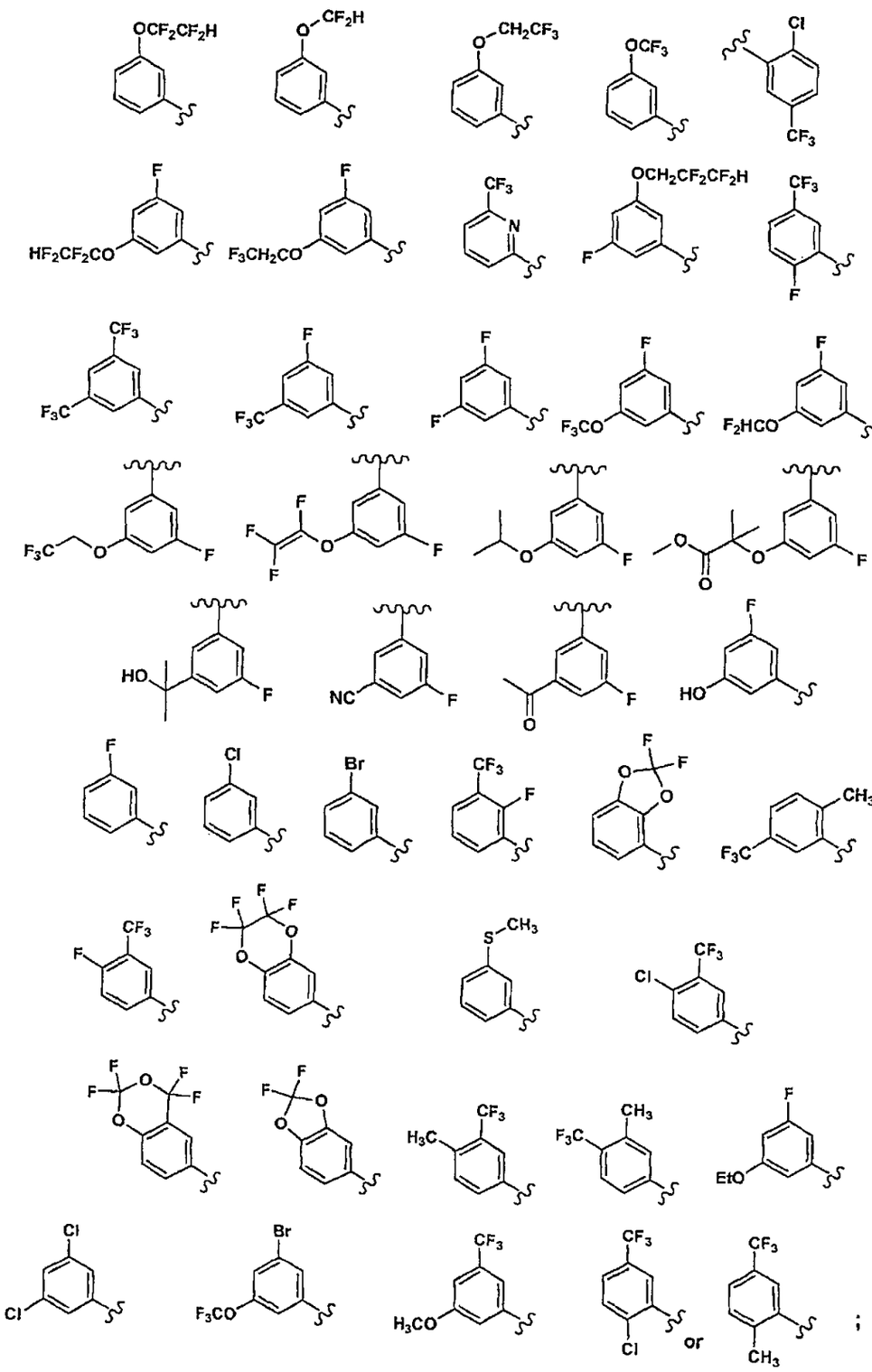
A is:


F3CO
HF2CO
OCF2H
OCF2CF2H
NC
H2N
Br
Cl
F
S
OH
OMe

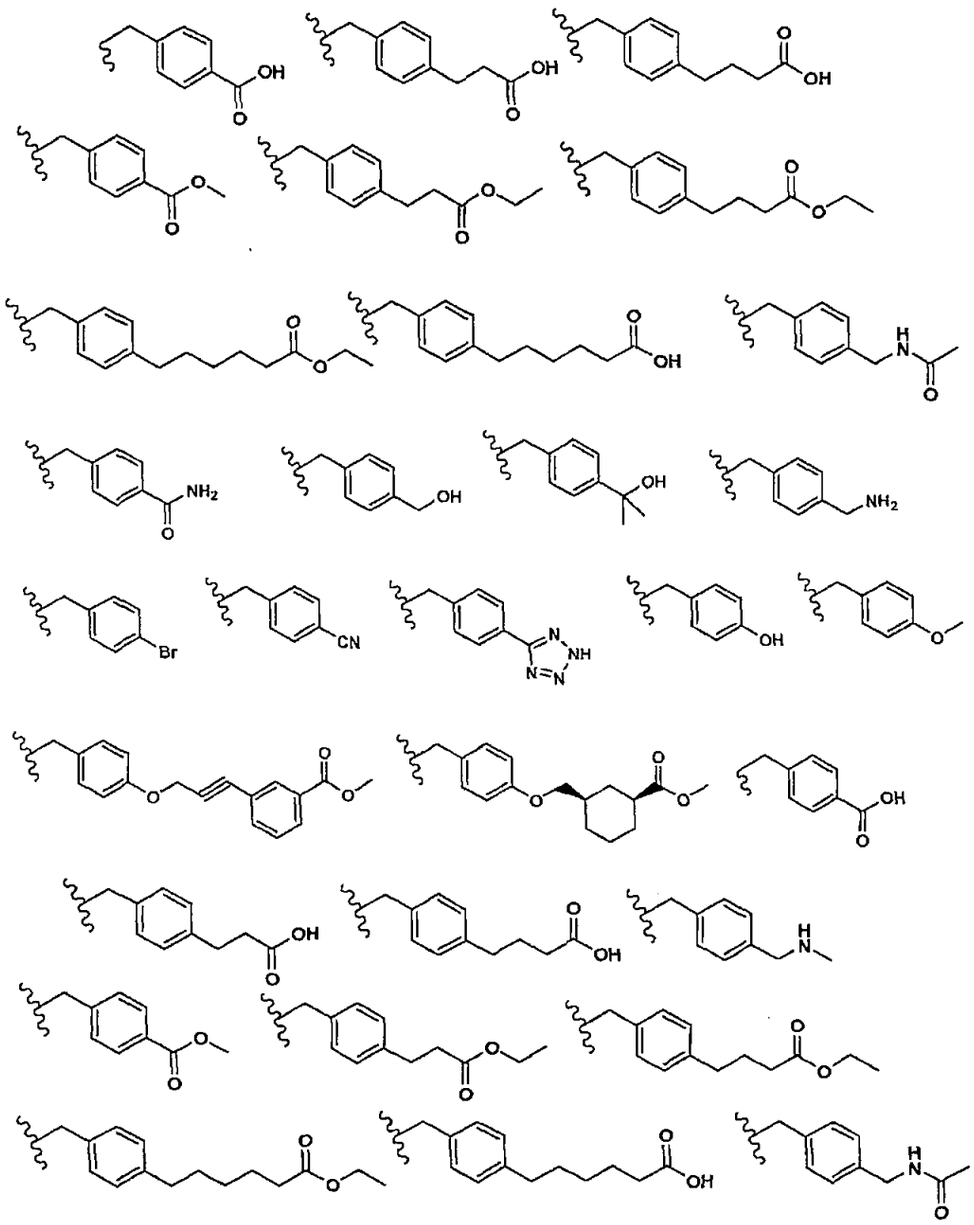


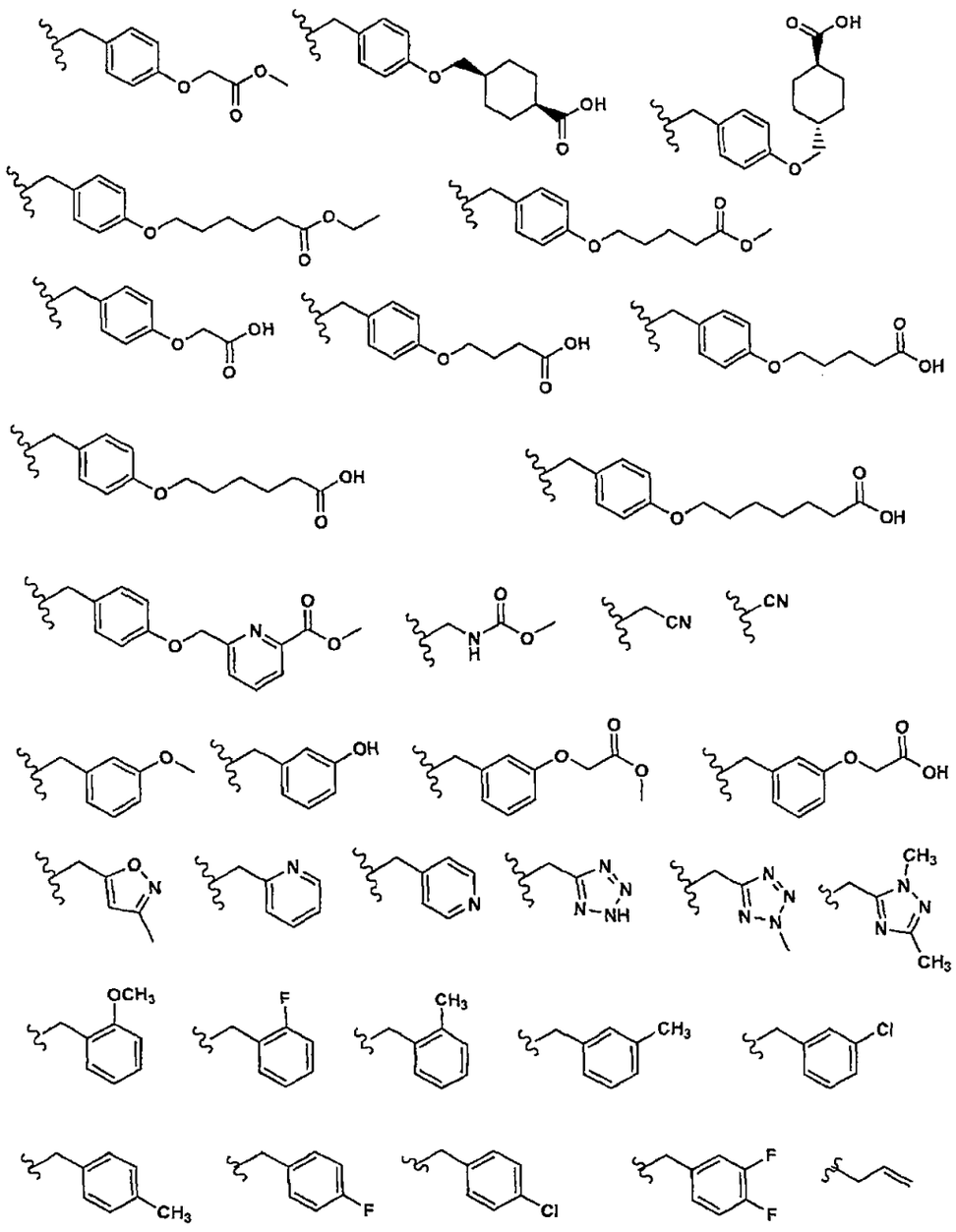


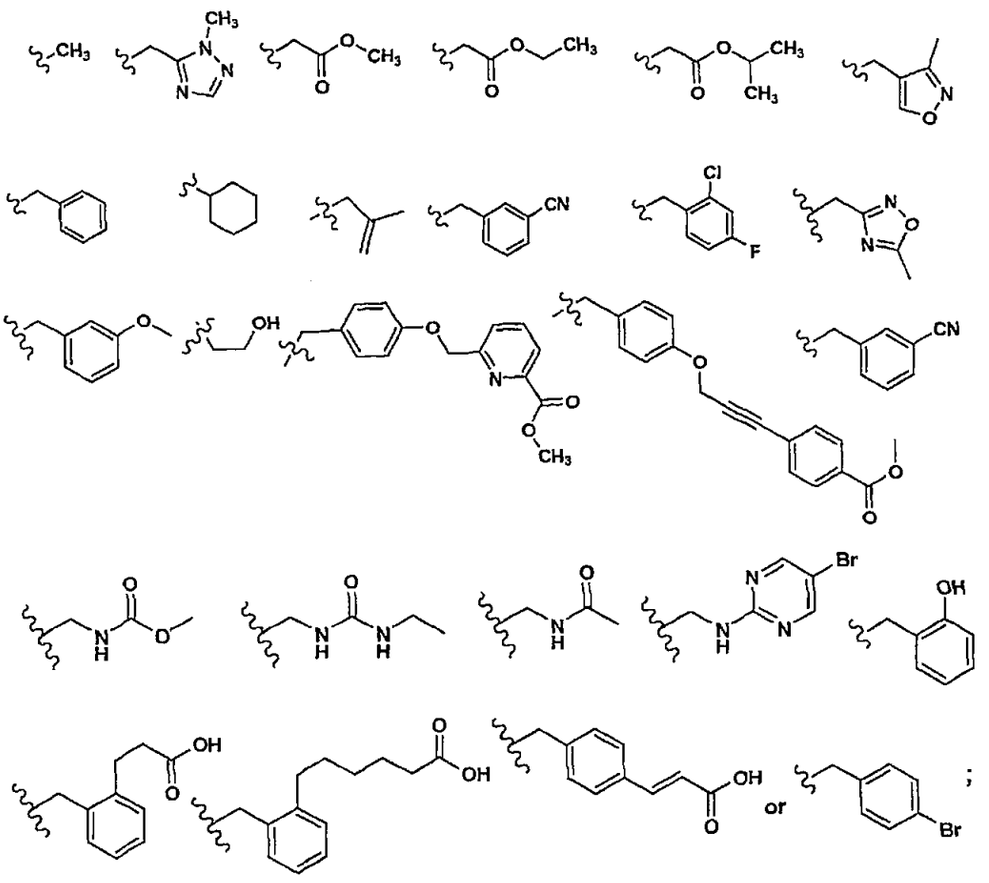
B is:



C is:

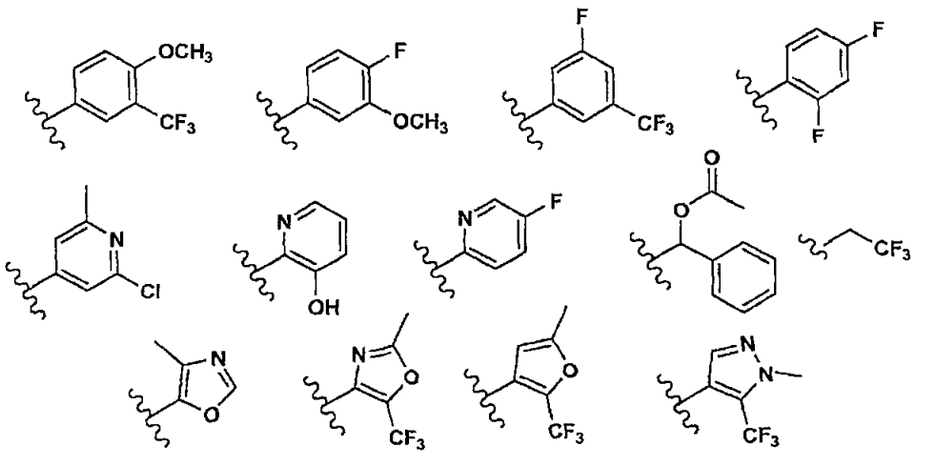


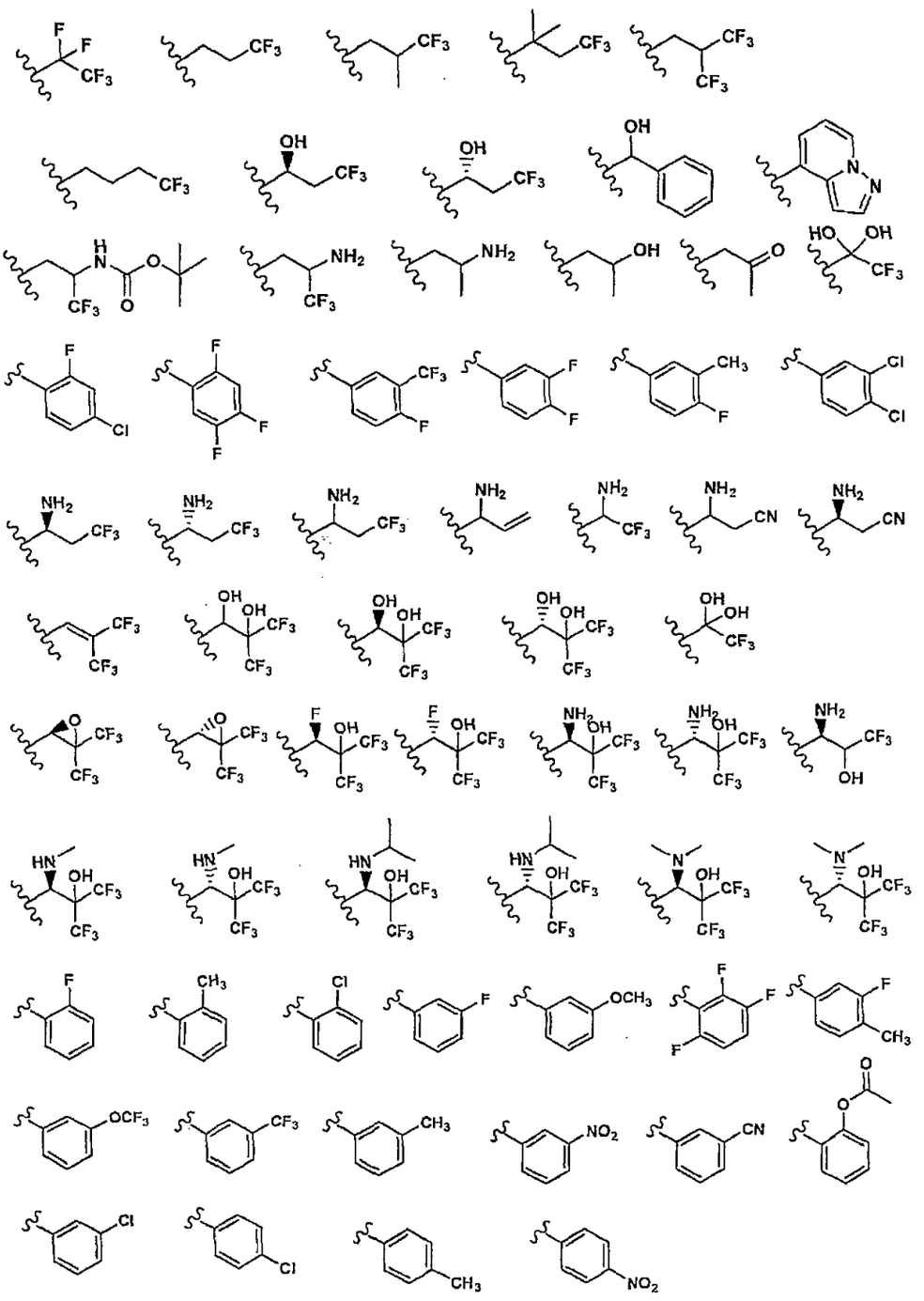


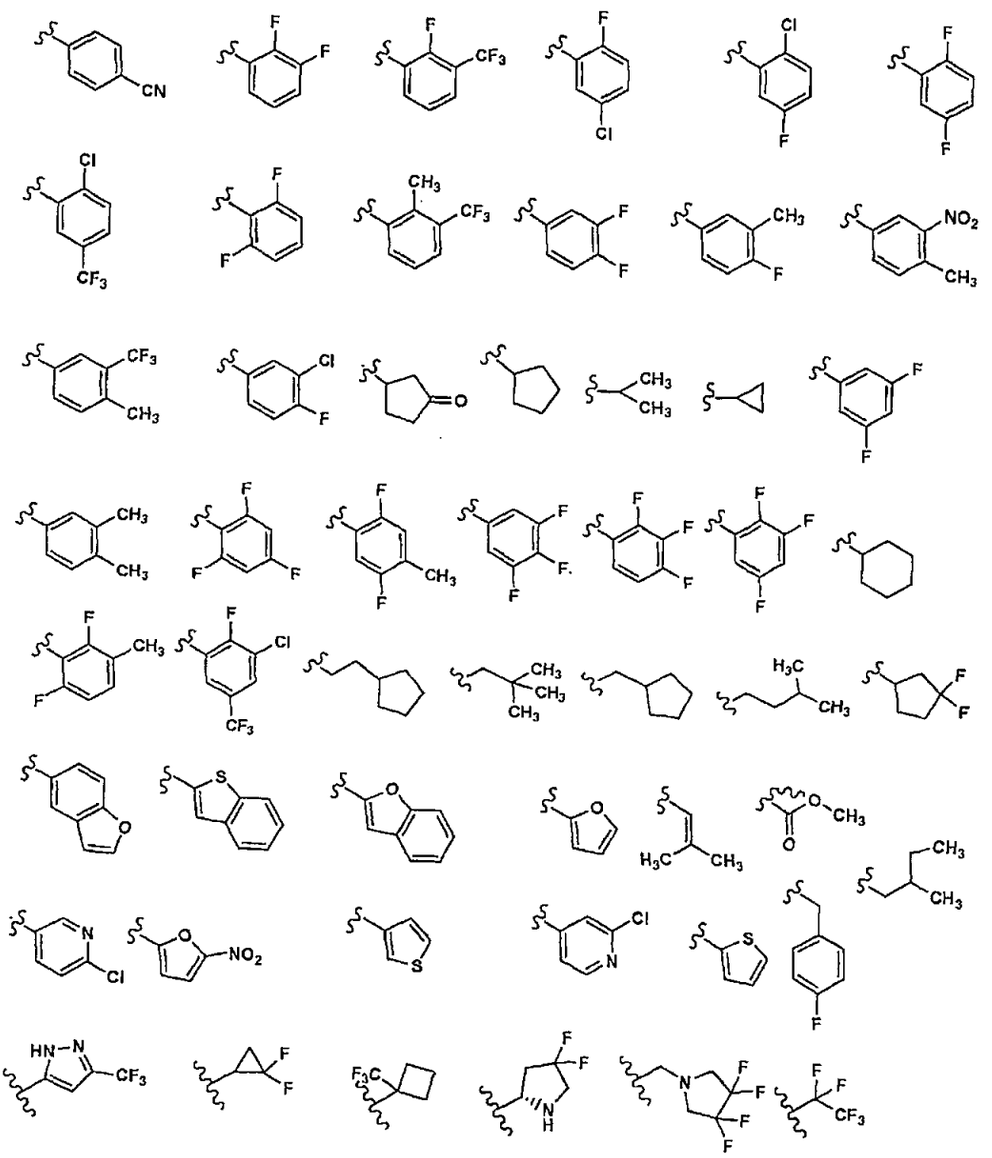


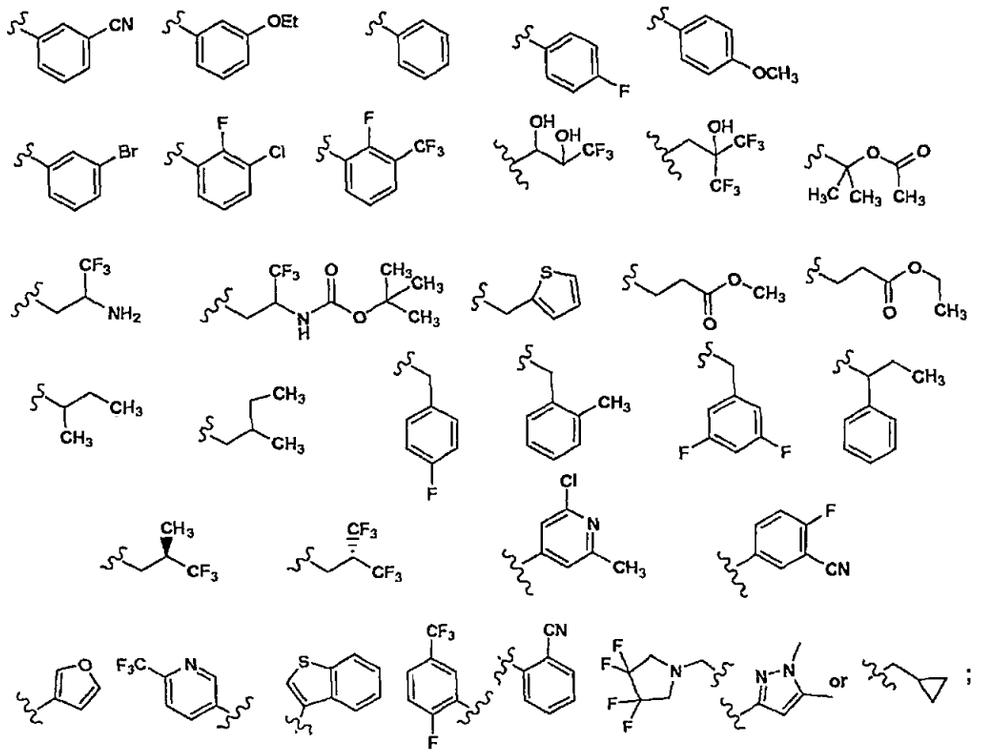
$R_1$ is H or:

(a) $-C(O)R_3$, wherein $R_3$:

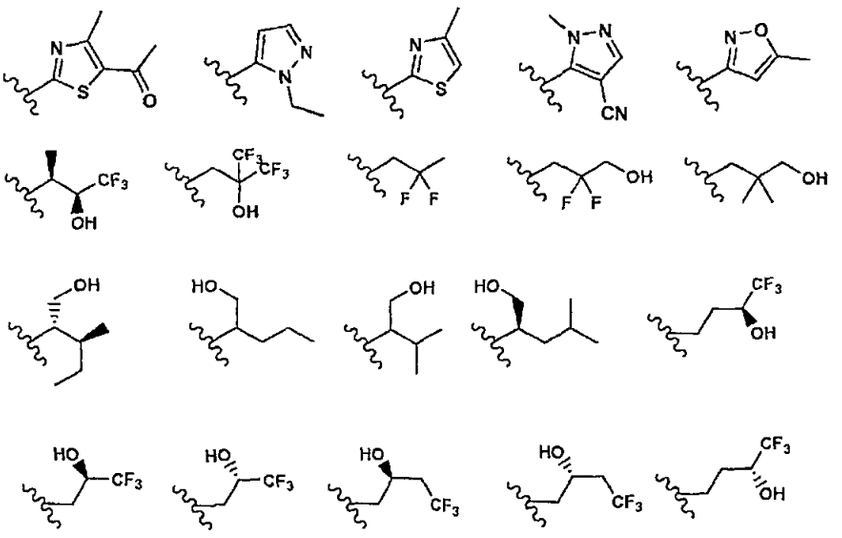


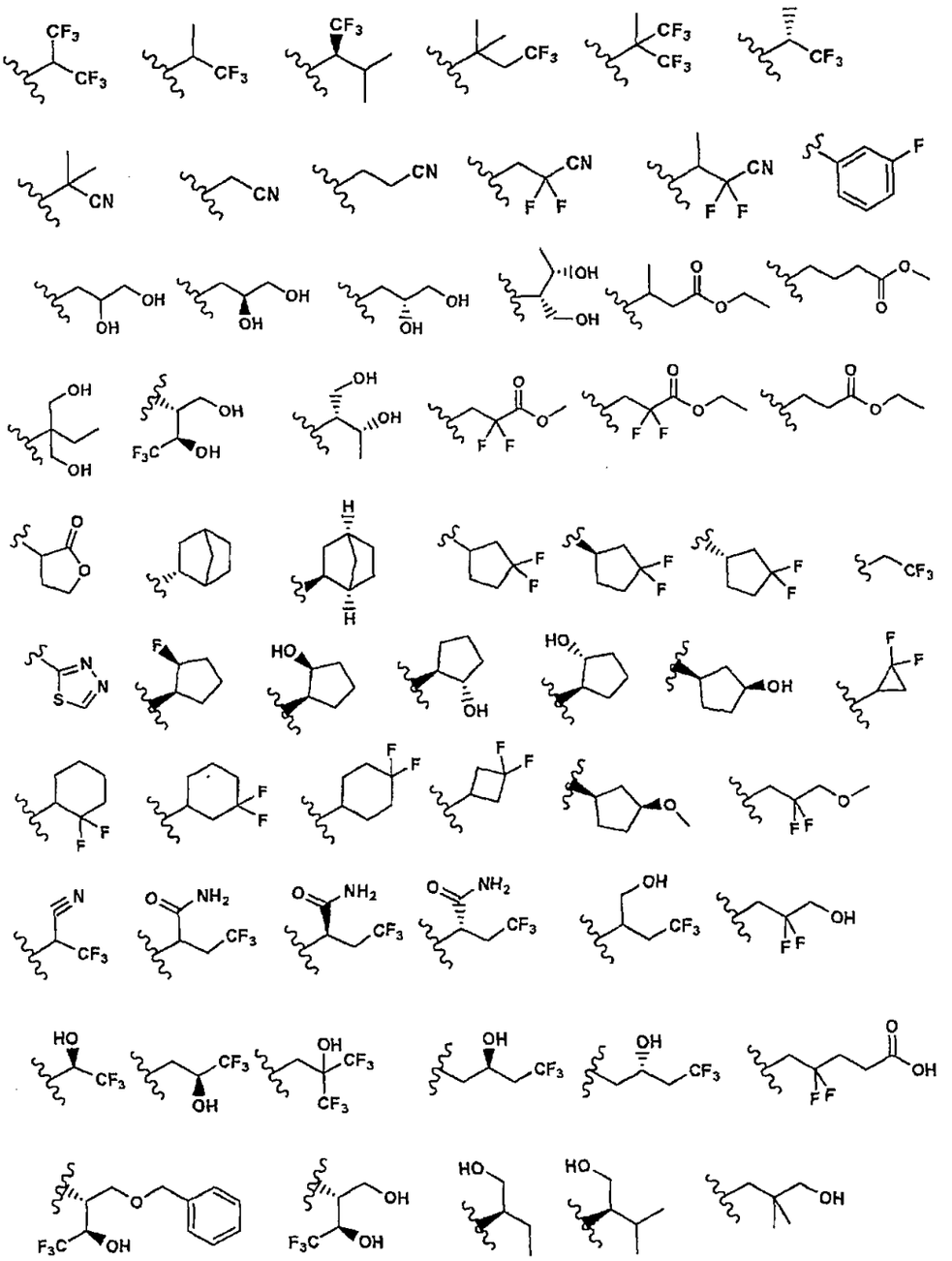


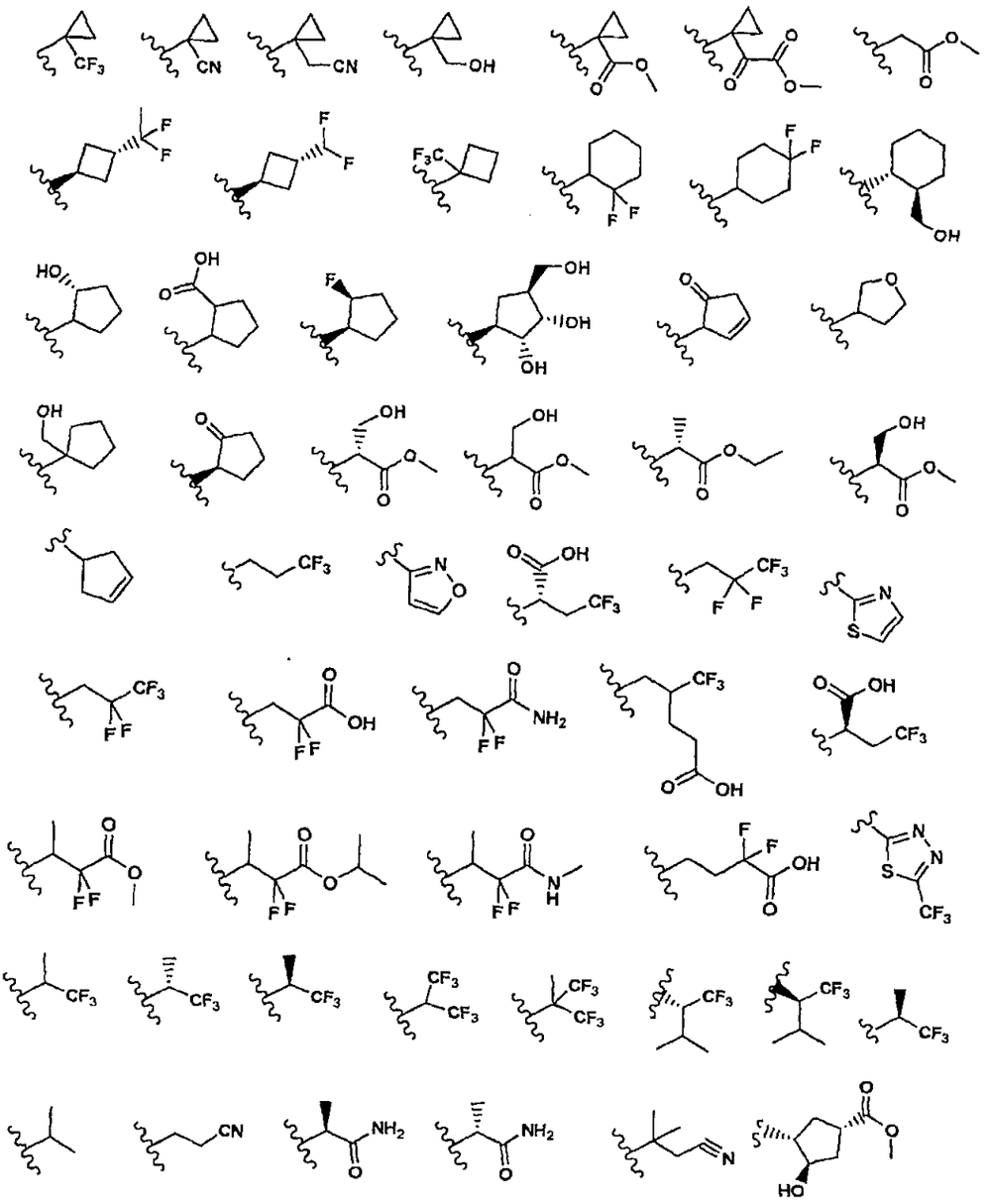


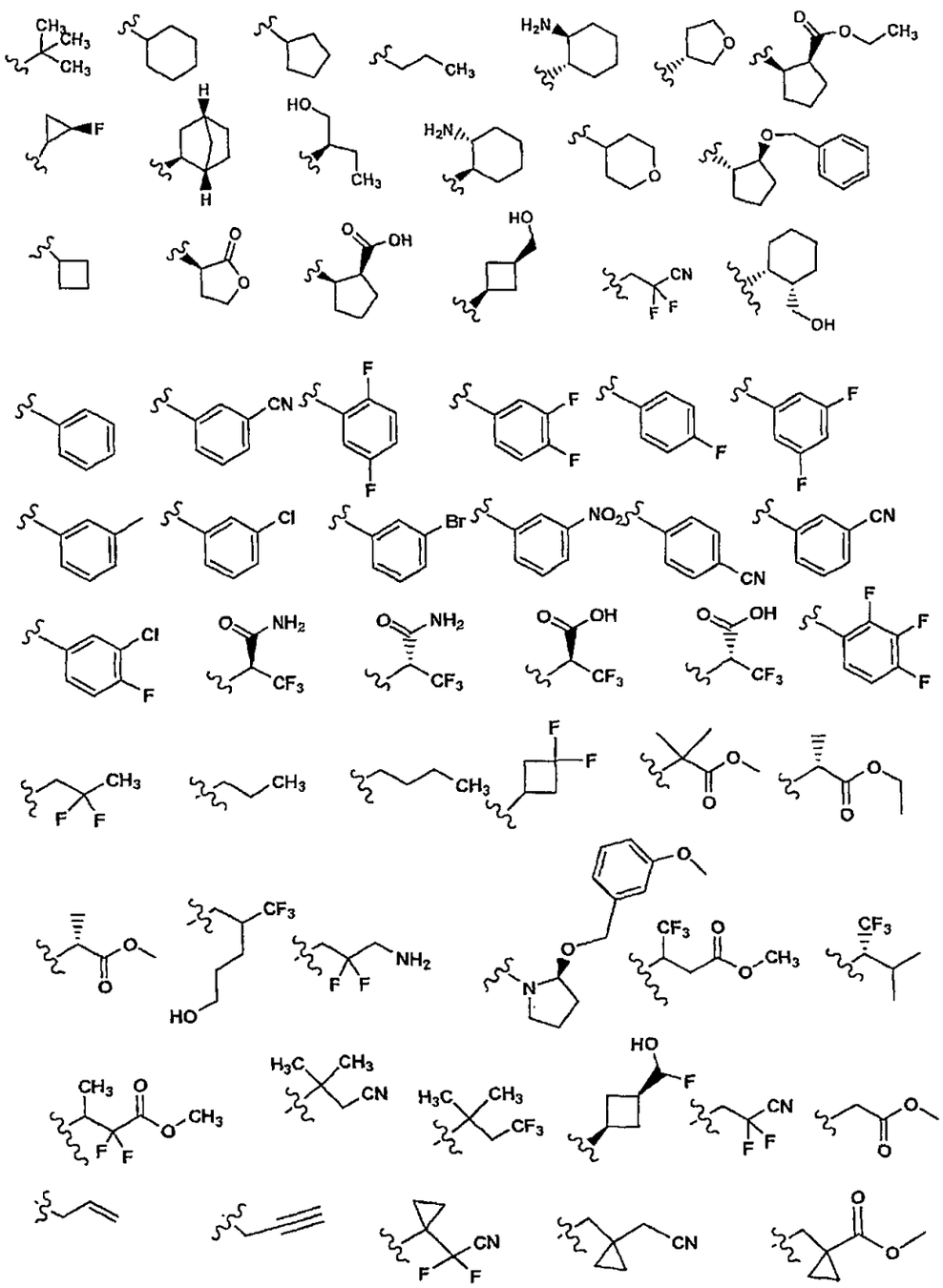


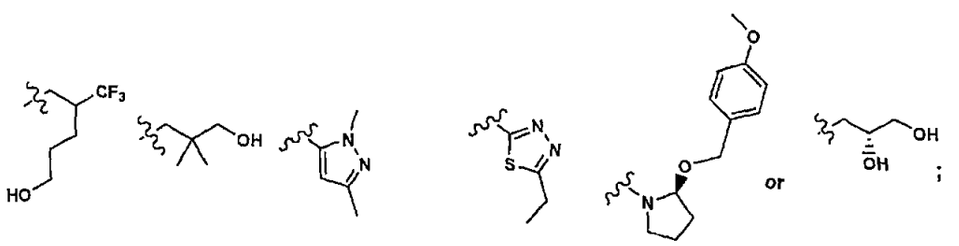
(b) -C(O)NHR$_3$, wherein the R$_3$ is:



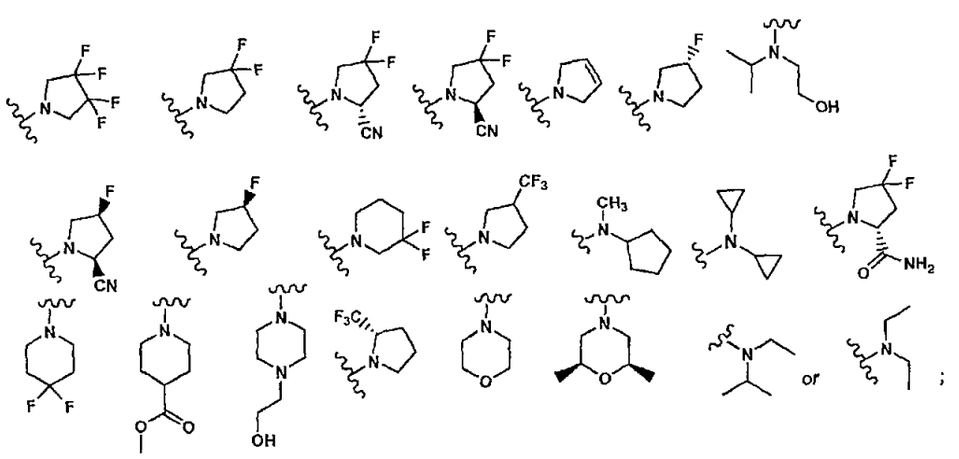




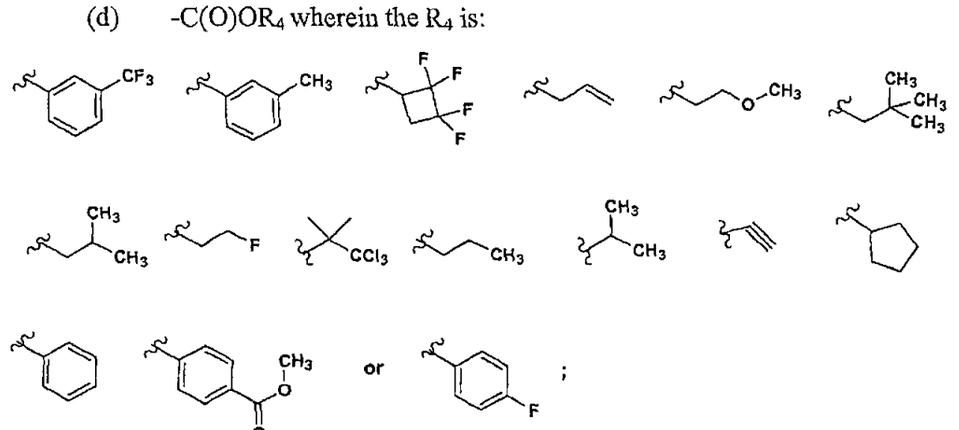




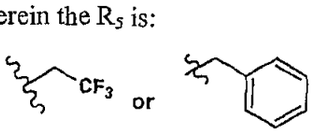
(c) -C(O)$NR_2R_3$, wherein the $NR_2R_3$ is:



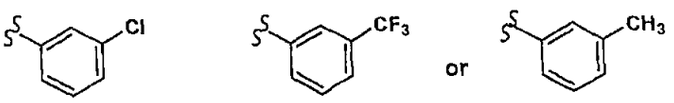
(d) -C(O)$OR_4$ wherein the $R_4$ is:



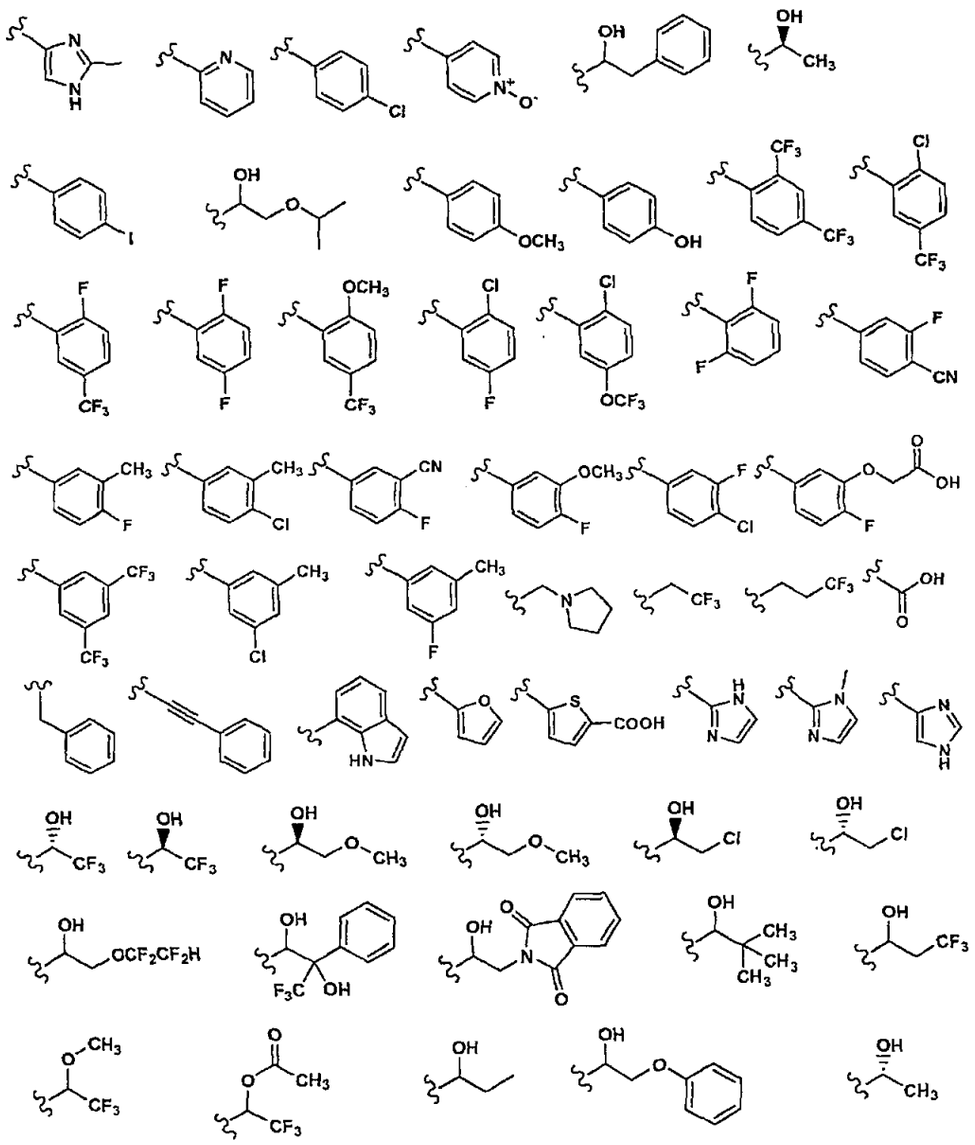
(e) $-SO_2R_5$ wherein the $R_5$ is:

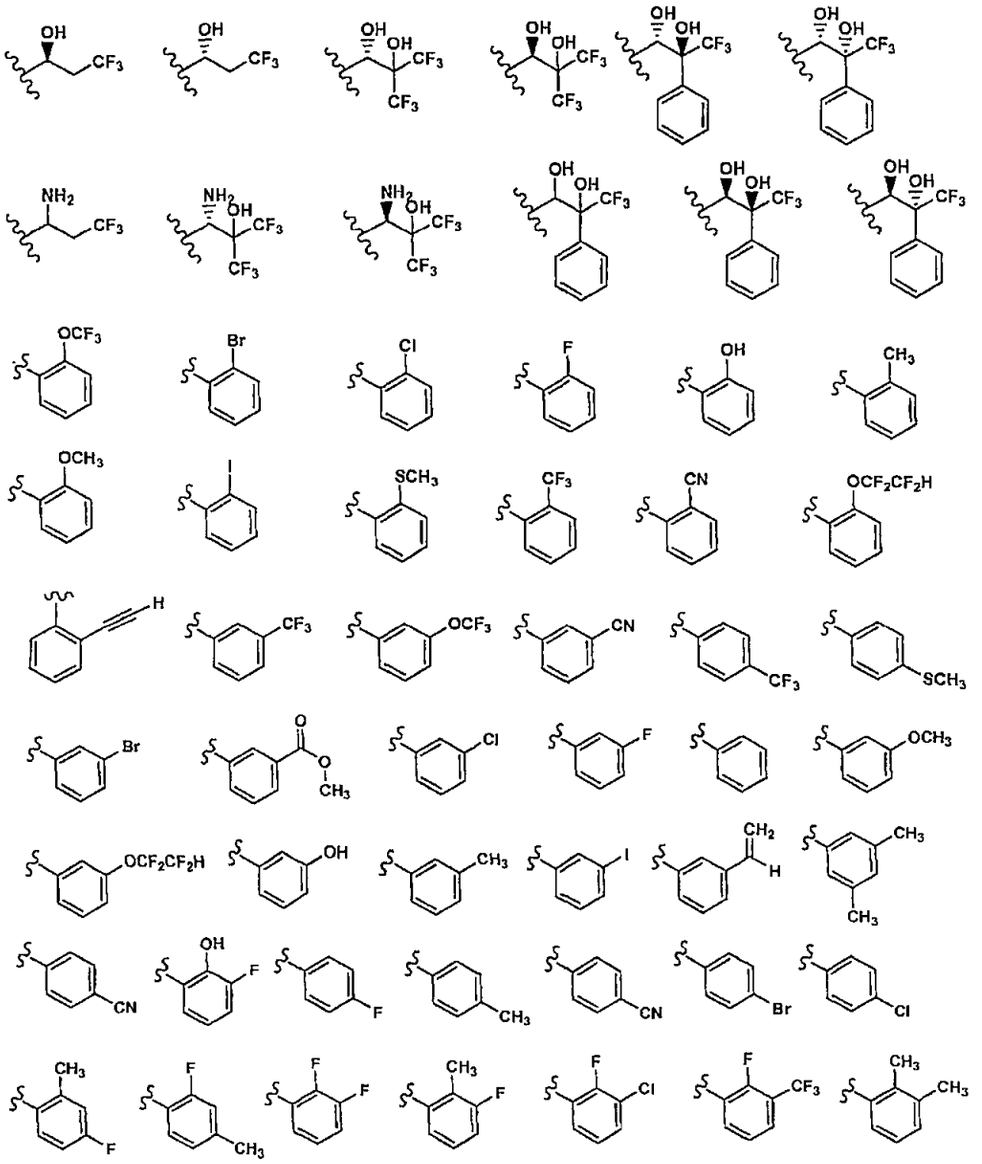


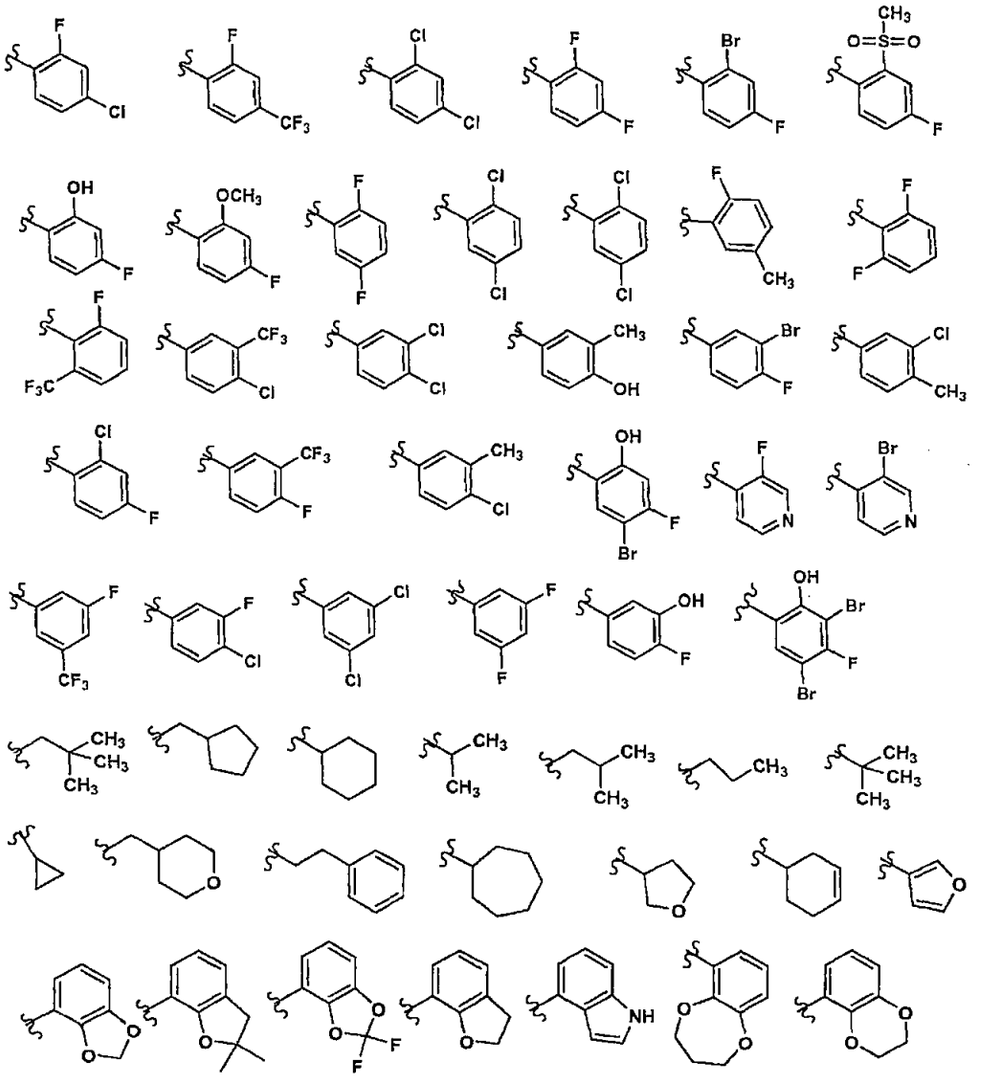
(f) -CSNHR$_7$ wherein the R$_7$ is:

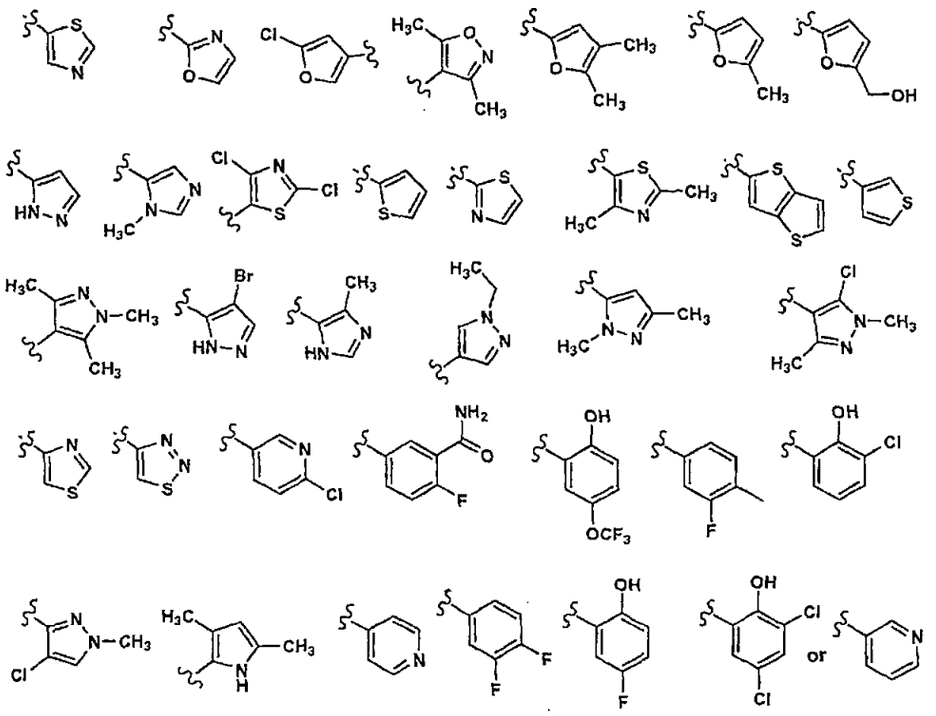


(g) –CH$_2$R$_8$ wherein the R$_8$ is:

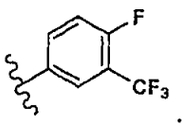








(h) –C(S)$R_3$, wherein $R_3$:



**[0046]** In another embodiment, compounds of the present invention are selected from the compounds exemplified in the examples, for example, Examples 273, 293, 305, and 337.

**[0047]** In yet another embodiment, pharmaceutical compositions comprised of compounds of the present invention alone or in combination with a pharmaceutically acceptable carrier and/or at least one additional therapeutic agent.

**[0048]** In still yet another embodiment, methods of inhibiting the cholesteryl ester transfer protein comprising administering to a mammal in need of treatment a compound and/or pharmaceutical composition of the present invention are provided.

**[0049]** In one embodiment, methods for treating, preventing or slowing the progression of Alzheimer's, atherosclerosis, venous thrombosis, coronary artery

disease, coronary heart disease, coronary vascular disease, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia in a mammal (including a human being either male or female) by administering to a mammal in need of such treatment an atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0050]** In another embodiment, methods for treating, preventing or slowing the progression of atherosclerosis in a mammal by administering to a mammal in need of such treatment an atherosclerotic treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0051]** In another embodiment, methods for treating, preventing or slowing the progression of peripheral vascular disease in a mammal by administering to a mammal in need of such treatment a peripheral vascular disease treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0052]** In yet another embodiment, methods for treating, preventing or slowing the progression of dyslipidemia in a mammal by administering to a mammal in need of such treatment a dyslipidemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0053]** In still yet another embodiment, methods for treating, preventing or slowing the progression of hyperbetalipoproteinemia in a mammal by administering to a mammal in need of such treatment a hyperbetalipoproteinemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0054]** In one embodiment, methods for treating, preventing or slowing the progression of hypoalphalipoproteinemia in a mammal by administering to a mammal in need of such treatment a hypoalphalipoproteinemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0055]** In another embodiment, methods for treating, preventing or slowing the progression of hypercholesterolemia in a mammal by administering to a mammal in need of such treatment a hypercholesterolemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0056]** In yet another embodiment, methods for treating, preventing or slowing the progression of hypertriglyceridemia in a mammal by administering to a mammal in need of such treatment a hypertriglyceridemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0057]** In still yet another embodiment, methods for treating, preventing or slowing the progression of familial-hypercholesterolemia in a mammal by administering to a mammal in need of such treatment a familial-hypercholesterolemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0058]** In one embodiment, methods for treating, preventing or slowing the progression of cardiovascular disorders in a mammal by administering to a mammal in need of such treatment a cardiovascular disorder treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0059]** In another embodiment, methods for treating, preventing or slowing the progression of angina in a mammal by administering to a mammal in need of such treatment an angina treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0060]** In yet another embodiment, methods for treating, preventing or slowing the progression of ischemia in a mammal by administering to a mammal in need of

such treatment an ischemic disease treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0061]** In still yet another embodiment, methods for treating, preventing or slowing the progression of cardiac ischemia in a mammal by administering to a mammal in need of such treatment a cardiac ischemic treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0062]** In one embodiment, methods for treating, preventing or slowing the progression of stroke in a mammal by administering to a mammal in need of such treatment a stroke treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0063]** In one embodiment, methods for treating, preventing or slowing the progression of a myocardial infarction in a mammal by administering to a mammal in need of such treatment a myocardial infarction treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0064]** In another embodiment, methods for treating, preventing or slowing the progression of reperfusion injury in a mammal by administering to a mammal in need of such treatment a reperfusion injury treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0065]** In another embodiment, methods for treating, preventing or slowing the progression of angioplastic restenosis in a mammal by administering to a mammal in need of such treatment an angioplastic restenosis treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0066]** In yet another embodiment, methods for treating, preventing or slowing the progression of hypertension in a mammal by administering to a mammal in need of such treatment a hypertension treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0067]** In yet another embodiment, methods for treating, preventing or slowing the progression of the ascular complications of diabetes in a mammal by administering to a mammal in need of such treatment a vascular complications of

diabetes treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0068]** In still yet another embodiment, methods for treating, preventing or slowing the progression of obesity in a mammal by administering to a mammal in need of such treatment an obesity treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0069]** In one embodiment, methods for treating, preventing or slowing the progression of endotoxemia in a mammal by administering to a mammal in need of such treatment an endotoxemia treating, preventing or slowing amount of a compound and/or pharmaceutical composition of the present invention are provided.

**[0070]** In another embodiment, methods for treating, preventing or slowing the progression of a disease requiring cholesteryl ester transfer protein inhibitor therapy comprising administering, concurrently or sequentially, to a mammal in need of treatment, prevention or slowing a therapeutically effective amount of a compound of the present invention and at least one additional therapeutic agent.

**[0071]** In yet another embodiment, methods of inhibiting remnant lipoprotein production comprising administering to a mammal a compound and/or pharmaceutical composition of the present invention are provided.

**[0072]** In still yet another embodiment, methods of raising HDL cholesterol in a mammal comprising administering to a mammal in need of treatment a compound and/or pharmaceutical composition of the present invention are provided.

**[0073]** Mono fluorinated phenols have been widely used as synthetic blocks for many bioactive compounds. To date, there have been several methods reported in the literature for the synthesis of such phenols. For example, such phenols may be prepared by: (i) electrophilic fluorination of phenols using a range of $F^+$ reagents; (ii) hydrolysis of bromofluorobenzene or chlorofluorobenzene catalysized by a copper reagent; (iii) diazotization of a corresponding fluoroaniline; (iv) selective hydroxy substitution of difluorobenzoic acid with solid sodium hydroxide in 1,3-dimethyl-2-imidazolidinone (see, Journal of Fluorine Chemistry, 121:97-99 (2003) and Bioorganic & Medicinal Chemistry, 12:5661-5675 (2004)); and (iv) the replacement of fluoroatom of activated arylfluorides such as fluoroanthracene-9,10-diones, fluorobenz[g]isoquinoline-5,10-diones and fluoronitrobenzenes with sodium

trimethylsilanoate in specific solvent THF (see Synthetic Communications, 28(18):3415-3422). However, most of these methods use reagents that unsafe, highly hazardous and/or not readily available. In addition, these methods may only be suitable for the synthesis of 2- or 4-fluorophenols, and/or produce the desired compounds in low yields.

**[0074]** Thus, although there are a variety of methods used to produce mono fluorinated phenols, there is a continuing need and a continuing search in this field of art for alternative methods to produce mono fluorinated phenols under safe conditions and in greater yields.

**[0075]** In one embodiment, processes for the preparation of mainly a compound of formula **WW**, B-$OCF_2CF_2H$, comprising reducing a mixture comprised of a compound of formula **WW** and a compound of formula **YY**, B-$OCF_2CF_2Br$, with zinc dust under acidic conditions, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$, and 20) –$CONR_6R_6$ and $R_6$, $R_9$ and $R_{10}$ are defined as set forth above, are provided.

**[0076]** In one embodiment, processes for the preparation of a mixture comprised of a compound of formula **WW** and a compound of formula **YY**, B-$OCF_2CF_2Br$, comprising reacting a compound of formula **ZZ**, B-OH, with 1,2-dibromotetrafluoroethane under basic conditions, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$ and $R_6$, $R_9$ and $R_{10}$ are defined as set forth above, are provided.

**[0077]** In one embodiment, processes for the preparation of a compound of formula **ZZ** comprising reacting a compound of formula **AAA**, B-F, with potassium trimethylsilanoate in a solvent other than THF, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$ and $R_6$, $R_9$ and $R_{10}$ are defined as set forth above, are provided.

**[0078]** In another embodiment, processes for the preparation of compound of formula **WW**, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -Oalkyl, and 4) cyano, are provided. The present inventions provides such methods.

**[0079]** In one embodiment, processes for the preparation of mainly a compound of formula **WW**, wherein the acid is trifluoroacetic acid, acetic acid, formic acid and other acidic solvents known in the art, preferably acetic acid, are provided.

**[0080]** In another embodiment, processes for the preparation of mainly a compound of formula **WW**, wherein the step of reducing the mixture of a compound of formula **WW** and a compound of formula **YY** to form mainly a compound of

formula **WW** comprises heating the reaction mixture at about 50° C for about one to about 15 hours, preferably for about five (5) hours, are provided.

**[0081]** In yet another one embodiment, processes for the preparation of a mixture of a compound of formula **WW** and a compound of formula **YY**, wherein the base is sodium hydride, sodium methoxide, potassium methoxide, potassium carbonate, sodium carbonate, cesium carbonate, lithium carbonate, and ammonium carbonate, preferably cesium carbonate, are provided.

**[0082]** In still yet another embodiment, processes for the preparation of a mixture of a compound of formula **WW** and a compound of formula **YY**, wherein the step of reacting a compound of formula **ZZ** with 1,2-dibromotetrafluoroethane is carried out in a solvent, are provided.

**[0083]** In another embodiment, processes for the preparation of a mixture of a compound of formula **WW** and a compound of formula **YY**, wherein the solvent is diglyme, DMSO, DMF or NMP, preferably, DMSO, are provided.

**[0084]** In one embodiment, processes for the preparation of a mixture of a compound of formula **WW** and a compound of formula **YY**, wherein the step of reacting a compound of formula **ZZ** with 1,2-dibromotetrafluoroethane comprises heating the reaction mixture at about 50° to about 140° C, preferably at about 50° C, for about ten (10) minutes to about 15 hours, preferably about five (5) hours, are provided.

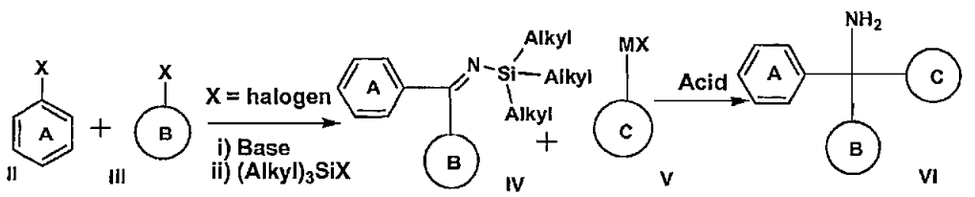
**[0085]** In another embodiment, processes for the preparation of a compound of formula **ZZ**, wherein the solvent is diglyme, dioxane, DMF or diethoxyethane, preferably diglyme or diethoxyethan, are provided.

**[0086]** In yet another embodiment, processes for the preparation of a compound of formula **ZZ**, wherein the step of reacting a compound of formula **AAA** with potassium trimethylsilanoate in a solvent other than THF comprises heating the reaction mixture at about 100° to about 140° C, preferably at about 120° C, for about three (3) hours to about three (3) days, preferably, for about five (5) hours, are provided.

## SYNTHESIS

[0087] Generally, compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes A to W. Exemplary compounds of the present invention were prepared by the methods illustrated in the examples set forth below. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Combinatorial techniques may be employed in the preparation of compounds, for example, where the intermediates possess groups suitable for these techniques.

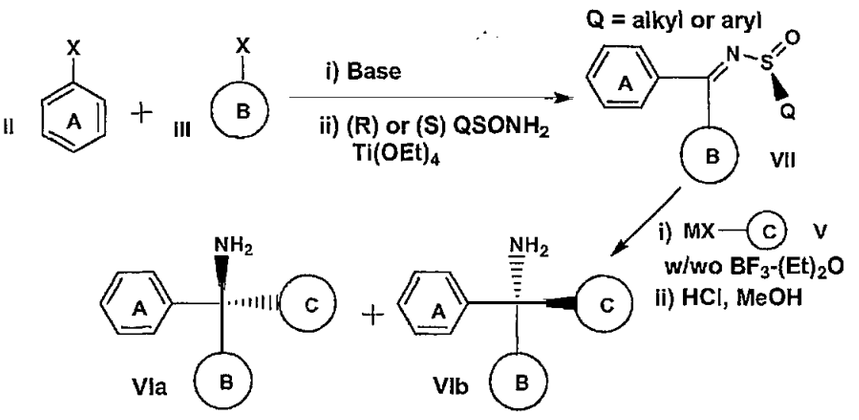
**Scheme A**




[0088] As illustrated in Scheme A, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is a nitrile group or a halogen group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, or a nitrile group, followed by treatment with a base, such as nBuLi. Alternatively, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is an aldehyde group or a halogen group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, or an aldehyde group, followed by treatment with a base, such as nBuLi, followed by treatment with an oxidizing agent such as, $MnO_4$ or Jone's Reagent. The resulting mixture can then be treated with a tri-alkyl silyl halide reagent, such as trimethylsilyl chloride, to yield a trimethylsilyl imide intermediate of Formula IV. To the imide

intermediate of Formula IV can be added a metal halide (MX) reagent, such as an alkyl lithium complex, a magnesium bromide complex or a magnesium chloride complex, or a zinc bromide or zinc chloride complex, of Formula V, where the metal halide complex is made from a reagent wherein the composition of **C** is as described under Formula Ia & Ib, followed by treatment with acid, such as HCl, to remove the silyl group, to yield the racemic intermediate of Formula VI. As will be described in the proceeding schemes, the racemic intermediate of Formula VI will allow for the generation of compounds of Formula Ia or Ib via the routes to be described.

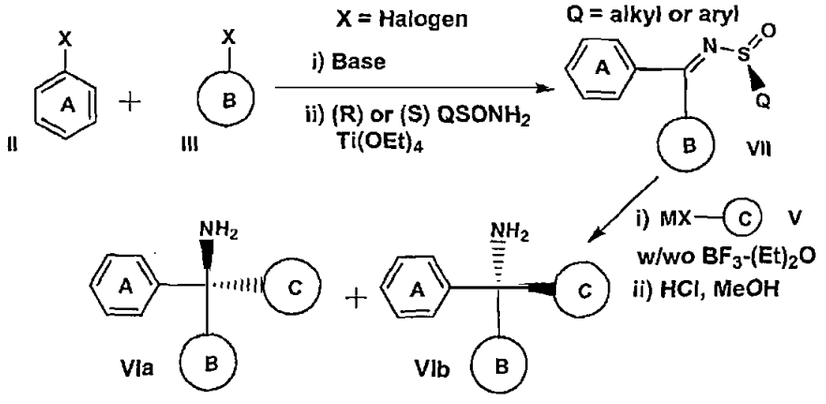
**Scheme B**




**[0089]** As illustrated in Scheme B, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is a nitrile group or a halogen group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, or a nitrile group, followed by treatment with a base, such as nBuLi. Alternatively, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is an aldehyde group or a halogen group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X)

attached to the reagent of Formula III is a halide group, such as bromine, or an aldehyde group, followed by treatment with a base, such as nBuLi, followed by treatment with an oxidizing agent such as, $MnO_4$ or Jone's Reagent. The resulting mixture can then be treated with a substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide, along with $Ti(OEt)_4$, to yield a the sulfinyl imide intermediate of Formula VII. To the sulfinyl imide intermediate of Formula VII can be added a metal halide reagent (MX), such as a magnesium bromide complex or a magnesium chloride complex, or a zinc bromide or zinc chloride complex, of Formula V, where the metal halide complex is made from a reagent wherein the composition of C is as described under Formula Ia & Ib, with or without a Lewis acid, such as $BF_3 \cdot (Et)_2O$, followed by treatment with acid, such as HCl, to hydrolyze the sulfinamide, to yield the intermediates of Formula VIa and VIb. By application of substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide one skilled in the art can enrich the formation of the (R) antipode (Formula VIa) versus the (S) antipode (Formula VIb) or the (S) antipode (Formula VIb) versus the (R) antipode (Formula VIa), respectively. As will be described in the proceeding schemes, the intermediate of Formula VIa and VIb will allow for the generation of compounds of Formula Ia or Ib via the routes to be described.

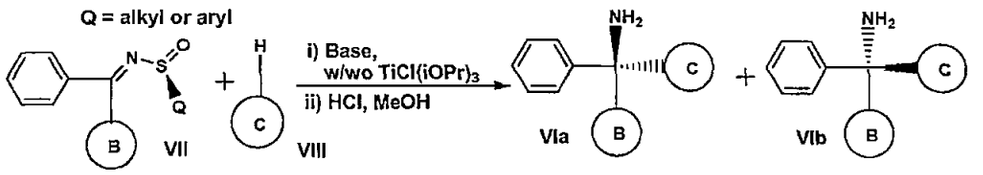
**Scheme C**



**[0090]** As illustrated in Scheme C, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is an alkyl ester group, such as a methyl or an ethyl ester, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, followed by treatment with a base, such as nBuLi. The resulting mixture can then be treated with a substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide, along with $Ti(OEt)_4$, to yield a the sulfonylimide intermediate of Formula VII. In addition, as illustrated in Scheme C, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is a halide group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is an alkyl ester group, such as a methyl or an ethyl ester, followed by treatment with a base, such as nBuLi. The resulting mixture can then be treated with a substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide, along with $Ti(OEt)_4$, to yield a the sulfinyl imide intermediate of Formula VII. To the sulfinyl imide intermediate of Formula VII can be added a metal halide reagent, such as an alkyl lithium complex, a magnesium bromide or a magnesium chloride complex, or a zinc bromide or zinc chloride complex, of Formula V, where the metal halide complex is made from a reagent wherein the composition of C is as described under Formula Ia & Ib, with or without a Lewis acid, such as $BF_3 \cdot (Et)_2O$, followed by treatment with acid, such as HCl, to hydrolyze the sulfinamide, to yield the intermediates of Formula VIa and VIb. By application of substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide one

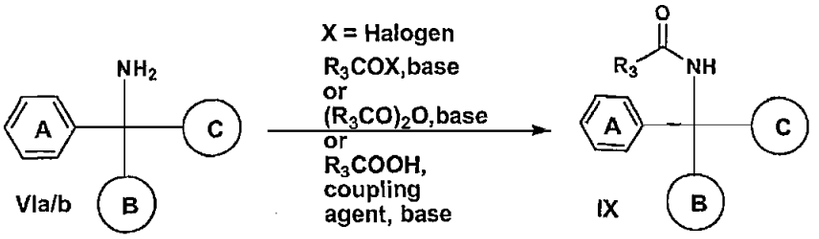
skilled in the art can enrich the formation of the (R) antipode (Formula VIa) versus the (S) antipode (Formula VIb) or the (S) antipode (Formula VIb) versus the (R) antipode (Formula VIa), respectively. As will be described in the proceeding schemes, the intermediate of Formula VIa and VIb will allow for the generation of compounds of Formula Ia or Ib via the routes to be described.

**Scheme D**



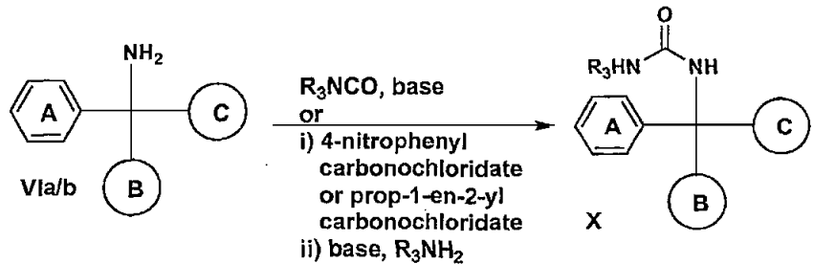

**[0091]** As illustrated in Scheme D, to the sulfinyl imide intermediate of Formula VII can be added a base, such as LDA or nBuLi, with or with out the addition of $TiCl(iOPr)_3$, and a reagent of Formula VIII, wherein the composition of C is as described under Formula Ia & Ib, with the requirement that at least one of the substituents attached to the reagent of Formula VIII is a hydrogen that can be deprotonated to yield a reactive anion species, followed by treatment with acid, such as HCl, to hydrolyze the sulfinamide, to yield the intermediates of Formula VIa and VIb. By application of substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide one skilled in the art can enrich the formation of the (R) antipode (Formula VIa) versus the (S) antipode (Formula VIb) or the (S) antipode (Formula VIb) versus the (R) antipode (Formula VIa), respectively. As will be described in the proceeding schemes, the intermediate of Formula VIa and VIb will allow for the generation of compounds of Formula Ia or Ib via the routes to be described.

Scheme E




[0092] As illustrated in Scheme E, an advanced intermediate of Formula VIa/b can be treated with an acylating agent, such as an acid halide of Formula $R_3COX$, where X = a halogen, such as chlorine or bromine, or an anhydride of Formula $(R_3CO)_2O$, with or without the presence of a base, such as triethylamine, pyridine or N-ethyl-N-isopropylpropan-2-amine, to generate an amide derivative of Formula IX, where $R_3$ is derived from the afore mentioned acylating agent or anhydride and is as described for Formula Ia and Ib. Alternatively, one can treat an advanced intermediate of Formula VIa/b with a carboxylate intermediate of Formula $R_3COOH$, along with a coupling agent, such as EDCI, DCC or other agents known to one skilled in the art for facilitating amide bond formation, along with or without a base, such as triethylamine, pyridine or N-ethyl-N-isopropylpropan-2-amine, to generate an amide derivative of Formula IX, which is a compound of Formula Ia and Ib, where $R_3$ is as described for Formula Ia and Ib.

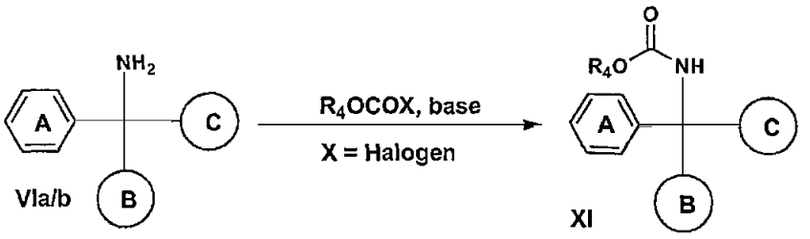
Scheme F




[0093] As illustrated in Scheme F, an advanced intermediate of Formula VIa/b can be treated with an isocyanate of Formula $R_3NCO$, with or without the presence of a base, such as triethylamine, pyridine or N-ethyl-N-isopropylpropan-2-amine, to generate an urea derivative of Formula X, where $R_3$ is derived from the afore mentioned isocyanate reagents and is as described for Formula Ia and Ib.

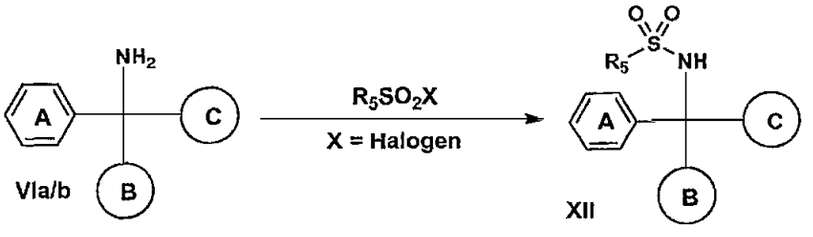
Alternatively, one can react an advanced intermediate of Formula VIa/b with an agent such as 4-nitrophenyl carbonochloridate or prop-1-en-2-yl carbonochloridate, to create a reactive carbamate intermediate which can then be reacted with an amine or amine salt intermediate of Formula $R_3NH_2$, with or without the presence of a base, such as triethylamine, pyridine or N-ethyl-N-isopropylpropan-2-amine, to generate an urea derivative of Formula X, which is a compound of Formula Ia and Ib, where $R_3$ is as described for Formula Ia and Ib.

**Scheme G**



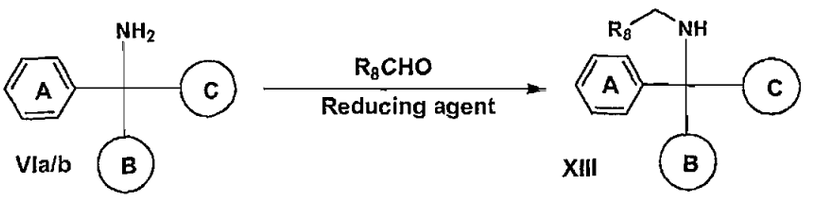

**[0094]** As illustrated in Scheme G, an advanced intermediate of Formula VIa/b can be treated with a carbonochloridate of Formula $R_4OCOCl$, in the presence of a base, such as potassium carbonate, to generate a carbamate derivative of Formula XI, which is a compound of Formula Ia and Ib, where $R_4$ is derived from the afore mentioned carbonochloridate reagents and is as described for Formula Ia and Ib.

**Scheme H**



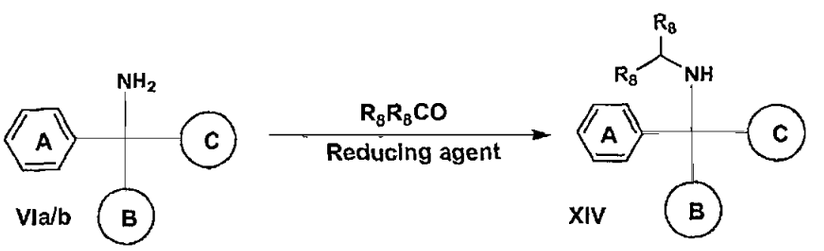

**[0095]** As illustrated in Scheme H, an advanced intermediate of Formula VIa/b can be treated with a sulfonyl chloride of Formula $R_5SO_2Cl$, in the presence of a base, such as triethylamine, pyridine or N-ethyl-N-isopropylpropan-2-amine, to generate a sulfonamide derivative of Formula XII, which is a compound of Formula Ia and Ib, where $R_5$ is derived from the afore mentioned sulfonyl chloride reagents and is as described for Formula Ia and Ib.

**Scheme I**



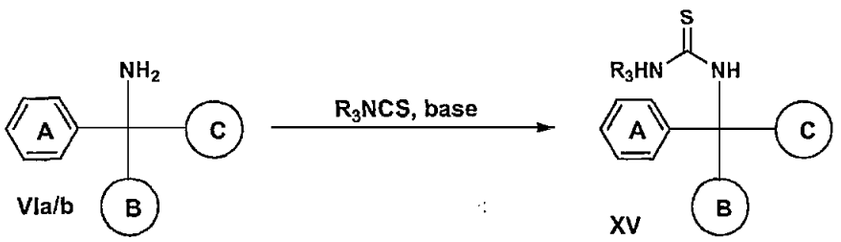

**[0096]** As illustrated in Scheme I, an advanced intermediate of Formula VIa/b can be treated with an aldehyde of Formula $R_8CHO$, with or without a catalytic amount of an acid, such as acetic acid, followed by treatment with a reducing agent, such as $NaBH(OAc)_3$, to generate an alkyl amine derivative of Formula XIII, which is a compound of Formula Ia and Ib, where $R_8$ is derived from the afore mentioned aldehyde reagents and is as described for Formula Ia and Ib.

**Scheme J**



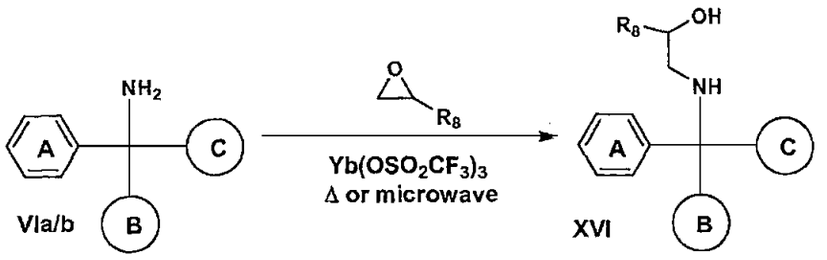

**[0097]** As illustrated in Scheme J, an advanced intermediate of Formula VIa/b can be treated with ketone of Formula $R_8R_8CO$, with or without a catalytic amount of an acid, such as acetic acid, followed by treatment with a reducing agent, such as $NaBH(OAc)_3$, to generate an alkyl amine derivative of Formula XIV, which is a compound of Formula Ia and Ib, where $R_8$ is derived from the afore mentioned ketone reagents and is as described for Formula Ia and Ib.

**Scheme K**



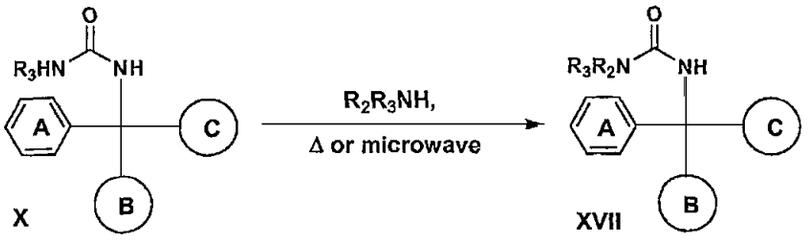

**[0098]** As illustrated in Scheme K, an advanced intermediate of Formula VIa/b can be treated with an isothiocyanate of Formula $R_3NCS$, with or without a base, such as triethylamine, pyridine or N-ethyl-N-isopropylpropan-2-amine, to generate a thiourea derivative of Formula XV, which is a compound of Formula Ia and Ib, where $R_3$ is derived from the afore mentioned isothiocyanate reagents and is as described for Formula Ia and Ib.

**Scheme L**



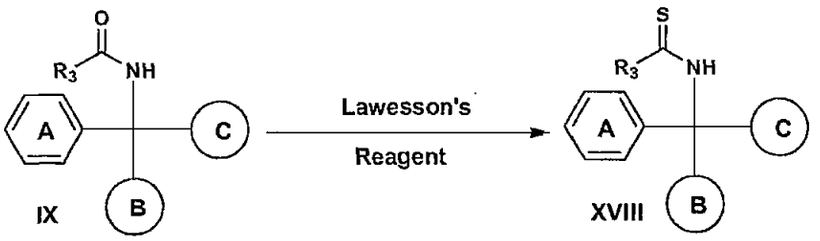

**[0099]** As illustrated in Scheme L, an advanced intermediate of Formula VIa/b can be treated with an oxirane reagent, of Formula $CH_2OCHR_8$, in the presence of a catalyst, such as $Sc(OSO_2CF_3)_3$ or $Yb(OSO_2CF_3)_3$, with standard heating or via irradiation in a microwave, to generate an alkyl hydoxy amine derivative of Formula XVI, which is a compound of Formula Ia and Ib, where $R_8$ is derived from the afore mentioned oxirane reagents and is as described for Formula Ia and Ib.

**Scheme M**



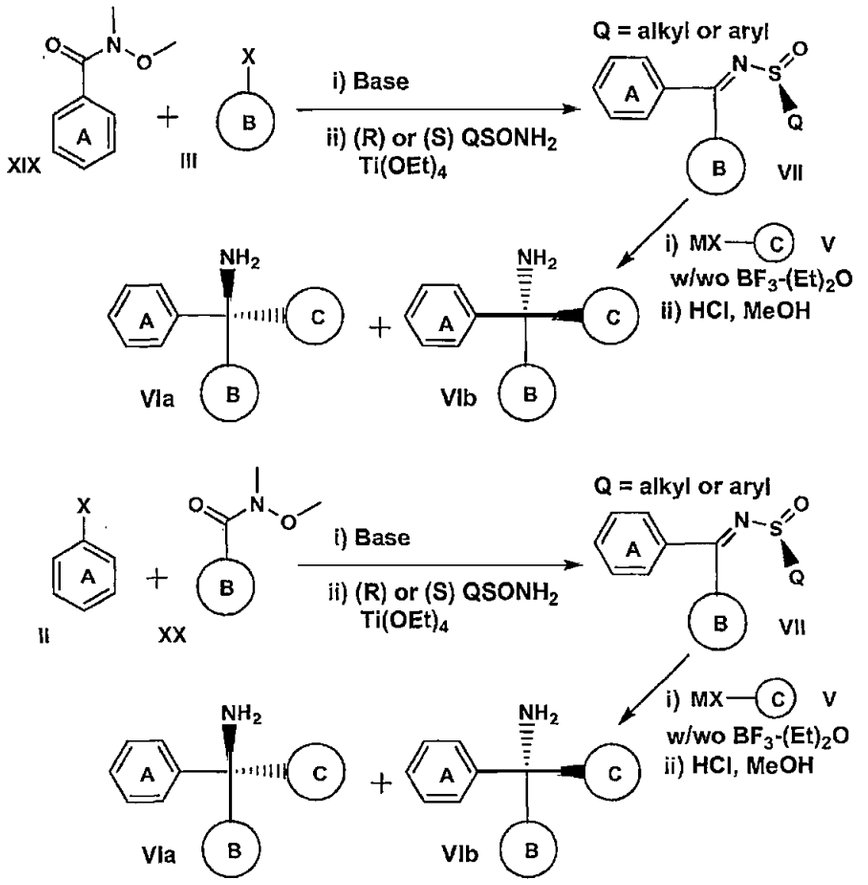

**[00100]** As illustrated in Scheme M, a reagent of Formula X, which is a compound of Formula Ia and Ib, can be treated with a disubstituted amine reagent of Formula $R_2R_3NH$, with heating or via irradiation in a microwave, to obtained a disubstituted urea derivative of Formula XVII, which is a compound of Formula Ia and Ib, where $R_2$ and $R_3$ is derived from the afore mentioned disubstituted amine reagent and is as described for Formula Ia and Ib.

**Scheme N**




**[00101]** As illustrated in Scheme N, a reagent of Formula IX, which is a compound of Formula Ia and Ib, can be treated with an agent, such as Lawesson's reagent or any other reagent known to one skilled in the art for conversion of an amide functional group to a thioamide functional group, to obtained a thioamide derivative of Formula XVIII, which is a compound of Formula Ia and Ib, where $R_3$ is derived as described for Formula Ia and Ib.

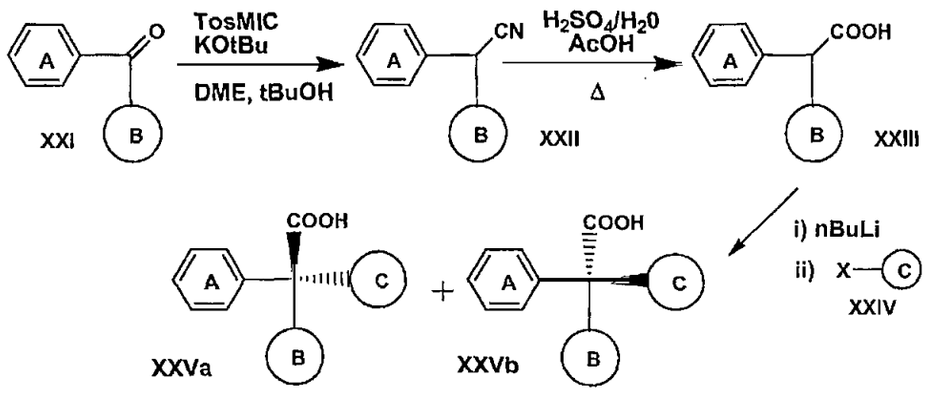
Scheme O




**[00102]** As illustrated in Scheme O, a substituted phenyl reagent of Formula XIX, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents attached to the reagent of Formula XIX is a N-methoxy-N-methylacetamide group, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, followed by treatment with a base, such as nBuLi. The resulting mixture can then be treated with a substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide, along with $Ti(OEt)_4$, to yield a the sulfinyl imide intermediate of Formula VII. To the sulfinyl imide intermediate of Formula VII can be added a metal halide reagent (MX), such as a magnesium bromide complex or a

magnesium chloride complex, or a zinc bromide or zinc chloride complex, of Formula V, where the metal halide complex is made from a reagent wherein the composition of **C** is as described under Formula Ia & Ib, with or without a Lewis acid, such as $BF_3$•$(Et)_2O$, followed by treatment with acid, such as HCl, to hydrolyze the sulfinamide, to yield the penultimate intermediates of Formula VIa and VIb. In addition, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents attached to the reagent of Formula II is a halide group, such as bromine, can be combined with a reagent of Formula XX, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula XX, is a N-methoxy-N-methylacetamide group, followed by treatment with a base, such as nBuLi. The resulting mixture can then be treated with a substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide, along with $Ti(OEt)_4$, to yield a the sulfinyl imide intermediate of Formula VII. To the sulfinyl imide intermediate of Formula VII can be added a metal halide reagent (MX), such as a magnesium bromide complex or a magnesium chloride complex, or a zinc bromide or zinc chloride complex, of Formula V, where the metal halide complex is made from a reagent wherein the composition of **C** is as described under Formula Ia & Ib, with or without a Lewis acid, such as $BF_3$•$(Et)_2O$, followed by treatment with acid, such as HCl, to hydrolyze the sulfinamide, to yield the penultimate intermediates of Formula VIa and VIb. By application of substituted sulfinamide reagent, such as (R)-4-methylbenzenesulfinamide or (R)-4-methylbenzenesulfinamide or (S)-2-methylpropane-2-sulfinamide or (R)-2-methylpropane-2-sulfinamide one skilled in the art can enrich the formation of the (R) antipode (Formula VIa) versus the (S) antipode (Formula VIb) or the (S) antipode (Formula VIb) versus the (R) antipode (Formula VIa), respectively. As will be described in the proceeding schemes, the penultimate intermediate of Formula VIa and VIb will allow for the generation of compounds of Formula Ia or Ib via the routes to be described.

Scheme P

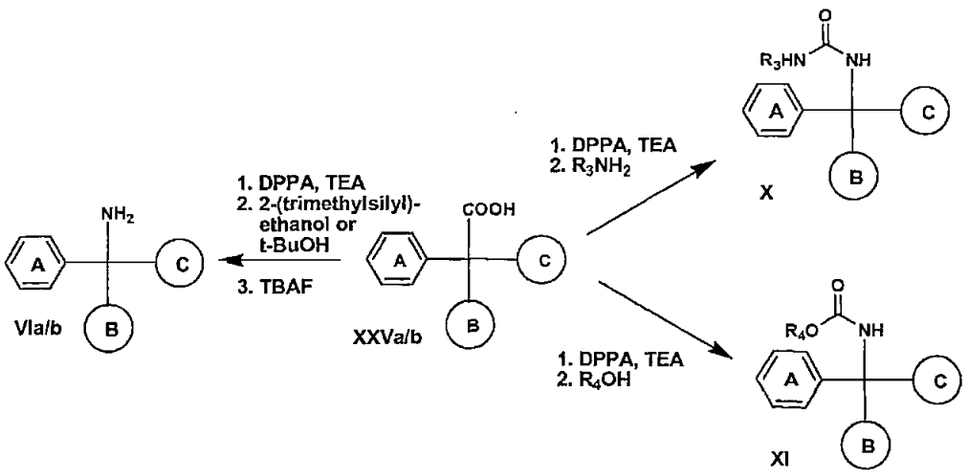



**[00103]** As illustrated in Scheme A and Scheme P, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is a nitrile group or a halogen group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, or a nitrile group, followed by treatment with a base, such as nBuLi, followed by treatment with aqueous acid, such as 1N HCl, to form a benzophenone intermediate of Formula XXI. Alternatively, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is an aldehyde group or a halogen group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, or an aldehyde group, followed by treatment with a base, such as nBuLi, followed by treatment with aqueous acid, such as 1N HCl, to form a benzophenone intermediate of Formula XXI. Alternately, as illustrated in Scheme C and Scheme P, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is an alkyl ester group, such as a methyl or an ethyl ester, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula

Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, such as bromine, followed by treatment with a base, such as nBuLi, followed by treatment with aqueous acid, to yield a benzophenone intermediate of Formula XXI. In addition, as illustrated in Scheme C and Scheme P, a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula II is a halide group, such as bromine, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is an alkyl ester group, such as a methyl or an ethyl ester, followed by treatment with a base, such as nBuLi, followed by treatment with aqueous acid, to yield a benzophenone intermediate of Formula XXI. As illustrated in Scheme O and Scheme P, a substituted phenyl reagent of Formula XIX, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents attached to the reagent of Formula XIX is a N-methoxy-N-methylacetamide group, can be combined with a reagent of Formula III, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula III is a halide group, followed by treatment with a base, such as nBuLi, followed by treatment with aqueous acid, to yield a benzophenone intermediate of Formula XXI, or a substituted phenyl reagent of Formula II, wherein the composition of **A** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents attached to the reagent of Formula II is a halide group, such as bromine, can be combined with a reagent of Formula XX, wherein the composition of **B** is as described under Formula Ia & Ib, with the requirement that at least one of the substituents (X) attached to the reagent of Formula XX, is a N-methoxy-N-methylacetamide group, followed by treatment with a base, such as nBuLi, followed by treatment with aqueous acid, to yield a benzophenone intermediate of Formula XXI. Numerous alternate approaches well known to one skilled in the art can also be employed to generate a benzophenone intermediate of Formula XXI.

[00104] As illustrated in Scheme P, an intermediate benzophenone of Formula XXI can be treated with an agent such as 1-(isocyanomethylsulfonyl)-4-methylbenzene (TosMIC) and a base, such as potassium tert-butoxide, to yield an intermediate of Formula XXII. Hydrolysis of an intermediate of Formula XXII can be accomplished by treatment with an acid, such as aqueous $H_2SO_4$ and acetic acid, to yield an intermediate of Formula XXIII. An intermediate of Formula XXIII can be treated with a base, such as n-butyl lithium, followed by an alkyl halide reagent of Formula XXIV, where X is a halide, such as chlorine, bromine or iodine and the composition of **C** is as described under Formula Ia and Ib, to yield an intermediate of Formula XXVa and XXVb, which are key intermediates for the synthesis of compounds of Formula Ia and Ib.

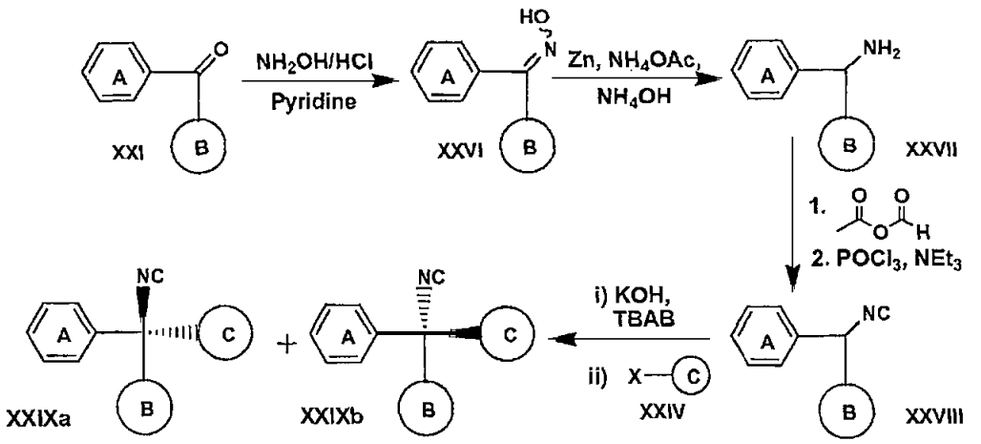
**Scheme Q**




[00105] As illustrated in Scheme Q, an intermediate of Formula XXVa/b can be treated with an agent such as diphenylphosphoryl azide (DPPA) in the presence of a base, such as triethyl amine (TEA), followed by treatment with an agent, such as 2-(trimethylsilyl)ethanol or tert-butyl alcohol and eventual cleavage of the resulting intermediate carbamate by treatment with agents such as tetrabutylammonium fluoride (TBAF) or trifluoroacetic acid, to yield the advanced intermediate of Formula VIa/b, which is a key intermediate for the synthesis of compounds of Formula Ia and Ib. An intermediate of Formula XXVa/b can be treated with an agent such as diphenylphosphoryl azide (DPPA) in the presence of a base, such as triethyl

amine (TEA), followed by treatment with an agent of formula $R_3NH_2$, were $R_3$ is defined as described under Formula Ia and Ib, to give compounds of Formula X, which are compounds of Formula Ia and Ib. In addition, an intermediate of Formula XXVa/b can be treated with an agent such as diphenylphosphoryl azide (DPPA) in the presence of a base, such as triethyl amine (TEA), followed by treatment with an agent of formula $R_4OH$, were $R_4$ is defined as described under Formula Ia and Ib, to give compounds of Formula XI, which are compounds of Formula Ia and Ib.

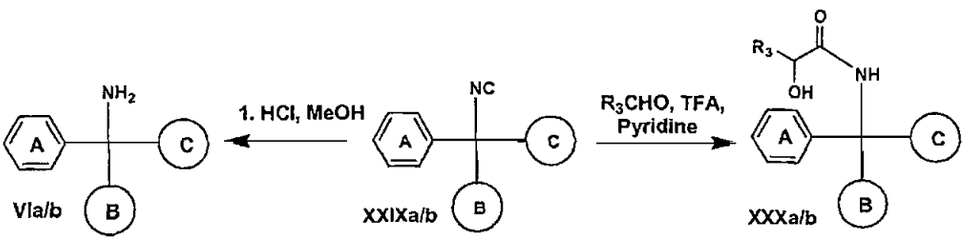
**Scheme R**




**[00106]** As illustrated in Scheme R, an intermediate of Formula XXI, made as described in Schemes P, can be treated with a reagent such as $NH_2OH$, in the presence of an acid such as HCl, followed by treatment with a base such as pyridine, to yield an intermediate of Formula XXVI. An intermediate of Formula XXVI can be treated with a reducing agent such as zinc, along with $NH_4OAc$ and $NH_4OH$, to yield an intermediate of Formula XXVII. An intermediate of Formula XXVII can be treated with a formylating agent, such as acetic formic anhydride, followed by dehydration through treatment with an agent such as $POCl_3$, to yield the isonitrile intermediate of Formula XXVIII. The isonitrile intermediate of Formula XXVIII can be treated with a base, such as aqueous KOH, along with tetrabutylammonium bromide, followed by an alkyl halide reagent of Formula XXIV where the composition of **C** is as described under Formula Ia and Ib, and the X can be a halide, such as chlorine, bromine or iodine, to yield intermediates of Formula XXIXa and XXIXb, which are key intermediates for the synthesis of compounds of Formula Ia

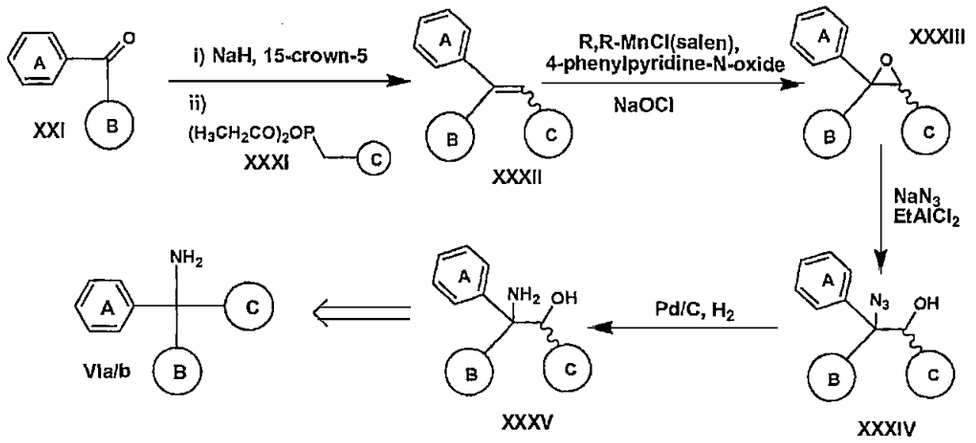
and Ib. The formation of an intermediate of Formula XXIXa or XXIXb from an intermediate of Formula XXVIII, as described above, can also be performed in the presence of a chiral catalyst such as, but not limited to, N-benzylcinchoninium chloride or N-benzylcinchonidinium chloride, to enrich the formation of the intermediate of Formula XXIXa over the intermediate of Formula XXIXb or to enrich the formation of the intermediate of Formula XXIXb over the intermediate of Formula XXIXa as needed to make compounds of Formula Ia and Ib.

**Scheme S**



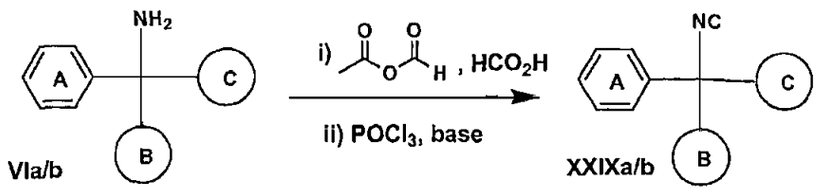

**[00107]** As illustrated in Scheme S, an intermediate of Formula XXIXa/b can be converted to an intermediate of Formula VIa/b by treatment with an acid such as HCl in methanol. As described in earlier schemes, and intermediate of Formula VIa/b is a key intermediate for the synthesis of compounds of Formula Ia and Ib. In addition, an intermediate of Formula XXIXa/b can be treated directly with an aldehyde of Formula $R_3CHO$, where the definition of $R_3$ is as described under Formula Ia and Ib, and an acid, such as trifluoroacetic acid, in the presence of a base, such as pyridine, to yield compounds of Formula XXXa/b, which are a compounds of Formula Ia and Ib.

**Scheme T**



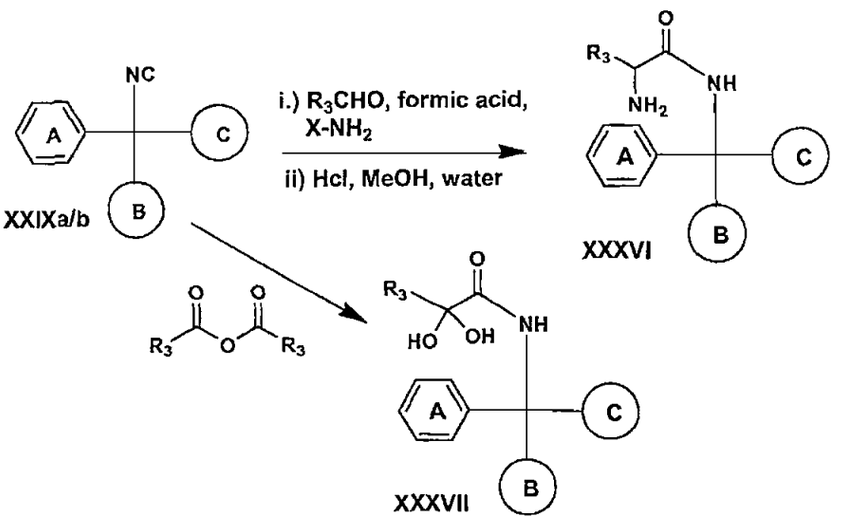

**[00108]** As illustrated in Scheme T, an intermediate of Formula XXI, made as described in Schemes P, can be reacted with a reagent of Formula XXXI, where the composition of C is as described under Formula Ia and Ib, to yield a styrene intermediate of Formula XXXII. A reagent of Formula XXXII can be derived from a variety of commercially available intermediates or can readily be made by one skilled in the art. A styrene intermediate of Formula XXXII can be treated with an expoxidizing agent, such assodium chlorite in the presence of 4-phenylpyridine-N-oxide, with or without a chiral catalyst such as, (1R, 2R)-(-)-[1,2-cyclo-hexanediamino-N, N'-bis(3,5-di-t-butyl-salicylidene)] manganese (III) chloride, (R,R-MnCl (salen)), to obtain an oxirane intermediate of Formula XXXIII. Treatment of the oxirane intermediate of Formula XXXIII with an agent such as $NaN_3$, in the presence of a Lewis acid such as ethylaluminum dichloride, yields the azide intermediate of Formula XXXIV. Reduction of the azide intermediate of Formula XXXIV can be achieved over palladium on charcoal in the presence of $H_2$ gas to generate the advanced intermediate of Formula XXXIV. An intermediate of Formula XXXV is embodied by the intermediate of Formula VIa/b which is a key intermediate on route to the synthesis of compounds of Formula Ia and Ib.

Scheme U




**[00109]** As illustrated in Scheme U, an intermediate of Formula VIa/b, can be converted to an intermediate of compound XXXIIIa/b by treatment with a formylating agent, such as, acetic formic anhydride, followed by a dehydrating agent, such as phosphorous oxychloride, along with a base, such as triethylamine. As described in Scheme S, an intermediate of Formula XXIXa/b can be utilized to make compounds of Formula Ia and Ib.

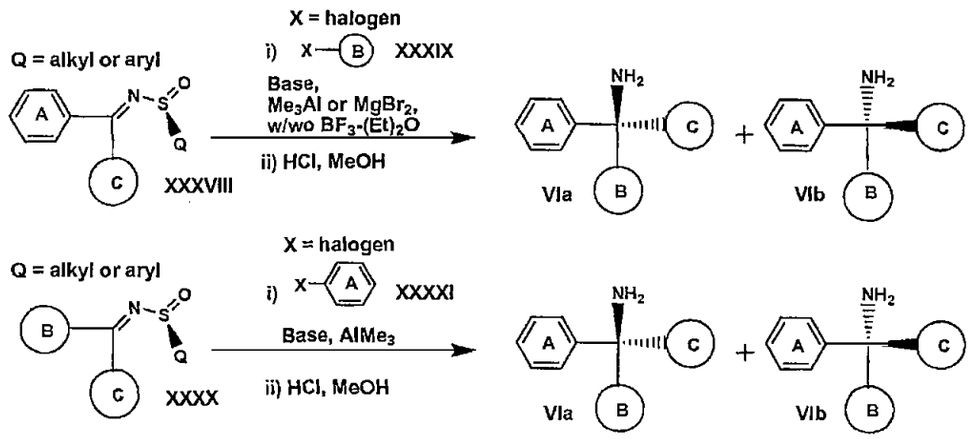
Scheme V




**[00110]** As illustrated in Scheme V, an intermediate of Formula XXIXa/b, can be treated with an aldehyde reagent of Formula $R_3CHO$, where $R_3$ is as described for Formula Ia and Ib, along with an acid, such as formic acid, and an amine reagent, of general formula $X\text{-}NH_2$, where X represents a cleavable protection group selected readily by one skilled in the art, followed by treatment with and acid, such as HCl, in the presence of an alcohol and water, to yield a compound of Formula XXXVI, which is a compound of Formula Ia and Ib. Alternately a reagent of Formula XXIXa/b can be treated with an anhydride reagent of Formula $(R_3CO)_2O$, where $R_3$ is as described

for Formula Ia and Ib, to yield a compound of Formula XXXVII, which is a compound of Formula Ia and Ib.

**Scheme W**




**[00111]** As illustrated in Scheme W, by applications of routes described in Schemes A, B, C and O for the synthesis of an intermediate of Formula VII, one skilled in the art can make intermediates of Formula XXXVII and XXXX, where the definition of A, B and C are as defined for Formula Ia and Ib. An intermediate of Formula XXXVIII can be reacted with an intermediate of Formula XXXIX, where X is a halogen, such as bromine, iodine or chlorine, and the definition of C is as described for Formula Ia and Ib, in the presence of a base, such as n-butyl lithium or tert-butyl lithium, along with a metalating agent such as, $CH_3Al$ or $MgBr_2$, followed by hydrolysis of the sulfinamide, to yield the intermediate of Formula VIa and VIb, which is a key intermediate on route to compounds of Formula Ia and Ib. An intermediate of Formula XXXX can be reacted with an intermediate of Formula XXXXI, where X is a halogen, such as bromine, iodine or chlorine, and the definition of A is as described for Formula Ia and Ib, in the presence of a base, such as n-butyl lithium or tert-butyl lithium, along with a metalating agent such as, $CH_3Al$, followed by hydrolysis of the sulfinamide, to yield the intermediate of Formula VIa and VIb, which is a key intermediate on route to compounds of Formula Ia and Ib.

**[00112]** The above schemes give an overview of several general processes for the synthesis of compounds of Formula Ia and Ib. Additional compounds of Formula Ia

and Ib can readily be made by one of ordinary skill in the art by further modification of functional groups at positions A, B, C or $R_1$ of compounds of Formula Ia and Ib made by the processes illustrated in the included schemes. The Examples that follow described numerous applications of the routes described in Schemes A-W as well as additional routes to compounds of Formula Ia and Ib achieved through modification of functional groups at positions A, B, C or $R_1$ of compounds of Formula Ia and Ib.

## UTILITY

**[00113]** Compounds of the present invention have been shown to inhibit cholesterol ester transfer protein (CETP) by greater than 30% at two different concentrations of less than 100 uM, preferably with a potency less than 5 uM, more preferably with a potency less than 500 nM. Compounds of the invention were also found to inhibit cholesterol ester transfer activity using *in vitro* assays that contained up to 96% plasma, and to inhibit plasma cholesterol ester transfer activity in animals. Accordingly, compounds within the scope of the present invention inhibit the CETP protein, and as such are expected to be useful in the treatment, prevention, and/or slowing of the progression of various disorders.

**[00114]** For example, the compounds of the present invention, their prodrugs and the salts of such compounds and prodrugs can be adapted to therapeutic use as agents that inhibit cholesterol ester transfer protein activity in mammals, particularly humans. Thus, the compounds of the present invention are expected to be useful in elevating plasma HDL cholesterol, its associated components, and the functions performed by them in mammals, particularly humans. By virtue of their expected activity, these agents are also expected to reduce VLDL cholesterol, LDL cholesterol and their associated components in mammals, particularly humans. Hence, these compounds are expected to be useful for the treatment and correction of the various dyslipidemias observed to be associated with the development and incidence of atherosclerosis and cardiovascular disease, including hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypertriglyceridemia, and familial-hypercholesterolemia (see U.S. Patent 6,489,478, incorporated herein by reference).

**[00115]** Further, introduction of a functional CETP gene into an animal lacking CETP (mouse) results in reduced HDL levels (Agellon, L.B. et al., J. Biol. Chem.,

266:10796-10801 (1991)) and, increased susceptibility to atherosclerosis. (Marotti, K. R. et al., Nature, 364:73-75 (1993)). Also, inhibition of CETP activity with an inhibitory antibody raises HDL-cholesterol in hamster (Evans, G.F. et al., J. Lipid Research, 35:1634-1645 (1994)) and rabbit (Whitlock, M.E. et al, J. Clin. Invest., 84:129-137 (1989)). Suppression of increased plasma CETP by intravenous injection with antisense oligodeoxynucleotides against CETP mRNA reduced atherosclerosis in cholesterol-fed rabbits (Sugano, M. et al., J. Biol. Chem., 273:5033-5036 (1998)). Importantly, human subjects deficient in plasma CETP, due to a genetic mutation possess markedly elevated plasma HDL-cholesterol levels and apolipoprotein A-I, the major apoprotein component of HDL. In addition, most demonstrate markedly decreased plasma LDL cholesterol and apolipoprotein B (the major apolipoprotein component of LDL. (Inazu, A. et al., N. Engl. J. Med., 323:1234-1238 (1990)).

**[00116]** Given the negative correlation between the levels of HDL cholesterol and HDL associated lipoproteins, and the positive correlation between triglycerides, LDL cholesterol, and their associated apolipoproteins in blood with the development of cardiovascular, cerebral vascular and peripheral vascular diseases, the compounds of the present invention, their prodrugs and the salts of such compounds and prodrugs, by virtue of their pharmacologic action, are expected to be useful for the treatment, prevention, the arrestment and/or regression of atherosclerosis and its associated disease states. These include cardiovascular disorders (e.g., angina, cardiac ischemia and myocardial infarction), complications due to cardiovascular disease therapies (e.g., reperfusion injury and angioplastic restenosis), hypertension, stroke, and atherosclerosis associated with organ transplantation.

**[00117]** Because of the beneficial effects widely associated with elevated HDL levels, an agent which inhibits CETP activity in humans, by virtue of its HDL increasing ability, also provides valuable avenues for therapy in a number of other disease areas as well.

**[00118]** Accordingly, given the ability of the compounds of the present invention, their prodrugs and the salts of such compounds and prodrugs to alter lipoprotein composition via inhibition of cholesterol ester transfer, they are expected to be useful in the treatment, prevention and/or slowing of the progression of vascular complications associated with diabetes. Hyperlipidemia is present in most subjects

with diabetes mellitus (Howard, B.V., J. Lipid Res. 28:613 (1987)). Even in the presence of normal lipid levels, diabetic subjects experience a greater risk of cardiovascular disease (Kannel, W.B. et al., Diabetes Care, 2:120 (1979)). CETP-mediated cholesteryl ester transfer is known to be abnormally increased in both insulin-dependent (Bagdade, J.D. et al., Eur. J. Clin. Invest., 21:161 (1991)) and non-insulin dependent diabetes (Bagdade, J.D. et al., Atherosclerosis, 104:69 (1993)). It has been suggested that the abnormal increase in cholesterol transfer results in changes in lipoprotein composition, particularly for VLDL and LDL, that are more atherogenic (Bagdade, J.D. et al., J. Lipid Res., 36:759 (1995)). These changes would not necessarily be observed during routine lipid screening. Thus, it is expected that the present invention will be useful in reducing the risk of vascular complications as a result of the diabetic condition.

**[00119]** In addition, the compounds of the present invention are expected to be useful in the treatment of obesity. In both humans (Radeau, T. et al., J. Lipid Res., 36(12):2552-2561 (1995)) and nonhuman primates (Quinet, E. et al., J. Clin. Invest., 87(5):1559-1566 (1991)) mRNA for CETP is expressed at high levels in adipose tissue. The adipose message increases with fat feeding (Martin, L.J. et al., J. Lipid Res., 34(3):437-446 (1993)), and is translated into functional transfer protein and through secretion contributes significantly to plasma CETP levels. In human adipocytes the bulk of cholesterol is provided by plasma LDL and HDL (Fong, B.S. et al., Biochimica et Biophysica Acta, 1004(1):53-60 (1989)). The uptake of HDL cholesteryl ester is dependent in large part on CETP (Benoist, F. et al., J. Biol. Chem., 272(38):23572-23577 (1997)). This ability of CETP to stimulate HDL cholesteryl uptake, coupled with the enhanced binding of HDL to adipocytes in obese subjects (Jimenez, J.G. et al., Int. J. Obesity, 13(5):699-709 (1989)), suggests a role for CETP, not only in generating the low HDL phenotype for these subjects, but in the development of obesity itself by promoting cholesterol accumulation. Inhibitors of CETP activity that block this process therefore serve as useful adjuvants to dietary therapy in causing weight reduction.

**[00120]** CETP inhibitors are useful in the treatment of inflammation due to Gram-negative sepsis and septic shock. For example, the systemic toxicity of Gram-negative sepsis is in large part due to endotoxin, a lipopolysaccharide (LPS) released

from the outer surface of the bacteria, which causes an extensive inflammatory response. Lipopolysaccharide can form complexes with lipoproteins (Ulevitch, R.J. et al., J. Clin. Invest. 67:827-837 (1981)). *In vitro* studies have demonstrated that binding of LPS to HDL substantially reduces the production and release of mediators of inflammation (Ulevitch, R.J. et al., J. Clin. Invest. 62:1313-1324 (1978)). *In vivo* studies show that transgenic mice expressing human apo-Al and elevated HDL levels are protected from septic shock (Levine, D.M. et al., Proc. Natl. Acad. Sci., 90:12040-12044 (1993)). Importantly, administration of reconstituted HDL to humans challenged with endotoxin resulted in a decreased inflammatory response (Pajkrt, D. et al., J. Exp. Med., 184:1601-1608 (1996)). The CETP inhibitors, by virtue of the fact that they raise HDL levels, attenuate the development of inflammation and septic shock.

**[00121]** Thus, the present invention provides methods for the prevention or treatment of one or more of the aforementioned disorders, comprising the step of administering to a subject in need thereof an effective amount of at least one compound of the present invention, its prodrug and the salt of such compound and prodrugs. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

**[00122]** In addition, the compounds of the present invention are expected to be useful in the inhibition of remnant lipoprotein production (Okamoto et al., WO 2005/030185).

**CETP Assay**

**[00123]** CETP inhibition can be determined at a specific concentration of test compound in any of the assays described herein. Potencies are more generally calculated by determining $IC_{50}$ values using these assays.

**CETP Scintillation Proximity Assay**

**[00124]** Compounds of the present invention inhibit CETP-dependent cholesterol ester transfer from HDL to LDL as described here. Dilutions of compounds in DMSO (1 µl) are added to BD plates (#353232). To this is added 20 µl of a mixture containing $^3$H-CE/HDL (0.15 µl), biotinylated LDL (~5 µg protein/ml final concentration) and unlabeled HDL (16 µg/ml final concentration) in a buffer containing 50 mM HEPES, pH 7.4, 150 mM NaCl and 0.05% sodium azide. Reactions are initiated by the addition of 10 µl of buffer containing purified human recombinant CETP, and incubated at 37°C. At the end of the reaction, 60 µl of LEADseeker beads (#RPNQ0261, 2 mg/ml in buffer containing 1 mg/ml BSA and 0.05 mg protein/ml HDL) are added, the plates are covered and subsequently read. Background activity is determined in a set of wells that receive buffer but no CETP. The level of inhibition is determined by comparing the readings in wells that contain compound to the readings in control wells containing DMSO.

**Plasma Cholesterol Ester Transfer Assay**

**[00125]** Compounds of the present invention were also tested for the ability to inhibit cholesterol ester transfer activity in plasma as described here. Dilutions of compounds in DMSO (1 µl) are added to 384-well polypropylene plates. To each well is added 29 ul of human plasma containing 0.15 ul $^3$H-CE/HDL. The reaction is incubated at 37°C and terminated by the addition of 6 ul of precipitation reagent (2:1:1 of water:1M $MgCl_2$:2% Dextralip 50), to precipitate LDL and VLDL. After 10 minutes at room temperature, 15 µl of the reaction is transferred to filter plates (Millipore, #MHVBN45) pre-wetted with 100 ul phosphate buffered saline. The plates are centrifuged (1800 rpm) at room temperature for 10 minutes, and 50 ul Microscint-20 is added. The plates are then sealed and read. Background activity is determined with plasma samples incubated at 4°C. The level of inhibition is determined by comparing the readings in wells that contain compound to the readings in control wells containing DMSO.

**In Vivo Cholesterol Ester Transfer Activity**

**[00126]** Compounds of the present invention have further been shown to inhibit plasma cholesterol ester transfer activity in mice that are dually transgenic for human CETP and apoB-100 (hCETP/apoB-100) as described here.

**[00127]** Mice (commercially available from Taconic) are fasted for two hours and plasma obtained before dosing. The animals are then dosed with vehicle or compound (p.o.). The vehicle may vary as needed to dissolve the compound, while at the same time having no, or minimal, activity on plasma cholesterol ester transfer activity. Plasma samples are collected again at various times after dosing and assayed for cholesterol ester transfer activity.

**[00128]** To measure CETP activity in plasma samples obtained from animals treated with compounds, the following methodology is employed. To a sample of plasma (typically between 9 and 30 ul), 1 µl of diluted $^3$H-CE/HDL is added (0.15 µl $^3$H-CE/HDL and 0.85 ul assay buffer) to label endogenous HDL. Assay buffer contains 50 mM HEPES, pH 7.4, and 150 mM NaCl. The reaction is incubated at 37°C, and LDL/VLDL precipitated with 3 µl of precipitation reagent (4:1:1 of water:0.5M $MgCl_2$:1% Dextralip 50). The tubes are centrifuged for 15-30 minutes at 10,000 x g (10°C), the supernatants discarded, and the pellets dissolved in 140 µl of 2% SDS. Half of the SDS solution (70 µl) is transferred to scintillation tubes, scintillation fluid is added, and radioactivity measured in a scintillation counter. Background activity is determined for each sample with an aliquot incubated at 4°C. Plasma cholesterol ester transfer inhibition is calculated by comparing the transfer activity in a plasma sample obtained after dosing to the transfer activity in the plasma sample obtained from the same animal before dosing. All data are background subtracted.

**[00129]** The *in vivo* assay described above (with appropriate modifications within the skill in the art) may be used to determine the activity of other lipid or triglyceride controlling agents as well as the compounds of this invention. The assays set forth above also provide a means whereby the activities of the compounds of the present invention, their prodrugs and the salts of such compounds and prodrugs (or the other agents described herein) can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for determining

dosage levels in mammals, including humans, for the treatment of the above described disease/conditions.

**HDL Cholesterol Protocol**

**[00130]** The ability of CETP inhibitors to increase HDL cholesterol (HDL-C) can be shown in mammalian subjects via methods known to one of ordinary skill in the art (see Evans, G.F. et al., J. Lipid Research, 35:1634-1645 (1994)). For example, compounds of the present invention have been shown to be efficacious in the elevation of HDL-C in golden syrian hamsters. The hamsters are fed a moderate fat diet containing variable amounts of coconut oil and cholesterol to alter their HDL-C and LDL-C levels. The moderately fat-fed hamsters are fasted and bled to determine baseline HDL-C levels, then dosed orally with compound for three days in an appropriate vehicle. The animals are fasted and bled again on the third day of dosing, and the results are compared to the baseline HDL-C levels. The compounds increase HDL-C in this model in a dose-dependent manner, demonstrating their usefulness to alter plasma lipids.

**Antiobesity Protocol**

**[00131]** The ability of CETP inhibitors to cause weight loss can be assessed in obese human subjects with body mass index (BMI) $\geq 30$ kg/m$^2$. Doses of inhibitor are administered sufficient to result in an increase of $\geq 25\%$ in HDL cholesterol levels. BMI and body fat distribution, defined as waist (W) to hip (H) ratio (WHR), are monitored during the course of the 3-6 month studies, and the results for treatment groups compared to those receiving placebo.

**[00132]** The above assays can of course be varied by those skilled in the art.

**[00133]** The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the present invention, their prodrugs and the salts of such compounds and prodrugs capable of preventing, treating, and/or slowing the progression of one or more of the aforementioned disorders in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The

compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

**[00134]** The compounds of the present invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps.

**[00135]** Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of present invention may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as

celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

**[00136]** Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

**[00137]** Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3 butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

**[00138]** Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

**[00139]** Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

**[00140]** The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.001 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the

particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to the aforementioned disorders.

**[00141]** The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of the aforementioned disorders or other disorders.

**[00142]** For example, they may be used in combination with a HMG-CoA reductase inhibitor, a cholesterol synthesis inhibitor, a cholesterol absorption inhibitor, another CETP inhibitor, a MTP/Apo B secretion inhibitor, a PPAR modulator and other cholesterol lowering agents such as a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor, and a bile acid sequestrant. Other pharmaceutical agents would also include the following: a bile acid reuptake inhibitor, an ileal bile acid transporter inhibitor, an ACC inhibitor, an antihypertensive (such as NORVASC®), a selective estrogen receptor modulator, a selective androgen receptor modulator, an antibiotic, an antidiabetic (such as metformin, a PPARγ activator, a sulfonylurea, insulin, an aldose reductase inhibitor (ARI) and a sorbitol dehydrogenase inhibitor (SDI)), aspirin (acetylsalicylic acid) and niacin and combinations thereof.

**[00143]** Any HMG-CoA reductase inhibitor may be used in the combination aspect of this invention. The term HMG-CoA reductase inhibitor refers to compounds which inhibit the bioconversion of hydroxymethylglutaryl-coenzyme A to mevalonic acid catalyzed by the enzyme HMG-CoA reductase. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol., 71:455-509 (1981) and references cited therein). A variety of these compounds are described and referenced below however other HMG-CoA reductase inhibitors will be known to those skilled in the art. U.S. Pat. No. 4,231,938 (the disclosure of which is hereby incorporated by reference) discloses certain compounds isolated after cultivation of a microorganism belonging to the genus *Aspergillus*, such as lovastatin. Also, U.S. Pat. No. 4,444,784 (the disclosure of which is hereby incorporated by reference) discloses synthetic derivatives of the aforementioned compounds, such as simvastatin. Also, U.S. Pat. No. 4,739,073 (the disclosure of which is incorporated by reference) discloses certain substituted indoles, such as

fluvastatin. Also, U.S. Pat. No. 4,346,227 (the disclosure of which is incorporated by reference) discloses ML-236B derivatives, such as pravastatin. Also, EP-491226A (the disclosure of which is incorporated by reference) discloses certain pyridyldihydroxyheptenoic acids, such as cerivastatin. In addition, U.S, Pat, No. 5,273,995 (the disclosure of which is incorporated by reference) discloses certain 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones such as atorvastatin and any pharmaceutically acceptable form thereof (i.e. LIPITOR®). Additional HMG-CoA reductase inhibitors include rosuvastatin and pitavastatin. Statins also include such compounds as rosuvastatin disclosed in U.S. RE37,314 E, pitavastatin disclosed in EP 304063 B1 and U.S. 5,011,930; mevastatin, disclosed in U.S. 3,983,140; velostatin, disclosed in U.S. 4,448,784 and U.S. 4,450,171; compactin, disclosed in U.S. 4,804,770; dalvastatin, disclosed in European Patent Application Publication No. 738510 A2; fluindostatin, disclosed in European Patent Application Publication No. 363934 A1; and dihydrocompactin, disclosed in U.S. 4,450,171.

**[00144]** Any PPAR modulator may be used in the combination aspect of this invention. The term PPAR modulator refers to compounds which modulate peroxisome proliferator activator receptor (PPAR) activity in mammals, particularly humans. Such modulation is readily determined by those skilled in the art according to standard assays known in the literature. It is believed that such compounds, by modulating the PPAR receptor, regulate transcription of key genes involved in lipid and glucose metabolism such as those in fatty acid oxidation and also those involved in high density lipoprotein (HDL) assembly (for example, apolipoprotein AI gene transcription), accordingly reducing whole body fat and increasing HDL cholesterol. By virtue of their activity, these compounds also reduce plasma levels of triglycerides, VLDL cholesterol, LDL cholesterol and their associated components such as apolipoprotein B in mammals, particularly humans, as welt as increasing HDL cholesterol and apolipoprotein AI. Hence, these compounds are useful for the treatment and correction of the various dyslipidemias observed to be associated with the development and incidence of atherosclerosis and cardiovascular disease, including hypoalphalipoproteinemia and hypertriglyceridemia. A variety of these compounds are described and referenced below, however, others will be known to those skilled in the art. International Publication Nos. WO 02/064549 and WO

02/064130, U.S. patent application 10/720,942, and U.S. patent application 60/552,114 disclose certain compounds which are PPARα activators.

**[00145]** Any other PPAR modulator may be used in the combination aspect of this invention. In particular, modulators of PPARβ and/or PPARγ may be useful in combination with compounds of the present invention. An example PPAR inhibitor is described in US 2003/0225158 as {5-Methoxy-2-methyl-4-[4-(4-trifluoromethyt-benzy]oxy)-benzylsulfany]-phenoxy}-acetic acid.

**[00146]** Any MTP/Apo B (microsomal triglyceride transfer protein and or apolipoprotein B) secretion inhibitor may be used in the combination aspect of this invention. The term MTP/Apo B secretion inhibitor refers to compounds which inhibit the secretion of triglycerides, cholesteryl ester, and phospholipids. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Wetterau, J.R., Science, 258:999 (1992)). A variety of these compounds are described and referenced below however other MTP/Apo B secretion inhibitors will be known to those skilled in the art, including implitapride (Bayer) and additional compounds such as those disclosed in WO 96/40640 and WO 98/23593, (two exemplary publications). For example, the following MTP/Apo B secretion inhibitors are particularly useful: 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4,]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide; 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-acetylamino-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide; (2-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-ethyl)-carbamic acid methyl ester; 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide; 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,2-diphenyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide; 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-ethoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide; (S)-N-{2-[benzyl(methyl)amino]-2-oxo-1-phenylethyl}-1-methyl-5-[4'-(trifluoromethyl)[1,1'-biphenyl]-2-carboxamido]-1H-indole-2-carboxamide; (S)-2-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-quinoline-6-carboxy;ic acid (pentylcarbamoyl-phenyl-methyl)-amide; 1H-indole-2-carboxamide,1-methyl-N-[(1S)-2-[methyl(phenylmethyl)amino]-2-oxo-1-phenylethyl]-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]; and N-[(1S)-2-

(benzylmethylamino)-2-oxo-1-phenylethyl]-1-methyl-5-[[[4'-(thfluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indole-2-carboxamide.

**[00147]** Any HMG-CoA synthase inhibitor may be used in the combination aspect of this invention. The term HMG-CoA synthase inhibitor refers to compounds which inhibit the biosynthesis of hydroxymethylglutaryl-coenzyme A from acetyl-coenzyme A and acetoacetyl-coenzyme A, catalyzed by the enzyme HMG-CoA synthase. Such inhibition is readily determined by those skilled in the art according to standard assays (Meth. Enzymol., 35:155-160 (1975); Meth. Enzymol., 110:19-26 (1985) and references cited therein). A variety of these compounds are described and referenced below, however other HMG-CoA synthase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,120,729 discloses certain beta-lactam derivatives. U.S. Pat. No. 5,064,856 discloses certain spiro-lactone derivatives prepared by culturing a microorganism (MF5253). U.S. Pat. No. 4,847,271 discloses certain oxetane compounds such as 11-(3-hydroxymethyl-4-oxo-2-oxetayl)-3,5,7-trimethyl-2,4-undecadienoic acid derivatives.

**[00148]** Any compound that decreases HMG-CoA reductase gene expression may be used in the combination aspect of this invention. These agents may be HMG-CoA reductase transcription inhibitors that block the transcription of DNA or translation inhibitors that prevent or decrease translation of mRNA coding for HMG-CoA reductase into protein. Such compounds may either affect transcription or translation directly, or may be biotransformed to compounds that have the aforementioned activities by one or more enzymes in the cholesterol biosynthetic cascade or may lead to the accumulation of an isoprene metabolite that has the aforementioned activities. Such compounds may cause this effect by decreasing levels of SREBP (sterol receptor binding protein) by inhibiting the activity of site-1 protease (SIP) or agonizing the oxysterol receptor or SCAP. Such regulation is readily determined by those skilled in the art according to standard assays (Meth. Enzymol., 110:9-19 (1985)). Several compounds are described and referenced below, however other inhibitors of HMG-CoA reductase gene expression will be known to those skilled in the art. U.S. Pat. No. 5,041,432 discloses certain 15-substituted lanosterol derivatives. Other oxygenated sterols that suppress synthesis of HMG-CoA reductase are discussed by E.I. Mercer (Prog. Lip. Res., 32:357-416 (1993)).

**[00149]** Any compound having activity as a CETP inhibitor can serve as the second compound in the combination therapy aspect of the present invention. The term CETP inhibitor refers to compounds that inhibit the cholesteryl ester transfer protein (CETP) mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. Such CETP inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., U.S. Pat. No. 6,140,343). A variety of CETP inhibitors will be known to those skilled in the art, for example, those disclosed in U.S. Patent Nos. 6,140,343 and 6,197,786. CETP inhibitors disclosed in these patents include compounds, such as [2R,4S] 4-[(3,5-bis-trifluoromethylbenzyl)methoxycarbonylamino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (torcetrapib). CETP inhibitors are also described in U.S. Patent No. 6,723,752, which includes a number of CETP inhibitors including (2R)-3-{[3-(4-chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino}-1,1,1-trifluoro-2-propanol. Moreover, CETP inhibitors included herein are also described in U.S. Patent Application No. 10/807,838 and PCT Publication No. WO 2006/090250. U.S. Patent No. 5,512,548 discloses certain polypeptide derivatives having activity as CETP inhibitors, while certain CETP-inhibitory rosenonolactone derivatives and phosphate-containing analogs of cholesteryl ester are disclosed in J. Antibiot., 49(8):815-816 (1996), and Bioorg. Med. Chem. Lett., 6:1951-1954 (1996), respectively.

**[00150]** Any squalene synthetase inhibitor may be used in the combination aspect of this invention. The term squalene synthetase inhibitor refers to compounds which inhibit the condensation of 2 molecules of farnesylpyrophosphate to form squalene, catalyzed by the enzyme squalene synthetase. Such inhibition is readily determined by those skilled in the art according to standard assays (Meth. Enzymol., 15:393-454 (1969) and Meth. Enzymol., 110:359-373 (1985) and references contained therein). A variety of these compounds are described in and referenced below however other squalene synthetase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,026,554 discloses fermentation products of the microorganism MF5465 (ATCC 74011) including zaragozic acid. A summary of other patented squalene synthetase inhibitors has been compiled (Curr. Op. Ther. Patents, 861-864 (1993)).

**[00151]** Any squalene epoxidase inhibitor may be used in the combination aspect of this invention. The term squalene epoxidase inhibitor refers to compounds which inhibit the bioconversion of squalene and molecular oxygen into squalene-2,3-epoxide, catalyzed by the enzyme squalene epoxidase. Such inhibition is readily determined by those skilled in the art according to standard assays (Biochim. Biophys. Acta, 794:466-471 (1984)). A variety of these compounds are described and referenced below, however other squalene epoxidase inhibitors will be known to those skilled in the art. U.S. Pat. Nos. 5,011,859 and 5,064,864 disclose certain fluoro analogs of squalene. EP publication 395,768 A discloses certain substituted allylamine derivatives. PCT publication WO 93/12069 A discloses certain amino alcohol derivatives. U.S. Pat. No. 5,051,534 discloses certain cyclopropyloxy-squalene derivatives.

**[00152]** Any squalene cyclase inhibitor may be used as the second component in the combination aspect of this invention. The term squalene cyclase inhibiter refers to compounds which inhibit the bioconversion of squalene-2,3-epoxide to lanosterol, catalyzed by the enzyme squalene cyclase. Such inhibition is readily determined by those skilled in the art according to standard assays (FEBS Lett., 244:347-350 (1989)). In addition, the compounds described and referenced below are squalene cyclase inhibitors, however other squalene cyclase inhibitors will also be known to those skilled in the art. PCT publication WO 94/10150 discloses certain 1,2,3,5,6,7,8,8a-octahydro-5,5,8(beta)-trimethyl-6-isoquinolineamine derivatives, such as N-trifluoroacetyl-1,2,3,5,6,7,8,8a-octahydro-2-allyl-5,5,8(beta)-trimethyl-6(beta)-isoquinolineamine. French patent publication 2697250 discloses certain beta, beta-dimethyl-4-piperidine ethanol derivatives such as 1-(1,5,9-trimethyldecyl)-beta,beta-dimethyl-4-piperidineethanol.

**[00153]** Any combined squalene epoxidase/squalene cyclase inhibitor may be used as the second component in the combination aspect of this invention. The term combined squalene epoxidase/squalene cyclase inhibitor refers to compounds that inhibit the bioconversion of squalene to lanosterol via a squalene-2,3-epoxide intermediate. In some assays it is not possible to distinguish between squalene epoxidase inhibitors and squalene cyclase inhibitors, however, these assays are recognized by those skilled in the art. Thus, inhibition by combined squalene

epoxidase/squalene cyclase inhibitors is readily determined by those skilled in art according to the aforementioned standard assays for squalene cyclase or squalene epoxidase inhibitors. A variety of these compounds are described and referenced below, however other squalene epoxidase/squalene cyclase inhibitors will be known to those skilled in the art. U.S. Pat. Nos. 5,084,461 and 5,278,171 disclose certain azadecalin derivatives. EP publication 468,434 discloses certain piperidyl ether and thio-ether derivatives such as 2-(1-piperidyl)pentyl isopentyl sulfoxide and 2-(1-piperidyl)ethyl ethyl sulfide. PCT publication WO 94/01404 discloses certain acyl-piperidines such as 1-(1-oxopentyl-5-phenylthio)-4-(2-hydroxy-1-methyl)-ethyl)piperidine. U.S. Pat. No. 5,102,915 discloses certain cyclopropyloxy-squalene derivatives.

**[00154]** The compounds of the present invention may also be administered in combination with naturally occurring compounds that act to lower plasma LDL cholesterol levels or raise plasma HDL levels via a pathway distinct from CETP inhibitors. These naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract and niacin. Niacin is a particularly attractive secondary agent for combination with a CETP inhibitor as it also raises HDL cholesterol levels. Furthermore, niacin lowers LDL cholesterol and triglycerides. Therefore, a combination of niacin and a CETP inhibitor would not only provide the potential for enhanced HDL-raising efficacy, it would yield a very favorable shift in the overall cardiovascular risk profile by decreasing LDL cholesterol and triglycerides. Niacin is commercially available in various dosage forms. Immediate release niacin may be purchase over-the-counter in pharmacies or health-food stores. A slow-release form of niacin is available and is known as Niaspan. Niacin may also be combined with other therapeutic agents such as iovastatin, an HMG-CoA reductase inhibitor. This combination therapy with iovastatin is known as ADVICOR™ (Kos Pharmaceuticals Inc.). In long term clinical trials, niacin either as monotherapy or in combination with HMG-CoA reductase inhibitors has been shown to reduce cardiovascular events, cardiovascular deaths and all cause mortality.

**[00155]** Any cholesterol absorption inhibitor can be used as an additional component in the combination aspect of the present invention. The term cholesterol absorption inhibition refers to the ability of a compound to prevent cholesterol

contained within the lumen of the intestine from entering into the intestinal cells and/or passing from within the intestinal cells into the lymph system and/or into the blood stream. Such cholesterol absorption inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Lipid Res., 34:377-395 (1993)). Cholesterol absorption inhibitors are known to those skilled in the art and are described, for example, in PCT WO 94/00480. An example of a recently approved cholesterol absorption inhibitor is ZETIA™ (ezetimibe) (Schering-Plough/Merck).

**[00156]** Any ACAT inhibitor may be used in the combination therapy aspect of the present invention. The term ACAT inhibitor refers to compounds that inhibit the intracellular esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase. Such inhibition may be determined readily by one of skill in the art according to standard assays, such as the method of Heider et al. described in J. Lipid Res., 24:1127 (1983). A variety of these compounds are known to those skilled in the art, for example, U.S. Patent No. 5,510,379 discloses certain carboxysulfonates, while WO 96/26948 and WO 96/10559 both disclose urea derivatives having ACAT inhibitory activity. Examples of ACAT inhibitors include compounds such as Avasimibe (Pfizer), CS-505 (Sankyo) and Eflucimibe (Ell Lilly and Pierre Fabre).

**[00157]** A lipase inhibitor may be used in the combination therapy aspect of the present invention. A lipase inhibitor is a compound that inhibits the metabolic cleavage of dietary triglycerides or plasma phospholipids into free fatty acids and the corresponding glycerides (e.g. EL, HL, etc.). Under normal physiological conditions, lipolysis occurs via a two-step process that involves acylation of an activated serine moiety of the lipase enzyme. This leads to the production of a fatty acid-lipase hemiacetal intermediate, which is then cleaved to release a diglyceride. Following further deacylation, the lipase-fatty acid intermediate is cleaved, resulting in free lipase, a glyceride and fatty acid. In the intestine, the resultant free fatty acids and monoglycerides are incorporated into bile acid-phospholipid micelles, which are subsequently absorbed at the level of the brush border of the small intestine. The micelles eventually enter the peripheral circulation as chylomicrons. Such lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol. 286:190-231). Pancreatic lipase mediates the

metabolic cleavage of fatty acids from triglycerides at the 1- and 3-carbon positions. The primary site of the metabolism of ingested fats is in the duodenum and proximal jejunum by pancreatic tipase, which is usually secreted in vast excess of the amounts necessary for the breakdown of fats in the upper small intestine. Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions. Such pancreatic lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol. 286:190-231).

**[00158]** Gastric lipase is an immunologically distinct lipase that is responsible for approximately 10 to 40% of the digestion of dietary fats. Gastric lipase is secreted in response to mechanical stimulation, ingestion of food, the presence of a fatty meal or by sympathetic agents. Gastric lipolysis of ingested fats is of physiological importance in the provision of fatty acids needed to trigger pancreatic lipase activity in the intestine and is also of importance for fat absorption in a variety of physiological and pathological conditions associated with pancreatic insufficiency. See, for example, Abrams, C.K. et al., Gastroenterology, 92:125 (1987). Such gastric lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol., 286:190-231).

**[00159]** A variety of gastric and/or pancreatic lipase inhibitors are known to one of ordinary skill in the art. Preferred lipase inhibitors are those inhibitors that are selected from the group consisting of lipstatin, tetrahydrolipstatin (orlistat), valilactone, esterastin, ebelactone A, and ebelactone B. The compound tetrahydrolipstatin is especially preferred. The lipase inhibitor, N-3-trifluoromethylphenyl-N'-3-chloro-4'-trifluoromethylphenylurea, and the various urea derivatives related thereto, are disclosed in U.S. Patent No. 4,405,644. The lipase inhibitor, esteracin, is disclosed in U.S. Patent Nos. 4,189,438 and 4,242,453. The lipase inhibitor, cyclo-O,O'-[(1,6-hexanediyl)-bis-(iminocarbonyl)]dioxime, and the various bis(iminocarbonyl)dioximes related thereto may be prepared as described in Petersen et al., Liebig's Annalen, 562:205-229 (1949).

**[00160]** A variety of pancreatic lipase inhibitors are described herein below. The pancreatic lipase inhibitors lipstatin, (2S, 3S, 5S, 7Z, 10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-7,10-hexadecanoic acid lactone, and

tetrahydrolipstatin (orlistat), (2S, 3S, 5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexadecanoic 1,3 acid lactone, and the variously substituted N-formylleucine derivatives and stereoisomers thereof, are disclosed In U.S. Patent No. 4,598,089. For example, tetrahydrolipstatin is prepared as described in, e.g., U.S. Patent Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874. The pancreatic lipase inhibitor, FL-386, 1-[4-(2-methylpropyl)cyclohexyl]-2-[(phenylsulfonyl)oxy]ethanone, and the variously substituted sulfonate derivatives related thereto, are disclosed in U.S. Patent No. 4,452,813. The pancreatic lipase inhibitor, WAY-121898, 4-phenoxyphenyl-4-methylpiperidin-l-yl-carboxylate, and the various carbamate esters and pharmaceutically acceptable salts related thereto, are disclosed in U.S. Patent Nos. 5,512,565; 5,391,571 and 5,602,151. The pancreatic lipase inhibitor, valilactone, and a process for the preparation thereof by the microbial cultivation of *Actinomycetes* strain MG147-CF2, are disclosed in Kitahara, et al., J. Antibiotics, 40(11):1647-1650 (1987). The pancreatic lipase inhibitors, ebelactone A and ebelactone B, and a process for the preparation thereof by the microbial cultivation of *Actinomycetes* strain MG7-G1, are disclosed in Umezawa et al., J. Antibiotics, 33:1594-1596 (1980). The use of ebelactones A and B in the suppression of monoglyceride formation is disclosed in Japanese Kokai 08-143457, published June 4, 1996.

**[00161]** Other compounds that are marketed for hyperlipidemia, including hypercholesterolemia and which are intended to help prevent or treat atherosclerosis include bile acid sequestrants, such as Welchol®, Colestid®, LoCholest® and Questran®; and fibric acid derivatives, such as Atromid®, Lopid® and Tricot®.

**[00162]** Diabetes can be treated by administering to a patient having diabetes (especially Type II), insulin resistance, impaired glucose tolerance, metabolic syndrome, or the like, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a compound of the present invention in combination with other agents (e.g., insulin) that can be used to treat diabetes. This includes the classes of anti-diabetic agents (and specific agents) described herein.

**[00163]** Any glycogen phosphorylase inhibitor can be used as the second agent in combination with a compound of the present invention. The term glycogen

phosphorylase inhibitor refers to compounds that inhibit the bioconversion of glycogen to glucose-1-phosphate which is catalyzed by the enzyme glycogen phosphorylase. Such glycogen phosphorylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Med. Chem. 41:2934-2938 (1998)). A variety of glycogen phosphorylase inhibitors are known to those skilled in the art including those described in WO 96/39384 and WO 96/39385.

**[00164]** Any aldose reductase inhibitor can be used in combination with a compound of the present invention. The term aldose reductase inhibitor refers to compounds that inhibit the bioconversion of glucose to sorbitol, which is catalyzed by the enzyme aldose reductase. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (e.g., J. Malone, "Red Celt Sorbitol, an Indicator of Diabetic Control", Diabetes, 29:861-864 (1980)). A variety of aldose reductase inhibitors are known to those skilled in the art, such as those described in U.S. Patent No. 6,579,879, which includes 6-(5-chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one.

**[00165]** Any sorbitol dehydrogenase inhibitor can be used in combination with a compound of the present invention. The term sorbitol dehydrogenase inhibitor refers to compounds that inhibit the bioconversion of sorbitol to fructose which is catalyzed by the enzyme sorbitol dehydrogenase. Such sorbitol dehydrogenase inhibitor activity is readily determined by those skilled in the art according to standard assays (e.g., Analyt. Biochem., 280:329-331 (2000)). A variety of sorbitol dehydrogenase inhibitors are known, for example, U.S. Patent Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

**[00166]** Any glucosidase inhibitor can be used in combination with a compound of the present invention. A glucosidase inhibitor inhibits the enzymatic hydrolysis of complex carbohydrates by glycoside hydrolases, for example amylase or maltase, into bioavailable simple sugars, for example, glucose. The rapid metabolic action of glucosidases, particularly following the intake of high levels of carbohydrates, results in a state of alimentary hyperglycemia which, in adipose or diabetic subjects, leads to enhanced secretion of insulin, increased fat synthesis and a reduction in fat

degradation. Following such hyperglycemias, hypoglycemia frequently occurs, due to the augmented levels of insulin present. Additionally, it is known chyme remaining in the stomach promotes the production of gastric juice, which initiates or favors the development of gastritis or duodenal ulcers. Accordingly, glucosidase inhibitors are known to have utility in accelerating the passage of carbohydrates through the stomach and inhibiting the absorption of glucose from the intestine. Furthermore, the conversion of carbohydrates into lipids of the fatty tissue and the subsequent incorporation of alimentary fat into fatty tissue deposits is accordingly reduced or delayed, with the concomitant benefit of reducing or preventing the deleterious abnormalities resulting therefrom. Such glucosidase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Biochemistry, 8:4214 (1969)). A generally preferred glucosidase inhibitor includes an amylase inhibitor. An amylase inhibitor is a glucosidase inhibitor that inhibits the enzymatic degradation of starch or glycogen into maltose. Such amylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Meth. Enzymol., 1:149 (1955)). The inhibition of such enzymatic degradation is beneficial in reducing amounts of bioavailable sugars, including glucose and maltose, and the concomitant deleterious conditions resulting therefrom.

**[00167]** A variety of glucosidase inhibitors are known to one of ordinary skill in the art and examples are provided below. Preferred glucosidase inhibitors are those inhibitors that are selected from the group consisting of acarbose, adiposine, voglibose, miglitol, emiglitate, camiglibose, tendamistate, trestatin, pradimicin-Q and salbostatin. The glucosidase inhibitor, acarbose, and the various amino sugar derivatives related thereto are disclosed in U.S. Patent Nos. 4,062,950 and 4,174,439 respectively. The glucosidase inhibitor, adiposine, is disclosed in U.S. Patent No. 4,254,256. The glucosidase inhibitor, voglibose, 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epi-inositol and the various N-substituted pseudo-aminosugars related thereto, are disclosed in U.S. Patent No. 4,701,559. The glucosidase inhibitor, miglitol, (2R,3R,4R,5S)-1-(2-hydroxyethyl)-2-(hydroxymethyl)-3,4,5-piperidinetriol, and the various 3,4,5-trihydroxypiperidines related thereto, are disclosed in U.S. Patent No. 4,639,436. The glucosidase inhibitor, emiglitate, ethyl p-[2-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-

(hydroxymethyl)piperidino]ethoxy]-benzoate, the various derivatives related thereto and pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Patent No. 5,192,772. The glucosidase inhibitor, MDL-25637, 2,6-dideoxy-7-O-β-D-glucopyrano-syl-2,6-imino-D-glycero-L-gluco-heptitol, the various homodisaccharides related thereto and the pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Patent No. 4,634,765. The glucosidase inhibitor, camiglibose, methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxymethyl)piperidino]-(α-D-glucopyranoside sesquihydrate, the deoxy-nojirimycin derivatives related thereto, the various pharmaceutically acceptable salts thereof and synthetic methods for the preparation thereof, are disclosed in U.S. Patent Nos. 5,157,116 and 5,504,078. The glycosidase inhibitor, salbostatin and the various pseudosaccharides related thereto, are disclosed In U.S. Patent No. 5,091,524.

**[00168]** A variety of amylase inhibitors are known to one of ordinary skill in the art. The amylase inhibitor, tendamistat and the various cyclic peptides related thereto, are disclosed in U.S. Patent No. 4,451,455. The amylase inhibitor AI-3688 and the various cyclic polypeptides related thereto are disclosed in U.S. Patent No. 4,623,714. The amylase inhibitor, trestatin, consisting of a mixture of trestatin A, trestatin B and trestatin C and the various trehalose-containing aminosugars related thereto are disclosed in U.S. Patent No. 4,273,765.

**[00169]** Additional anti-diabetic compounds, which can be used as the second agent in combination with a compound of the present invention, include, for example, the following: biguanides (e.g., metformin), insulin secretagogues (e.g., sulfonylureas and glinides), glitazones, non-glitazone PPARγ agonists, PPARβ agonists, inhibitors of DPP-IV, inhibitors of PDE5, inhibitors of GSK-3, glucagon antagonists, inhibitors of f-1,6-BPase(Metabasis/Sankyo), GLP-1/analogs (AC 2993, also known as exendin-4), insulin and insulin mimetics (Merck natural products). Other examples would include PKC-β inhibitors and AGE breakers.

**[00170]** The compounds of the present invention can be used in combination with anti-obesity agents. Any anti-obesity agent can be used as the second agent in such combinations and examples are provided herein. Such anti-obesity activity is readily determined by those skilled in the art according to standard assays known in the art.

**[00171]** Suitable anti-obesity agents include phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, $\beta_3$ adrenergic receptor agonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4-agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (e.g., sibutramine), sympathomimetic agents, serotoninergic agents, cannabinoid receptor (CB-1) antagonists (e.g., rimonabant described in U.S. Pat. No. 5,624,941 (SR-141,716A), purine compounds, such as those described in US Patent Publication No. 2004/0092520; pyrazolo[1,5-a][1,3,5]triazine compounds, such as those described in US Non-Provisional Patent Application No. 10/763,105; and bicyclic pyrazolyl and imidazolyl compounds, such as those described in U.S. Provisional Application No. 60/518,280, dopamine agonists (e.g., bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (e.g., tetrahydrolipstatin, i.e. orlistat), bombesin agonists, anorectic agents (e.g., a bombesin agonist), Neuropeptide-Y antagonists, thyroxine, thyromimetic agents, dehydroepiandrosterones or analogs thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (e.g., Axokine™), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists, and the like. Rimonabant (SR-141,716A also known under the trade name Acomplia™ available from Sanofi-Aventis) can be prepared as described in U.S. Patent No. 5,624,941. Other suitable CB-1 antagonists include those described in U.S. Patent Nos. 5,747,524, 6,432,984 and 6,518,264; U.S. Patent Publication Nos. US2004/0092520, US2004/0157839, US2004/0214855, and US2004/0214838; U.S. Patent Application Serial No. 10/971,599; and PCT Patent Publication Nos. WO 02/076949, WO 031075660, WO 04/048317, WO 04/013120, and WO 04/012671.

**[00172]** Preferred apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors for use as anti-obesity agents are gut-selective MTP inhibitors, such as dirlotapide described in U.S. Patent No. 6,720,351; 4-(4-(4-(4-((2-((4-methyl-4H-1,2,4-triazol-3-ylthio)methyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-

yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-sec-butyl-2H-1,2,4-triazol-3(4H)-one (R103757) described in U.S. Patent Nos. 5,521,186 and 5,929,075; and implitapide (BAY 13-9952) described in U.S. Patent No. 6,265,431. As used herein, the term "gut-selective" means that the MTP Inhibitor has a higher exposure to the gastro-intestinal tissues versus systemic exposure.

**[00173]** Any thyromimetic can be used as the second agent in combination with a compound of the present Invention. Such thyromimetic activity is readily determined by those skilled in the art according to standard assays (e.g., Atherosclerosis, 126: 53-63 (1996)). A variety of thyromimetic agents are known to those skilled in the art, for example those disclosed in U.S. Patent Nos. 4,766,121 ; 4,826,876; 4,910,305; 5,061,798; 5,284,971; 5,401,772; 5,654,468; and 5,569,674. Other antiobesity agents include sibutramine which can be prepared as described in U.S. Patent No. 4,929,629 and bromocriptine which can be prepared as described in U.S. Patent Nos. 3,752,814 and 3,752,888.

**[00174]** The compounds of the present invention can also be used in combination with other antihypertensive agents. Any anti-hypertensive agent can be used as the second agent in such combinations and examples are provided herein. Such antihypertensive activity is readily determined by those skilled in the art according to standard assays (e.g., blood pressure measurements).

**[00175]** Examples of presently marketed products containing antihypertensive agents include calcium channel blockers, such as Cardizem®, Adalat®, Calan®, Cardene®, Covera®, Dilacor®, DynaCirc®, Procardia XL®, Sular®, Tiazac®, Vascor®, Verelan®, Isoptin®, Nimotop®, Norvasc®, and Plendile; angiotensin converting enzyme (ACE) inhibitors, such as Accupril®, Altace®, Captopril®, Lotensin®, Mavik®, Monopril®, Prinivil®, Univasc®, Vasotec® and Zestril®.

**[00176]** Amlodipine and related dihydropyridine compounds are disclosed in U.S. Patent No. 4,572,909, as potent anti-ischemic and antihypertensive agents. U.S. Patent No. 4,879,303 discloses amlodipine benzenesulfonate salt (also termed amlodipine besylate). Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine, amlodipine besylate, amlodipine maleate and other pharmaceutically acceptable acid addition salts of amlodipine have

utility as antihypertensive agents and as antiischemic agents. Amlodipine besylate is currently sold as Norvasc®.

**[00177]** Calcium channel blockers which are within the scope of this invention include, but are not limited to: bepridil, which may be prepared as disclosed in U.S. Patent No. 3,962, 238 or U.S. Reissue No. 30,577; clentiazem, which may be prepared as disclosed in U.S. Patent No. 4,567,175; diltiazem, fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; gallopamil, which may be prepared as disclosed in U.S. Patent No. 3,261,859; mibefradil, which may be prepared as disclosed in U.S. Patent No. 4,808,605; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; semotiadil, which may be prepared as disclosed in U.S. Patent No. 4,786,635; terodiline, which may be prepared as disclosed in U.S. Patent No. 3,371,014; verapamil, which may be prepared as disclosed in U.S. Patent No. 3,261,859; aranipine, which may be prepared as disclosed in U.S. Patent No. 4,572,909; barnidipine, which may be prepared as disclosed in U.S. Patent No. 4,220,649; benidipine, which may be prepared as disclosed in European Patent Application Publication No. 106,275; cilnidipine, which may be prepared as disclosed in U.S. Patent No. 4,672,068; efonidipine, which may be prepared as disclosed in U.S, Patent No.4,885,284; elgodipine, which may be prepared as disclosed in U.S. Patent No. 4,952,592; felodipine, which may be prepared as disclosed in U.S. Patent No. 4,264,611; isradipine, which may be prepared as disclosed in U.S. Patent No. 4,466,972; lacidipine, which may be prepared as disclosed in U.S. Patent No. 4,801,599; lercanidipine, which may be prepared as disclosed in U.S. Patent No. 4,705,797; manidipine, which may be prepared as disclosed in U.S. Patent No. 4,892,875; nicardipine, which may be prepared as disclosed in U.S. Patent No. 3,985,758; nifedipine, which may be prepared as disclosed in U.S. Patent No. 3,485,847; nilvadipine, which may be prepared as disclosed in U.S. Patent No. 4,338,322; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; nisoldipine, which may be prepared as disclosed in U.S. Patent No. 4,154,839; nitrendipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; cinnarizine, which may be prepared as disclosed in U.S. Patent No. 2,882,271; flunarizine, which may be prepared as disclosed in U.S. Patent No. 3,773,939; lidoflazine, which may be

prepared as disclosed in U.S. Patent No. 3,267,104; Iomerizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; bencyclane, which may be prepared as disclosed in Hungarian Patent No. 151,865; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; and perhexiline, which may be prepared as disclosed in British Patent No. 1,025,578.

**[00178]** Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be prepared as disclosed in U.S. Patent No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Patent No, 4,410,520; captopril, which may be prepared as disclosed in U.S. Patent Nos. 4,046,889 and 4,105,776; ceronapril, which may be prepared as disclosed in U.S. Patent No. 4,462,790; delapril, which may be prepared as disclosed in U.S. Patent No. 4,385,051; enalapril, which may be prepared as disclosed in U.S. Patent No. 4,374,829; fosinopril, which may be prepared as disclosed in U.S. Patent No. 4,337,201; imadapril, which may be prepared as disclosed in U.S. Patent No. 4,508,727; lisinopril, which may be prepared as disclosed in U.S. Patent No. 4,555,502; moveltopril, which may be prepared as disclosed in Belgian Patent No. 893,553; perindopril, which may be prepared as disclosed in U.S. Patent No. 4,508,729; quinapril, which may be prepared as disclosed in U.S. Patent No. 4,344,949; ramipril, which may be prepared as disclosed in U.S. Patent No. 4,587,258; spirapril, which may be prepared as disclosed in U.S. Patent No. 4,470,972; temocapril, which may be prepared as disclosed in U.S. Patent No. 4,699,905; and trandolapril, which may be prepared as disclosed in U.S. Patent No. 4,933,361.

**[00179]** Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan, which may be prepared as disclosed in U.S. Patent No. 5,196,444; eprosartan, which may be prepared as disclosed in U.S. Patent No. 5,185,351; irbesartan, which may be prepared as disclosed in U.S. Patent No. 5,270,317; Iosartan, which may be prepared as disclosed in U.S, Patent No. 5,138,069; and valsartan, which may be prepared as disclosed in U.S. Patent No. 5,399,578.

**[00180]** Beta-adrenergic receptor blockers (beta- or β-blockers) which are within the scope of this invention include, but are not limited to: acebutolol, which may be

prepared as disclosed in U.S. Patent No. 3,857,952; alprenolol, which may be prepared as disclosed in Netherlands Patent Application No. 6,605,692; amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,305; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; atenolol, which may be prepared as disclosed in U.S. Patent No. 3,663,607 or 3,836,671 ; befunolol, which may be prepared as disclosed in U.S. Patent No. 3,853,923; betaxolol, which may be prepared as disclosed in U.S. Patent No. 4,252,984; bevantolol, which may be prepared as disclosed in U.S. Patent No. 3,857,981; bisoprolol, which may be prepared as disclosed in U.S. Patent No. 4,171,370; bopindolol, which may be prepared as disclosed in U.S. Patent No. 4,340,541; bucumolol, which may be prepared as disclosed in U.S. Patent No. 3,663,570; bufetolol, which may be prepared as disclosed in U.S. Patent No. 3,723,476; bufuralol, which may be prepared as disclosed in U.S. Patent No. 3,929,836; bunitrolol, which may be prepared as disclosed in U.S. Patent Nos. 3,940,489 and 3,961,071; buprandolol, which may be prepared as disclosed in U.S. Patent No. 3,309,406; butiridine hydrochloride, which may be prepared as disclosed in French Patent No. 1,390,056; butofilolol, which may be prepared as disclosed in U.S. Patent No. 4,252,825; carazolol, which may be prepared as disclosed in German Patent No. 2,240,599; carteolol, which may be prepared as disclosed in U.S. Patent No. 3,910,924; carvedilol, which may be prepared as disclosed in U.S. Patent No. 4,503,067; celiprolol, which may be prepared as disclosed in U.S. Patent No. 4,034,009; cetamolol, which may be prepared as disclosed in U.S. Patent No. 4,059,622; cloranolol, which may be prepared as disclosed in German Patent No. 2,213,044; dilevalol, which may be prepared as disclosed in Clifton et al., J. Med. Chem., 25:670 (1982); epanolol, which may be prepared as disclosed in European Patent Publication Application No. 41,491; indenolol, which may be prepared as disclosed in U.S. Patent No. 4,045,482; labetalol, which may be prepared as disclosed in U.S. Patent No. 4,012,444; levobunolol, which may be prepared as disclosed in U.S. Patent No. 4,463,176; mepindolol, which may be prepared as disclosed in Seeman et al., Heir. Chim. Acta, 54:241 (1971); metipranolol, which may be prepared as disclosed in Czechoslovakian Patent Application No. 128,471; metoprolol, which may be prepared as disclosed in U.S. Patent No. 3,873,600; moprolol, which may be prepared as disclosed in U.S.

Patent No. 3,501,7691; nadolol, which may be prepared as disclosed in U.S. Patent No. 3,935, 267; nadoxolol, which may be prepared as disclosed in U.S. Patent No. 3,819,702; nebivalol, which may be prepared as disclosed in U.S. Patent No. 4,654,362; nipradilol, which may be prepared as disclosed in U.S. Patent No. 4,394,382; oxprenolol, which may be prepared as disclosed in British Patent No. 1,077,603; perbutolol, which may be prepared as disclosed in U.S. Patent No. 3,551,493; pindolol, which may be prepared as disclosed in Swiss Patent Nos. 469,002 and 472,404; practolol, which may be prepared as disclosed in U.S. Patent No. 3,408,387; pronethalol, which may be prepared as disclosed in British Patent No. 909,357; propranolol, which may be prepared as disclosed in U.S. Patent Nos. 3,337,628 and 3,520,919; sotalol, which may be prepared as disclosed in Uloth et al., J. Med. Chem., 9:88 (1966); sufinalol, which may be prepared as disclosed in German Patent No. 2,728,641; talindol, which may be prepared as disclosed in U.S. Patent Nos. 3,935,259 and 4,038,313; tertatolol, which may be prepared as disclosed in U.S. Patent No. 3,960,891; tilisolol, which may be prepared as disclosed in U.S. Patent No. 4,129,565; timolol, which may be prepared as disclosed in U.S. Patent No. 3,655,663; toliprolol, which may be prepared as disclosed in U.S. Patent No. 3,432,545; and xibenolol, which may be prepared as disclosed in U.S. Patent No. 4,018,824.

**[00181]** Alpha-adrenergic receptor blockers (alpha- or α-blockers) which are within the scope of this invention include, but are not limited to: amosulalol, which may be prepared as disclosed in U.S. Patent No. 4,217,307; arotinolol, which may be prepared as disclosed in U.S. Patent No. 3,932,400; dapiprazole, which may be prepared as disclosed in U.S. Patent No. 4,252,721; doxazosin, which may be prepared as disclosed in U.S. Patent No. 4,188,390; fenspiride, which may be prepared as disclosed in U.S. Patent No. 3,399,192; indoramin, which may be prepared as disclosed in U.S. Patent No. 3,527,761; labetolol; naftopidil, which may be prepared as disclosed in U.S. Patent No. 3,997,666; nicergoline, which may be prepared as disclosed in U.S. Patent No. 3,228,943; prazosin, which may be prepared as disclosed in U.S. Patent No, 3,511,836; tamsulosin, which may be prepared as disclosed in U.S. Patent No. 4,703,063; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; trimazosin, which may be prepared as

disclosed in U.S. Patent No. 3,669,968; and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art.

**[00182]** The term "vasodilator," where used herein, is meant to include cerebral vasodilators, coronary vasodilators and peripheral vasodilators. Cerebral vasodilators within the scope of this invention include, but are not limited to: bencyclane; cinnarizine; citicoline, which may be isolated from natural sources as disclosed in Kennedy et al., J. Am. Chem. Soc., 77:250 (1955) or synthesized as disclosed in Kennedy, J. Biol. Chem., 222:185 (1956); cyclandelate, which may be prepared as disclosed in U.S. Patent No. 3,663,597; ciclonicate, which may be prepared as disclosed in German Patent No, 1,910,481; diisopropylamine dichloroacetate, which may be prepared as disclosed in British Patent No. 862,248; eburnamonine, which may be prepared as disclosed in Hermann et al., J. Am. Chem. Soc., 101:1540 (1979); fasudil, which may be prepared as disclosed in U.S. Patent No. 4,678,783; fenoxedil, which may be prepared as disclosed in U.S. Patent No. 3,818,021; flunarizine, which may be prepared as disclosed in U.S. Patent No, 3,773,939; ibudilast, which may be prepared as disclosed in U.S. Patent No. 3,850,941; ifenprodil, which may be prepared as disclosed in U.S. Patent No. 3,509,164; Iomerizine, which may be prepared as disclosed in U.S. Patent No. 4,663,325; nafronyl, which may be prepared as disclosed in U.S. Patent No. 3,334,096; nicametate, which may be prepared as disclosed in Blicke et al., J. Am. Chem. Soc., 64:1722 (1942); nicergoline, which may be prepared as disclosed above; nimodipine, which may be prepared as disclosed in U.S. Patent No. 3,799,934; papaverine, which may be prepared as reviewed in Goldberg, Chem. Prod. Chem. News, 17:371 (1954); pentifylline, which may be prepared as disclosed in German Patent No. 860,217; tinofedrine, which may be prepared as disclosed in U.S. Patent No. 3,563,997; vincamine, which may be prepared as disclosed in U.S. Patent No. 3,770,724; vinpocetine, which may be prepared as disclosed in U.S. Patent No. 4,035,750; and viquidil, which may be prepared as disclosed in U.S. Patent No. 2,500,444.

**[00183]** Coronary vasodilators within the scope of this invention include, but are not limited to: amotriphene, which may be prepared as disclosed in U.S. Patent No. 3,010,965; bendazol, which may be prepared as disclosed in J. Chem. Soc., 2426 (1958); benfurodil hemisuccinate, which may be prepared as disclosed in U.S. Patent

No. 3,355,463; benziodarone, which may be prepared as disclosed in U.S. Patent No. 3,012,042; chloracizine, which may be prepared as disclosed in British Patent No. 740,932; chromonar, which may be prepared as disclosed in U.S. Patent No, 3,282,938; clobenfural, which may be prepared as disclosed in British Patent No. 1,160,925; clonitrate, which may be prepared from propanediol according to methods well known to those skilled in the art, e.g., see Annalen, 1870, 155, 165; cloricromen, which may be prepared as disclosed in U.S. Patent No. 4,452,811; dilazep, which may be prepared as disclosed in U.S. Patent No. 3,532,685; dipyridamole, which may be prepared as disclosed in British Patent No. 807,826; droprenilamine, which may be prepared as disclosed in German Patent No. 2,521,113; efloxate, which may be prepared as disclosed in British Patent Nos. 803,372 and 824,547; erythrityl tetranitrate, which may be prepared by nitration of erythritol according to methods well-known to those skilled in the art; etafenone, which may be prepared as disclosed in German Patent No. 1,265,758; fendiline, which may be prepared as disclosed in U.S. Patent No. 3,262,977; floredil, which may be prepared as disclosed in German Patent No. 2,020,464; ganglefene, which may be prepared as disclosed in U.S.S.R. Patent No. 115,905; hexestrol, which may be prepared as disclosed in U.S. Patent No. 2,357,985; hexobendine, which may be prepared as disclosed in U.S. Patent No. 3,267,103; itramin tosylate, which may be prepared as disclosed in Swedish Patent No. 168,308; khellin, which may be prepared as disclosed in Baxter et al., J. Chem. Soc., 1949, S 30; lidoflazine, which may be prepared as disclosed in U.S. Patent No. 3,267,104; mannitol hexanitrate, which may be prepared by the nitration of mannitol according to methods well-known to those skilled in the art; medibazine, which may be prepared as disclosed in U.S. Patent No. 3,119,826; nitroglycerin; pentaerythritol tetranitrate, which may be prepared by the nitration of pentaerythritol according to methods well-known to those skilled in the art; pentrinitrol, which may be prepared as disclosed in German Patent No. 638,422-3; perhexilline, which may be prepared as disclosed above; pimefylline, which may be prepared as disclosed in U.S. Patent No. 3,350,400; prenylamine, which may be prepared as disclosed in U.S. Patent No. 3,152,173; propatyl nitrate, which may be prepared as disclosed in French Patent No. 1,103,113; trapidil, which may be prepared as disclosed in East German Patent No. 55,956; tricromyl, which may be prepared as disclosed in U.S. Patent No. 2,769,015;

trimetazidine, which may be prepared as disclosed in U.S. Patent No. 3,262,852; trolnitrate phosphate, which may be prepared by nitration of triethanolamine followed by precipitation with phosphoric acid according to methods well-known to those skilled in the art; visnadine, which may be prepared as disclosed in U.S. Patent Nos. 2,816,118 and 2,980,699.

**[00184]** Peripheral vasodilators within the scope of this invention include, but are not limited to: aluminum nicotinate, which may be prepared as disclosed in U.S. Patent No. 2,970,082; bamethan, which may be prepared as disclosed in Corrigan et al., J. Am. Chem. Soc., 67:1894 (1945); bencyclane, which may be prepared as disclosed above; betahistine, which may be prepared as disclosed in Walter et al., J. Am. Chem. Soc., 63:2771 (1941); bradykinin, which may be prepared as disclosed in Hamburg et al., Arch. Biochem. Biophys., 76:252 (1958); brovincamine, which may be prepared as disclosed in U.S. Patent No. 4,146,643; bufeniode, which may be prepared as disclosed in U.S. Patent No. 3,542,870; buflomedil, which may be prepared as disclosed in U.S. Patent No. 3,895,030; butalamine, which may be prepared as disclosed in U.S. Patent No. 3,338,899; cetiedil, which may be prepared as disclosed in French Patent No. 1,460,571; ciclonicate, which may be prepared as disclosed in German Patent No, 1,910,481; cinepazide, which may be prepared as disclosed in Belgian Patent No. 730,345; cinnarizine, which may be prepared as disclosed above; cyclandelate, which may be prepared as disclosed above; diisopropylamine dichloroacetate, which may be prepared as disclosed above; eledoisin, which may be prepared as disclosed in British Patent No. 984,810; fenoxedil, which may be prepared as disclosed above; flunarizine, which may be prepared as disclosed above; hepronicate, which may be prepared as disclosed in U.S. Patent No. 3,384,642; ifenprodil, which may be prepared as disclosed above; iloprost, which may be prepared as disclosed in U.S. Patent No. 4,692,464; inositol niacinate, which may be prepared as disclosed in Badgett et al., J. Am. Chem. Soc., 69:2907 (1947); isoxsuprine, which may be prepared as disclosed in U.S. Patent No. 3,056,836; kallidin, which may be prepared as disclosed in Biochem. Biophys. Res. Commun., 6:210 (1961); kallikrein, which may be prepared as disclosed in German Patent No. 1,102,973; moxisylyte, which may be prepared as disclosed in German Patent No. 905,738; nafronyl, which may be prepared as disclosed above; nicametate,

which may be prepared as disclosed above; nicergoline, which may be prepared as disclosed above; nicofuranose, which may be prepared as disclosed in Swiss Patent No. 366,523; nylidrin, which may be prepared as disclosed in U.S. Patent Nos. 2,661,372 and 2,661,373; pentifylline, which may be prepared as disclosed above; pentoxifylline, which may be prepared as disclosed in U.S. Patent No, 3,422,107; piribedil, which may be prepared as disclosed in U.S. Patent No. 3,299,067; prostaglandin $E_1$, which may be prepared by any of the methods referenced in the Merck Index, Twelfth Edition, Budaveri, Ed., New Jersey, p. 1353 (1996); suloctidil, which may be prepared as disclosed in German Patent No. 2,334,404; tolazoline, which may be prepared as disclosed in U.S. Patent No. 2,161,938; and xanthinol niacinate, which may be prepared as disclosed in German Patent No. 1,102,750.

**[00185]** The term "diuretic," within the scope of this invention, is meant to include diuretic benzothiadiazine derivatives, diuretic organomercurials, diuretic purines, diuretic steroids, diuretic sulfonamide derivatives, diuretic uracils and other diuretics such as amanozine, which may be prepared as disclosed in Austrian Patent No. 168,063; amiloride, which may be prepared as disclosed in Belgian Patent No. 639,386; arbutin, which may be prepared as disclosed in Tschitschibabin, Annalen, 1930, 479, 303; chlorazanil, which may be prepared as disclosed in Austrian Patent No. 168,063; ethacrynic acid, which may be prepared as disclosed in U.S. Patent No. 3,255,241; etozolin, which may be prepared as disclosed in U.S. Patent No. 3,072,653; hydracarbazine, which may be prepared as disclosed in British Patent No. 856,409; isosorbide, which may be prepared as disclosed in U.S. Patent No. 3,160,641; mannitol; metochalcone, which may be prepared as disclosed in Freudenberg et al., Ber., 1957, 90, 957; muzolimine, which may be prepared as disclosed in U.S. Patent No. 4,018,890; perhexiline, which may be prepared as disclosed above; ticrynafen, which may be prepared as disclosed in U.S. Patent No. 3,758,506; triamterene which may be prepared as disclosed in U.S. Patent No. 3,051,230; and urea.

**[00186]** Diuretic benzothiadiazine derivatives within the scope of this invention include, but are not limited to: althiazide, which may be prepared as disclosed in British Patent No. 902,658; bendroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,265,573; benzthiazide, McManus et al., 136th Am. Soc. Meeting

(Atlantic City, September 1959), Abstract of papers, pp 13-O; benzylhydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,108,097; buthiazide, which may be prepared as disclosed in British Patent Nos. 861,367 and 885,078; chlorothiazide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194 and 2,937,169; chlorthalidone, which may be prepared as disclosed in U.S. Patent No. 3,055,904; cyclopenthiazide, which maybe prepared as disclosed in Belgian Patent No. 587,225; cyclothiazide, which may be prepared as disclosed in Whitehead et al., J. Org. Chem., 26:2814 (1961); epithiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; ethiazide, which may be prepared as disclosed in British Patent No. 861,367; fenquizone, which may be prepared as disclosed in U.S. Patent No. 3,870,720; indapamide, which may be prepared as disclosed in U.S. Patent No. 3,565,911; hydrochlorothiazide, which may be prepared as disclosed in U.S. Patent No. 3,164,588; hydroflumethiazide, which may be prepared as disclosed in U.S. Patent No. 3,254,076; methyclothiazide, which may be prepared as disclosed in Close et al, J. Am. Chem. Soc., 82:1132 (1960); meticrane, which may be prepared as disclosed in French Patent Nos. M2790 and 1,365,504; metolazone, which may be prepared as disclosed in U.S. Patent No. 3,360,518; paraflutizide, which may be prepared as disclosed in Belgian Patent No. 620,829; polythiazide, which may be prepared as disclosed in U.S. Patent No. 3,009,911; quinethazone, which may be prepared as disclosed in U.S. Patent No. 2,976,289; teclothiazide, which may be prepared as disclosed in Close et al., J. Am. Chem. Soc., 82:1132 (1960); and trichlormethiazide, which may be prepared as disclosed in deStevens et al., Experientia, 16:113 (1960).

**[00187]** Diuretic sulfonamide derivatives within the scope of this invention include, but are not limited to: acetazolamide, which may be prepared as disclosed in U.S. Patent No. 2,980,679; ambuside, which may be prepared as disclosed in U.S. Patent No. 3,188,329; azosemide, which may be prepared as disclosed in U.S. Patent No. 3,665,002; bumetanide, which may be prepared as disclosed in U.S. Patent No. 3,634,583; butazolamide, which may be prepared as disclosed in British Patent No. 769,757; chloraminophenamide, which may be prepared as disclosed in U.S. Patent Nos. 2,809,194, 2,965,655 and 2,965,656; clofenamide, which may be prepared as disclosed in Olivier, Rec. Trav. Chim., 1918, 37, 307; clopamide, which may be

prepared as disclosed in U.S. Patent No. 3,459,756; clorexolone, which may be prepared as disclosed in U.S. Patent No. 3,183,243; disulfamide, which may be prepared as disclosed in British Patent No. 851,287; ethoxolamide, which may be prepared as disclosed in British Patent No. 795,174; furosemide, which may be prepared as disclosed in U.S. Patent No. 3,058,882; mefruside, which may be prepared as disclosed in U.S. Patent No. 3,356,692; methazolamide, which may be prepared as disclosed in U.S. Patent No. 2,783,241; piretanide, which may be prepared as disclosed in U.S. Patent No. 4,010,273; torasemide, which may be prepared as disclosed in U.S. Patent No. 4,018,929; tripamide, which may be prepared as disclosed in Japanese Patent No. 73 05,585; and xipamide, which may be prepared as disclosed in U.S. Patent No. 3,567,777.

**[00188]** Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture, in the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated. The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly within the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study has estimated that there will be 4.5 million hip fractures worldwide in 2050. Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

**[00189]** Those skilled in the art will recognize that anti-resorptive agents (for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin®, estrone, estriol or 17α- or 17β-ethynyl estradiol) may be used in conjunction with the compounds of the present invention.

**[00190]** Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate,

chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogesterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenproprionate, progesterone, quingestanol acetate, quingestrone, and tigestol. Preferred progestins are medroxyprogestrone, norethindrone and norethynedrel.

**[00191]** Exemplary bone resorption inhibiting polyphosphonates include polyphosphenates of the type disclosed in U.S. Patent 3,683,080. Preferred polyphosphonates are geminal diphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonata. Ibandronic acid is an especially preferred polyphosphonate. Alendronate and resindronate are especially preferred polyphosphonates. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-l-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-N,N-dimethyl-3-amino-l-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-l-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N-(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy-1,1-diphosphonic acid, hexane-6-amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

**[00192]** In particular, the compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Any estrogen agonist/antagonist may be

used in the combination aspect of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and/or prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods (Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, pp. 1-74 (1994); Grier, S.J. et al., "The Use of Dual-Energy X-Ray Absorptiometry In Animals", Inv. Radiol., 31(1):50-62 (1996); Wahner H.W. et al., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London, pp. 1-296 (1994)). A variety of these compounds are described and referenced below. Another preferred estrogen agonist/antagonist is 3-(4-{1,2-diphenyl-but-l-enyl)-phenyl)-acrylic acid, which is disclosed in Willson et al., Endocrinology, 138:3901-3911 (1997). Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine,2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and related compounds which are disclosed in U.S. Patent No. 4,536,516. Another related compound is 4-hydroxy tamoxifen, which is disclosed in U.S. Patent No. 4,623,660. A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)ethoxy)phenyl)hydrochloride) which is disclosed in U.S. Patent No. 4,418,068. Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. Patent No. 4,996,225. Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-pyrrolidine, which is disclosed in U.S. Patent No. 3,822,287. Also preferred is levormeloxifene.

**[00193]** Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrrolidinone, which is

disclosed in U.S. Patent No. 4,839,155. Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thiophen-6-ol which is disclosed in U.S. Patent No. 5,488,058. Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-ol, which is disclosed in U.S. Patent No. 5,484,795. Another preferred estrogen agonist/antagonist is (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT Publication No. WO 95/10513. Other preferred estrogen agonist/antagonists include the compounds, TSE-424 (Wyeth-Ayerst Laboratories) and arazoxifene.

**[00194]** Other preferred estrogen agonist/antagonists include compounds as described in U.S. Patent No. 5,552,412. Especially preferred compounds described therein are: *cis*-6-(`4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; (-)-*cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol (also known as lasofoxifene); *cis*-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; *cis*-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,44etrahydroisoquinoline; *cis*-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrahydronaphthalene-2-ol; and 1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

**[00195]** Other estrogen agonist/antagonists are described in U.S. Patent No. 4,133,814, which discloses derivatives of 2-phenyl-3-aroyl-benzothiophene and 2-phenyl-3-aroylbenzothiophene-l-oxide.

**[00196]** Other anti-osteoporosis agents, which can be used as the second agent in combination with a compound of the present invention, include, for example, the following: parathyroid hormone (PTH) (a bone anabolic agent); parathyroid hormone (PTH) secretagogues (see, e.g., U.S, Patent No. 6,132,774), particularly calcium receptor antagonists; calcitonin; vitamin D and vitamin D analogs.

**[00197]** Any selective androgen receptor modulator (SARM) can be used in combination with a compound of the present invention. A selective androgen receptor modulator (SARM) is a compound that possesses androgenic activity and

which exerts tissue-selective effects. SARM compounds can function as androgen receptor agonists, partial agonists, partial antagonists or antagonists. Examples of suitable SARMs include compounds such as cyproterone acetate, chlormadinone, flutamide, hydroxyflutamide, bicalutamide, nilutamide, spironolactone, 4-(trifluoromethyl)-2(1H)-pyrrolidino[3,2-g] quinoline derivatives, 1,2-dihydropyridino [5,6-g]quinoline derivatives and piperidino[3,2-g]quinolinone derivatives.

**[00198]** Cypterone, also known as (1*b*,2*b*)-6-chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione is disclosed in U.S. Patent No. 3,234,093. Chlormadinone, also known as 17-(acetyloxy)-6-chloropregna-4-,6-diene-3,20-dione, in its acetate form, acts as an anti-androgen and is disclosed in U.S. Patent No. 3,485,852. Nilutamide, also known as 5,5-dimethyl-3-[4-nito-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione and by the trade name Nilandron® is disclosed in U.S. Patent No. 4,097,578. Flutamide, also known as 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide and the trade name Eulexin® is disclosed in U.S. Patent 3,847,988. Bicalutamide, also known as 4'-cyano-a',a',a'-trifluoro-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide and the trade name Casodex® is disclosed in EP-100172. The enantiomers of biclutamide are discussed byTucker et al., J. Med. Chem., 31:885-887 (1988). Hydroxyflutamide, a known androgen receptor antagonist in most tissues, has been suggested to function as a SARM for effects on IL-6 production by osteoblasts as disclosed in Hofbauer et al., J. Bone Miner. Res., 14:1330-1337 (1999). Additional SARMs have been disclosed in U.S. Patent No. 6,017,924; WO 01/16108, WO 01/16133, WO 01/16139, WO 02/00617, WO 02/16310, U.S. Patent Application Publication No, US 2002/0099096, U.S. Patent Application Publication No. US 2003/0022868, WO 03/011302 and WO 03/011824.

**[00199]** Any compound having activity as an LXR modulator can serve as the second compound in the combination therapy aspect of the present invention. The term LXR modulator refers to compounds that modulate the liver X receptor (LXR), which has been identified as a regulator of cellular and whole body cholesterol metabolism. Such LXR modulation activity is readily determined by those skilled in the art according to standard assays (e.g., U.S. Pat. No. 6,140,343). A variety of LXR modulators will be known to those skilled in the art, for example, those disclosed in

U.S. Patent Application Publication Nos. 2003/01814206, 2005/0080111, and 2005/0245515.

**[00200]** All of the above referenced patents and patent applications are hereby incorporated by reference herein.

**[00201]** The combinations can be co-formulated or in the form of kits packaged to provide appropriate dosages for co-administration.

**[00202]** The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

**[00203]** The following examples further illustrate the present invention, but of course, should not be construed as in any way limiting its scope.

**[00204]** The following abbreviations are used herein:

ee = enantiomeric excess

DMF = dimethylformamide

EtOAc = ethyl acetate

LDA = lithium diisopropylamide

Hünig's Base = DIEA = $iPr_2NEt$ = N,N-diisopropylethylamine

Me = methyl

Et = ethyl

n-Bu = n-butyl

Bn = benzyl

iPr = isopropyl

Allyl = 1-propenyl

RT = retention time

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

TMS = trimethylsilyl

*t*-Bu = *tert*-butyl

MeI = methyl iodide

$(BOC)_2O$ = di-*tert*-butyl dicarbonate

$Ac_2O$ = acetic anhydride

TEA = $NEt_3$ = $Et_3N$ = triethylamine

*n*-BuLi = *n*-butyllithium

rt = room temperature

LC = liquid chromatography

Ph = phenyl

EtOH = ethanol

BuOH = butan-1-ol

DCE = dichloroethane

DMSO = dimethylsulfoxide

MS = molecular sieves

MS(ES) = Electro-Spray Mass Spectrometry

sat = saturated

AcOH = acetic acid

MeOH = methanol

$Et_2O$ = diethyl ether

Ac = acetyl

h = hours

EDCI = water soluble dicarbonyl diimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

HOBT = 1-hydroxy-benzotriazole

TBAF = tetrabutylammonium fluoride

$TBAF{\cdot}3H_2O$ = tetrabutylammonium fluoride trihydrate

DMA = dimethylacetamide

DME = 1,2-dimethoxyethane

HRMS = high resolution mass spectrometry

TBME = MTBE = methyl *tert*-butyl ether (i.e., 2-methoxy-2-methyl-propane)

PyBroP = bromo-tris-pyrrolidino-phosphonium hexafluorophosphate

PyBOP = benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

DEA = diethylamine

IPA = isopropylamine

TMSCl = trimethylsilylchloride

MS = mass spectrum

NMR = nuclear magnetic resonance

TMSI = trimethylsilyliodide

TMS = trimethylsilyl

PPA = polyphosphoric acid

LDA = lithium diisopropylamine

UV = ultraviolet

DCM = dichloromethane

DMAC = N,N-dimethylacetamide

DAST = diethylaminosulfurtrifluoride

HPLC = high performance liquid chromatography

SFC = super critical fluid chromatography

TBAB = tetrabutylammonium bromide

ACN = acetonitrile

IIDQ = polystyrene resin

TosMIC = tosylmethyl isocyanide

BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

$Pd_2(dba)_3$ = tris-(dibenzylideneacetone) dipalladium(0)

$Pd(PPh_3)_4$ = tetrakis(triphenylphosphine) palladium(0)

$[Ir(COD)Cl]_2$ = Chloro-1,5-cyclooctadiene iridium (I) dimer

Ar = argon

TBAB = tetrabutylammonium bromide

9-BBN = 9-borabicyclo[3.3.1]nonane

DEAD = diethyl azodicarboxylate

DPPA = diphenyl phosphoryl azide

NBS = N-bromosuccinimide

DMAP = 4-di(methylamino)pyridine

LAH = lithium aluminum hydride

NMP = 1-methyl-2-pyrrolidone

NMM = 1-methyl-2-morpholine

Super-hydride = lithium triethylborohydride

DIBAL-H = diisobutylaluminium hydride

Dess-Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one

Lawesson's reagent = 2,4-bis(4-methoxyphenyl)- 1,3,2,4-dithiadiphosphetane 2,4-disulfide

Jones[O] reagent = $CrO_3/H_2SO_4/H_2O$/acetone

$PCy_3$ = tricyclohexylphosphine

$Tf_2O$ = triflic anhydride = trifluoromethanesulfonic anhydride

$Bu_4NBr$ = tetrabutylammonium bromide

TBDMSCl = tert-butylchlorodimethylsilane

TFFH = fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate

R, R-MnCl (Salen) = (1R, 2R)-(-)-[1,2-cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]manganese (III) chloride

LiOTf = lithium trifluoromethanesulfonate

Tf = trifluoromethanesulfonate

$EtAlCl_2$ = ethyl aluminum dichloride

$ZnEt_2$ = diethyl zinc

TsOH = 4-methylbenzenesulfonic acid

Ts = 4-methylbenzenesulfonate

n-$Bu_2SnO_2$ = dibutyltin(IV) oxide

Boc = t-Boc = t-butoxycarbonyl

$Pd(OH)_2/C$ = palladium (II) hydroxide on carbon

Pd/C = palladium on carbon

Fmoc = 3, 9-fluorenylmethoxycarbonyl

Cbz = carbobenzoxy

allylMgBr = 1-propenyl magnesium bromide

diglyme = diethylene glycol dimethyl ether = 1-methoxy-2-(2-methoxyethoxy)ethane

TBME = tert-butyl methyl ether

L-proline = (S)-pyrrolidine-2-carboxylic acid

$P(t\text{-}Bu)_3$ = tri-t-butyl phosphine

triphosgene = bis(trichloromethyl) carbonate

**[00205]** Specifically exemplified compounds of Formula Ia and Ib are listed along with structure, name, HPLC retention time, molecular mass and the procedure employed to make such examples, in the proceeding text and in the tables set forth below. The absolute configuration of chiral examples was assigned by NMR comparison of the intermediate diastereomeric sulfinyl amides, but has not be confirmed by crystallographic assignment. Enantiomerically pure intermediate amines were obtained by separation of the racemic mixtures using SFC or by the chiral synthesis described in Procedures 4, 5 and 6.

**[00206]** The chromatography techniques used to determine the compound retention times in the tables are as follows:

(1) **LCMS** = Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm;

(2) **LCMS** = Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm;

(3) **LCMS** = Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm;

(4) **LCMS** = Waters Sunfire C18 column, 4.6 X 50 mm X 5μm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm;

(5) **LCMS** = YMC ODS column 4.6 x 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm;

(6) **LC** = Chromolith SpeedROD column, 4.6X 50mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm;

(7) **LC** = Phenomenex Synergi 4u POLAR-RP column, 21.2x100mm eluting with 10-90% ACN/$H_2O$ over 12 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm;

(8) **LCMS** = Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% ACN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm;

(9) **LC** = Chromolith SpeedROD column, 4.6X 50mm eluting with 10-90% ACN/$H_2O$ over 2 minutes containing 0.2% phosphoric acid, 5 mL/min, monitoring at 220 nm;

(10) **LCMS** = Waters Sunfire C18 column, 4.6 X 50 mm eluting with 10-90% ACN/$H_2O$ over 4 minutes containing 10 mM $NH_4OAc$; 4 mL/min, monitoring at 220 nm;

(11) **LC** = Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm;

(12) **LCMS** = Chromolith Performance RP-18e column, 4.6 X 100 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% trifluoroacetic acid, 5 mL/min, monitoring at 220 nm;

(13) **LC** = Chromolith Performance RP-18e column, 4.6 X 100 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm;

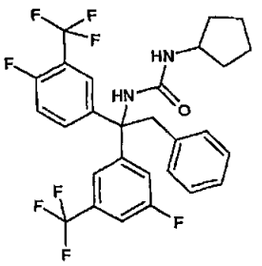
(14) **LCMS** = Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% ACN/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm;

(15) **LCMS** = Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% ACN/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm;

(16) **LCMS** = Waters Sunfire C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 8 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

**[00207]** The molecular mass of the compounds listed in the tables set forth below were determined by MS (ES) by the formula m/z.

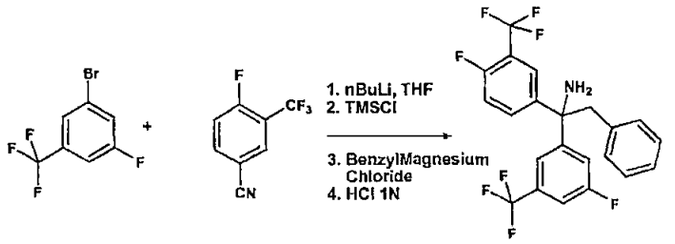
## EXAMPLE 1



**1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea**

### Procedure 1

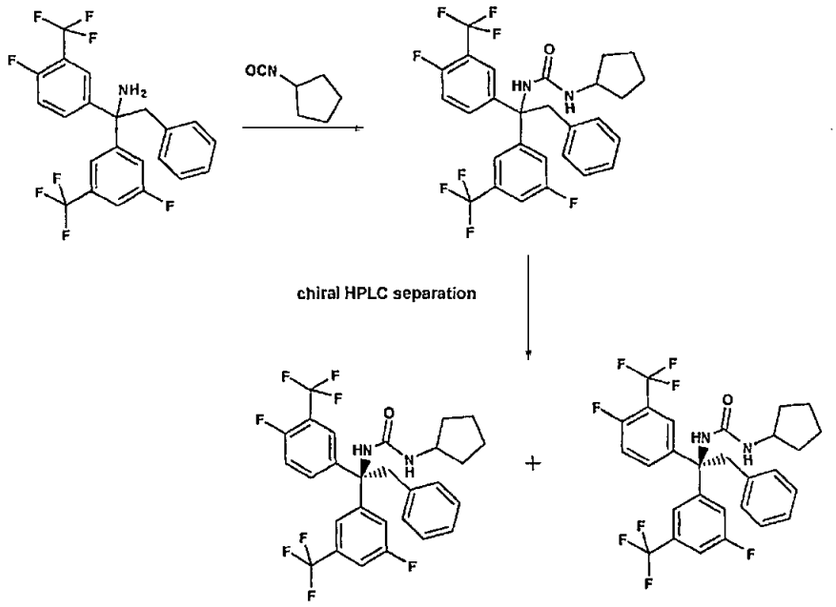
**1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethanamine**




**[00208]** An ether solution (40 mL) of 1-bromo-3-fluoro-5-(trifluoromethyl)benzene (2.0 g, 8.23 mmol) was stirred in an oven-dried round bottom flask at -78°C under Ar. n-BuLi (2.5 M in hexanes, 3.6 ml, 9.05 mmol, 1.1 eq) was added dropwise. The resulting solution was stirred at -78°C for 30 min. A solution of 4-fluoro-3-(trifluoromethyl)benzonitrile (1.55 g, 8.23 mmol, 1.0 eq) in $Et_2O$ (5 mL) was added dropwise. The resulting reddish mixture was stirred at -78°C for 2h. TMSCl (pretreated with $Et_3N$ (TMSCl:$Et_3N$ = 10:1, v:v), 1.14 mL, 1.2 eq) was added dropwise. The dry ice bath was removed, and the resulting slurry was stirred at room temperature for 2 h. The reaction was cooled to -78°C and a solution of benzyl magnesium chloride in THF (2.0 M, 8.4 mL, 2 eq) was added dropwise. The resulting mixture was slowly warmed up to room temperature and stirred at room temperature overnight. 1N HCl (100 mL) was added. The mixture was stirred at room temperature for 30 min, extracted with $Et_2O$ (2x), washed with 1N NaOH, $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The residue was

purified by flash column chromatography (silica gel, hexanes:ethyl acetate) to give 1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethanamine (1.6 g, yield: 44%). LC-MS ESI 3.42 min 429.2 (M-$NH_3$+H); $^1$H NMR (400 MHz, CHLOROFORM-D) δ ppm 7.66 (dd, *J*=6.7, 2.3 Hz, 1 H), 7.49 - 7.59 (m, 1 H), 7.45 (s, 1 H), 7.18 - 7.30 (m, 6 H), 6.74 (d, *J*=6.9 Hz, 2 H), 3.57 (m, 2 H).

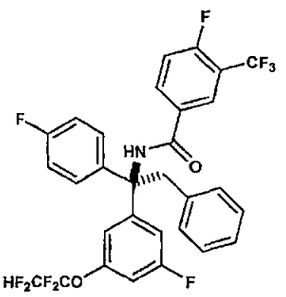
**Procedure 2**




**[00209]** 1-(4-Fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethanamine (300 mg, 0.67 mmol) and cyclopentyl isocyanate (0.4 mL, 5.3 eq) were stirred in 1,4-dioxane (2 mL) at room temperature overnight. The reaction mixture was concentrated, and purified by flash chromatography (silica gel, hexanes/EtOAc) to give the racemic mixture of 1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea (250 mg, yield: 67%). The racemate (250 mg) was dissolved in 10% isopropanol in heptane, and was resolved by chiral prep HPLC using an AD column (10%isopropanol/heptane/0.1%DEA, isocratic) to give the fast eluting enantiomer 1 (110 mg) corresponding to (*S*)-1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-

phenylethyl)urea, (analytical chiral HPLC (AD, 10%isopropanol/heptane/0.1%DEA, isocratic), retention time = 4.85 min) and the slow eluting enantiomer 2 (105 mg) corresponding to (*R*)-1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea, (analytical chiral HPLC (AD, 10%isopropanol/heptane/0.1%DEA, isocratic), retention time = 14.11 min) LCMS (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run), retention time = 4.33 min, 557.32 (M+H); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 - 7.44 (m, 2 H), 7.23 - 7.29 (m, 3 H), 7.13 - 7.21 (m, 4 H), 6.68 - 6.74 (m, 2 H), 4.84 (s, 1 H), 4.40 (s, br, 1 H), 3.84 - 3.95 (m, 3 H), 1.88 - 1.98 (m, 2 H), 1.56 - 1.68 (m, 4 H), 1.34 (d, *J*=6.36 Hz, 2 H).

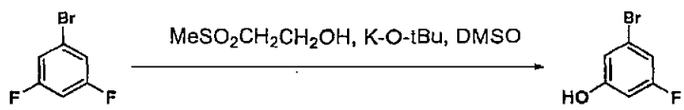
**EXAMPLE 2**




**(R)-4-Fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

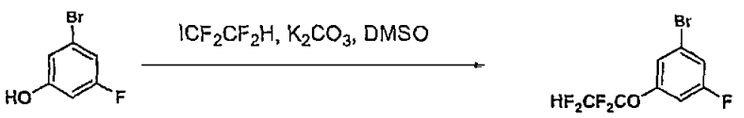
**Procedure 3**

**Preparation of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene**




**[00210]** To a solution of 1-bromo-3,5-difluorobenzene (30.6 mL, 0.266 mole) and 2-(methylsulfonyl)ethanol (66 g, 0.531 mole) in DMSO (240 mL) was added potassium tert-butoxide (76.6 g, 0.682 mole) at 0°C. The resulting mixture was stirred at room temperature for 3h and quench with 4N HCl slowly to pH ≤ 1. The desired product was extracted with $Et_2O$ (12 L) until no product was detected in the aqueous layer. The $Et_2O$ was evaporated under reduced pressure to one third the amount of the

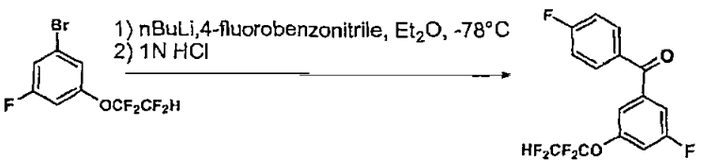
solvent and washed with 1N NaOH (12 L). Then, the NaOH solution was adjusted to pH= 3 and extracted with $Et_2O$ until no desired product was detected in the aqueous layer. The $Et_2O$ was evaporated under reduced pressure and passed through an $Al_2O_3$ column eluted with $Et_2O$ to afford 3-bromo-5-fluorophenol as a colorless oil (48 g, 94% yield). LC-MS 190.33 (M+H); Analytical HPLC = 2.26 minutes (0-100% $CH_3CN$ in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CD_3OD$) δ ppm 6.88 - 6.64 (m, 2H), 6.58 - 6.30 (m, 1 H), 4.99 (s, 1 H).




**[00211]** To a solution of 3-bromo-5-fluorophenol (47 g, 0.249 mole) and 2,2,3,3-tetrafluoroethyliodine (68 g, 0.298 mole) in DMSO (260 mL) was added potassium carbonate (137 g, 0.992 mole). The resulting mixture was stirred at 70°C for 16h. The inorganic salt was removed by filtration and the filter cake was washed with $Et_2O$ (500 mL). The filtrate was diluted with 500 mL of $H_2O$ and extracted with excess $Et_2O$ (1.5 L). The $Et_2O$ layer was washed with 0.5 N NaOH (250 mL), $H_2O$, brine, and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the crude product was passed through an $Al_2O_3$ column using $Et_2O$ as the eluting solvent to afford 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (63 g, yield: 87%) as yellowish oil. LC-MS (ESI): 290.21 (M+H), retention time = 3.66 minutes (0-100% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CD_3OD$) δ ppm 7.45 - 7.22 (m, 2 H), 7.10 (d, *J*=9.23 Hz, 1 H), 6.59 - 5.94 (m, 1 H).

**Procedure 4**

**(3-Fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methanone**

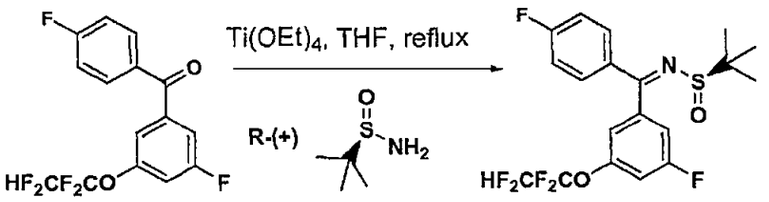



**[00212]** To an oven-dried round-bottomed flask cooled at -78°C, was added 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (7.20 g, 24.82 mmol) in anhydrous ether (300 mL) under Argon, and the mixture was stirred at -78°C for 10

min. n-BuLi (2.5 M in hexanes, 11.5 mL, 28.75 mmol, 1.16 eq) was added dropwise at -78°C. The reaction mixture was stirred at -78°C for 45 min. An $Et_2O$ solution (20 mL) of 4-fluorobenzonitrile (3.06 g, 25.29 mmol, 1.02 eq) was added dropwise. The resulting reddish solution was stirred at -78°C for 2 h. The reaction mixture was quenched by adding 1N HCl (200 mL), and the dry ice-acetone bath was removed. The resulting slurry was stirred at room temperature for 1 h followed by the addition of $Et_2O$ (100 mL). The organic layer was separated, and then washed with sat'd $NaHCO_3$, $H_2O$, brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (EtOAc/hexanes = 0 to 30%) to give (3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methanone as slightly tan oil (7.20 g, yield: 86.9%). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.85 - 7.80 (m, 2H), 7.40-7.37 (m, 2H), 7.20-7.14 (m, 3H), 5.92 (tt, *J*= 52, 2.8Hz, 1H); LC-MS (ESI) 335.31 (M+H), retention time = 3.81 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

**Procedure 5**

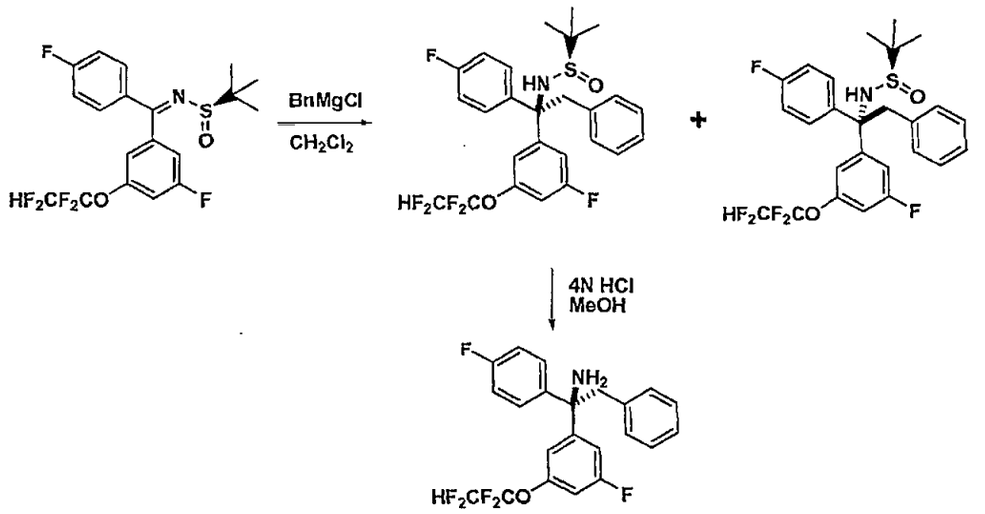
**(*R*,*E*/*Z*)-*N*-((3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methylene)-2-methylpropane-2-sulfinamide**




**[00213]** (3-Fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methanone (3.3 g, 9.88 mmol) was stirred in anhydrous THF (20 mL) at r.t. under $N_2$. *(R)*-(+)-2-Methylpropane-2-sulfinamide (1.21 g, 10 mmol, 1.01 eq) was added as one single portion, followed by addition of $Ti(OEt)_4$ (3.09 mL, 14.91 mmol, 1.51 eq). The resulting solution was heated at reflux for 48 hours. The cooled mixture was evaporated. $H_2O$ (100 mL) was added, followed by the addition of EtOAc (100 mL). The mixture was filtered through celite, and washed with EtOAc (200 mL). The filtrate was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel flash chromatography and was

eluted with hexanes and EtOAc (0-30% EtOAc in hexanes) to give (*R*)-*N*-((3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methylene)-2-methylpropane-2-sulfinamide as yellowish viscous oil which solidified after drying under vacuum as light yellow solids (3.50 g, yield: 81.0%). LC-MS ESI 437.88 (M+H), retention time = 3.83 min (10-90% MEOH in $H_2O$ with 0.1% TFA in a 4-min gradient); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 - 6.99 (br, m, 7H), 5.90 (tt, *J* = 52, 4 Hz, 1H), 1.31 (s, 9H).

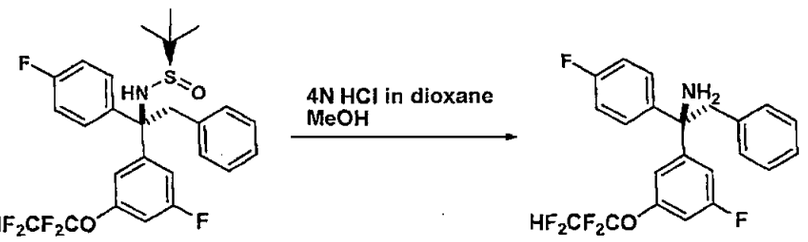
**Procedure 6**




**[00214]** (*R*)-*N*-((3-Fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methylene)-2-methylpropane-2-sulfinamide (150 mg, 0.34 mmol) was stirred in anhydrous $CH_2Cl_2$ (7 mL) at -78°C for 5 min under Argon. $BF_3{\cdot}Et_2O$ (0.10 mL, 2.0 eq) was added dropwise. The mixture was stirred at -78°C for 10 min. Benzylmagnesium chloride (1.0 M in $Et_2O$, 1.4 mL, 3.0 eq) was added slowly at -78°C, and the resulting mixture was stirred at -78°C for 1.5 h. The reaction mixture was quenched with sat. $NH_4Cl$ and then extracted with $Et_2O$ (2x). The combined organic portion was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 0-30%) to give the fast eluting fraction corresponding to (*R*)-N-((*S*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (29 mg): $^1$H NMR (400 MHz, $CDCl_3$) δ

ppm 1.23 (s, 9 H) 3.63 (d, *J*=12.4 Hz, 1H), 3.94 (d, *J*=12.4 Hz, 1H), 4.21 (s, 1H), 6.90 (m, 1H), 5.90 (m, 1H), 6.94-7.09 (m, 4H), 7.16-7.20 (m, 4H), 7.31-7.39 (m, 2H); LC-MS (ESI) 530.36 (M+H), retention time = 4.11 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); and the slow eluting fraction corresponding to (*R*)-N-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (146 mg, total yield: 96.4%): $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.35-7.43 (m, 2 H), 7.13-7.20 (m, 3 H), 7.07 (t, *J*=8.72 Hz, 2 H), 6.93 (dd, *J*=7.58, 1.77 Hz, 2 H), 6.84 (d, *J*=8.59 Hz, 1 H), 6.70 (m, 2 H), 5.85 (tt, *J* = 52, 4 Hz, 1H), 4.25 (s, 1 H), 4.02 (d, *J*=12.63 Hz, 1 H), 3.58 (d, *J*=12.63 Hz, 1 H), 1.20 (s, 9 H); $^{13}$C NMR ($CDCl_3$) δ ppm 23.02, 46.99, 56.53, 65.70, 104.55, 104.96, 105.37, 107.06, 107.47, 107.92, 108.17, 109.56, 109.97, 112.32, 112.55, 115.37, 115.58, 116.13, 116.41, 116.69, 119.12, 127.21, 128.14, 130.91, 130.99, 132.07, 134.34, 137.48, 137.51, 149.09, 149.21, 150.52, 150.45, 161.20, 163.67; LC-MS (ESI) 530.36 (M+H), retention time = 4.11 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

**(R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine**

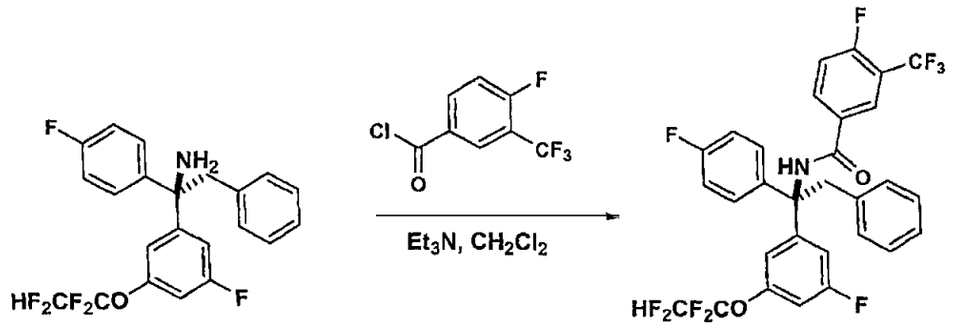



**[00215]** (*R*)-N-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (234 mg, 0.442 mmol) was stirred in 4N HCl in dioxane (1.5 mL) and MeOH (1.5 mL) at room temperature under Ar for 10 min. The reaction mixture was concentrated, and then purified by flash chromatography (silica gel, hexanes/EtOAc) to give (*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (169 mg, 90%). LC-MS (ESI) 409.16 (M-$NH_3$+H), retention time = 3.26 minutes (0-100% MeOH in $H_2O$ with 0.1% TFA in 4-min run); Analytical HPLC: 2.52 minutes (0-100% $CH_3CN$ in $H_2O$ with 0.1% TFA in 4-min run); $^1$H NMR (400 MHz, $CD_3OD$) δ ppm 7.29 -

7.50 (m, 2H), 6.87-7.22 (m, 8H),. 6.77 (d, *J*=6.15 Hz, 2H), 6.04 - 6.48 (m, 1 H), 3.57 (s, 2 H).

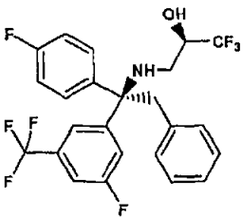
**Procedure 7**

**(*R*)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**



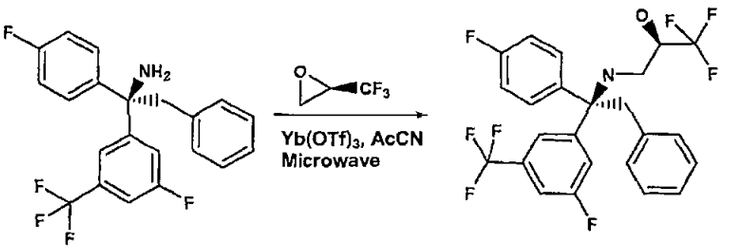

**[00216]** To a solution of (*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (30 mg, 0.079 mmol) in $CH_2Cl_2$ (0.2 mL) was added 4-fluoro-3-(trifluoromethyl)benzoyl chloride (0.048 mL, 0.158 mmol), followed by $Et_3N$ (0.04 mL, 0.158 mmol). The resulting mixture was stirred at room temperature for 5h. The crude product was purified on a preparative HPLC column type using 30 to 100% $CH_3CN$ in $H_2O$ with 0.1% TFA for 10 minutes as mobile phase. The solvent was removed under reduced pressure to afford (*R*)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (35 mg, 80% yield) as white powder. LC-MS (ESI) 568.30 (M+H), retention time = 4.27 min (0-100% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); Analytical HPLC: 3.95 min (0-100% $CH_3CN$ in $H_2O$ with 0.1% TFA in a 4-min run, purity 100%); $^1$H NMR (400MHz, $CD_3OD$) δ ppm 3.88 - 4.01 (m, 1 H), 4.10 (d, *J*=13.18 Hz, 1 H), 6.69 (d, *J*=7.47 Hz, 2 H), 6.97 - 7.51 (m, 11 H), 7.99 (d, *J*=5.71 Hz, 2 H), 8.90 (s, 1 H).

## EXAMPLE 3



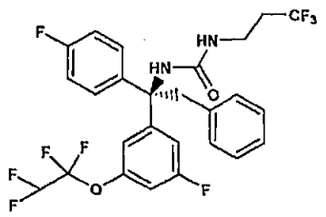
**(R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)propan-2-ol**

**Procedure 8**



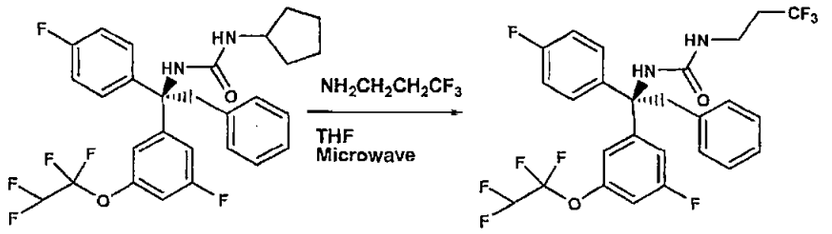

**[00217]** (*R*)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine was prepared as described in Procedures 4, 5 and 6. (*R*)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (50 mg, 0.133 mmol) was dissolved in anhydrous acetonitrile (0.26 mL). (*R*)-2-(trifluoromethyl)oxirane (0.07 mL, 0.625 mmol), (approximate 85:15 ratio of *R* to *S*) was added to the solution in a microwave vial followed by $Yb(OSO_2CF_3)_3$ (0.005 g, 0.008 mmol). The sealed vial was heated to 160°C for 30 minutes under microwave irradiation. The crude product was purified by preparative HPLC using 30-100% acetonitrile in $H_2O$ with 0.1% TFA as mobile phase to give (*R*)-1,1,1-trifluoro-3-((*R*)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)propan-2-ol as a colorless oil (30 mg, 46% yield). LC-MS (ESI): 361.15 (M+H), retention time = 4.10 min (0-100% MeOH in $H_2O$ with 0.1%TFA); Analytical HPLC: 3.49 min ($CH_3CN$ in $H_2O$ with 0.1% TFA in 4 min run, purity 100%); $^1H$ NMR (400 MHz, $CD_3OD$) δ ppm 2.59 - 2.73 (m, 1 H), 2.72 - 2.84 (m, 1 H), 3.69 (m, 2 H), 4.09 (m, 1 H), 6.61 - 6.82 (m, 2 H), 7.00 - 7.19 (m, 5 H), 7.20 -7.48 (m, 5 H).

## EXAMPLE 4



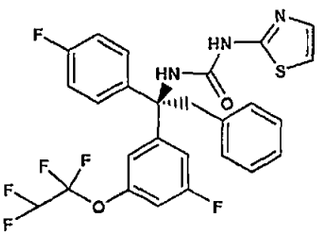
**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea**

**Procedure 9**



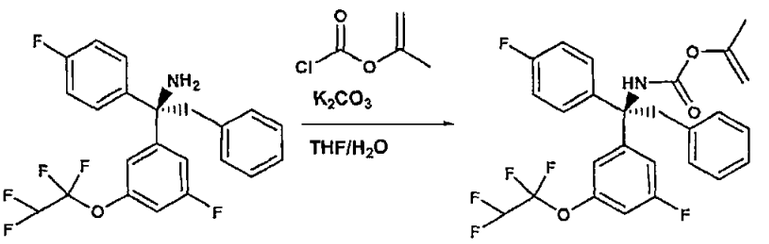

**[00218]** (*R*)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea was prepared as described in Procedure 2. To a microwave vial containing (*R*)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (20 mg, 0.037 mmol) was added a pre-mixed solution of 3,3,3-trifluromethylpropylamine (25 mg, 0.224 mmol) and $Et_3N$ ( 0.03 mL, 0.224 mmol) in THF (0.025 mL). The sealed vial was subjected to microwave irradiation at 150°C for 1500 sec followed by dilution with MeOH. The crude product was isolated by preparative HPLC column type using 30-100% acetonitrile in $H_2O$ with 0.1% TFA as mobile phase to afford (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea (76%) as white powder. LCMS (ESI): 565.36 (M+H), retention time = 3.96 min (0-100% MeOH in $H_2O$ in a 4-min run); $^1H$ NMR (400 MHz, $CD_3OD$) δ ppm 2.18 - 2.41 (m, 2 H), 3.34 (m, 2 H), 3.75 - 3.87 (m, 1 H), 3.88 - 4.00 (m, 1 H), 6.07 - 6.45 (m, 1 H), 6.71 (d, *J*=7.03 Hz, 2 H), 6.85 - 7.05 (m, 5 H), 7.05 - 7.22 (m, 5 H).

**EXAMPLE 5**

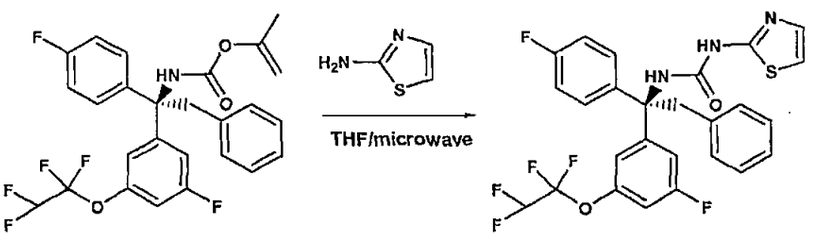


**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(thiazol-2-yl)urea**

**Procedure 10**



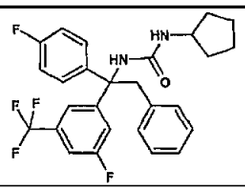
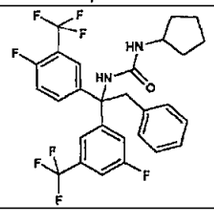
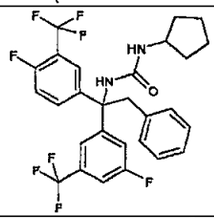
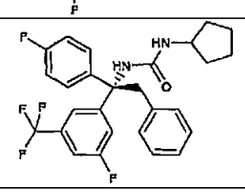
**[00219]** (*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (48 mg, 0.11 mmol) was stirred in THF (0.5 mL) and $H_2O$ (0.05 mL) at room temperature. $K_2CO_3$ (100 mg, 0.72 mmol,6.6 eq) was added followed by the addition of isopropenyl chloroformate (0.030 mL, 0.275mmol, 2.5 eq). The reaction mixture was stirred at room temperature overnight. The mixture was filtered, and the filtrate concentrated to dryness to give crude (*R*)-prop-1-en-2-yl 1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylcarbamate as colorless film (60mg, yield: quantative). LCMS: 4.18 min 409.27 (M-COOisopropenyl-$NH_3$+H) (4min gradient, MeOH/$H_2O$ 0.1%TFA).

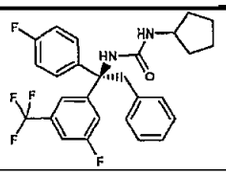
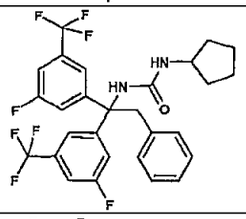
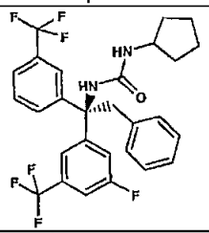
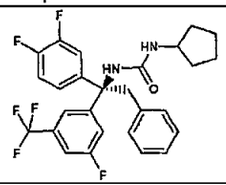
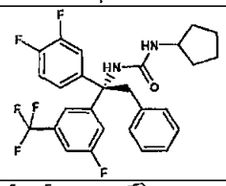
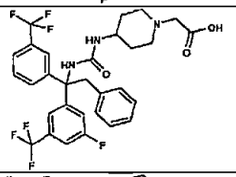
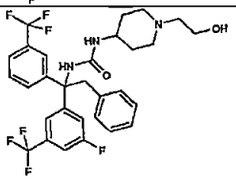


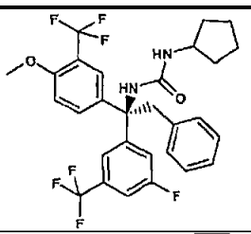
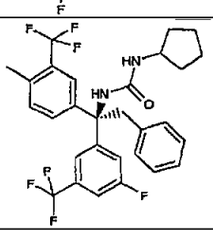
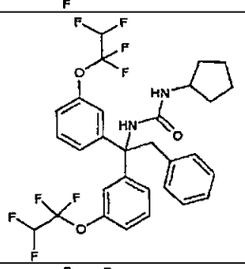
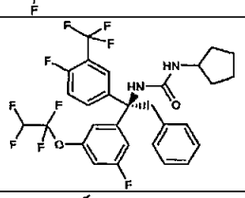
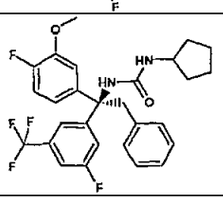
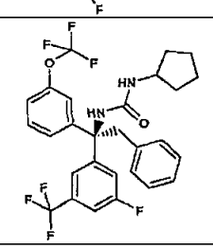
**[00220]** (*R*)-prop-1-en-2-yl 1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylcarbamate (15 mg, 0.029 mmol) and 2-aminothiazole

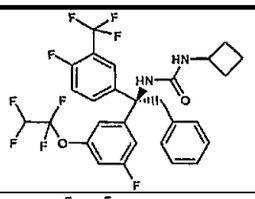
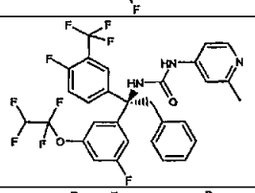
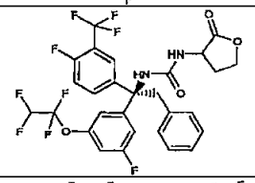
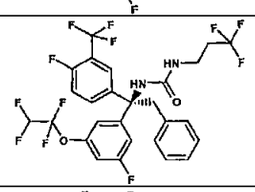
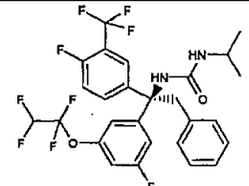
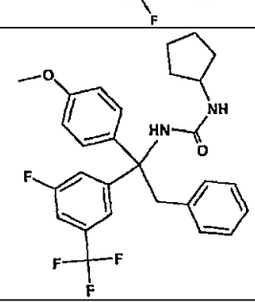
(8.2mg, 0.082mmol, 2.8 eq), and N-methylpyrrolidine (0.9 μl, 0.3 eq) were stirred in THF (0.3 mL) in a microwave vial. The reaction mixture was heated at 150°C for 20 min under microwave irradiation. After cooling, the solvent was evaporated. The residue was purified by reverse phase HPLC (20-90% $CH_3CN$ in $H_2O$ with 0.1%TFA) to give pure (*R*)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(thiazol-2-yl)urea as white solids (6.5 mg, yield:40.6 %). $^1$H NMR (400 MHz, $CDCl_3$-D) δ ppm 7.29 (m, 1H), 7.23-7.18 (m, 3H), 7.16 (t, *J* = 8.0 Hz, 2H), 7.02 (t, *J* = 8.5 Hz, 2H), 6.94-6.89 (m, 4H), 6.71 (d, *J*=6.82 Hz, 2H), 5.86 (tt, *J* = 47.1, 2.9Hz, 1H), 3.84-3.75 (m, 2H); LC-MS (ESI) 552.28 (M+H), retention time = 4.12 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

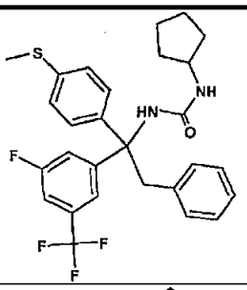
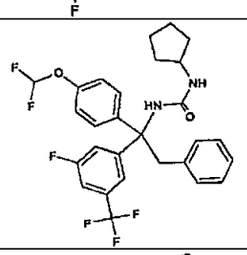
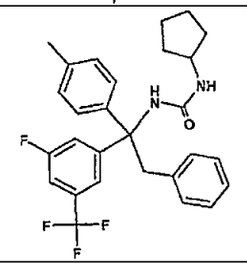
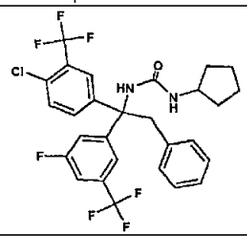
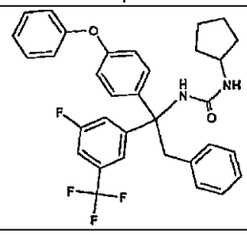
**TABLE 1**

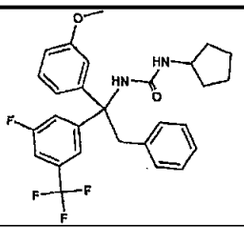
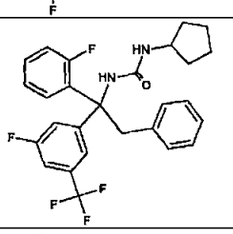
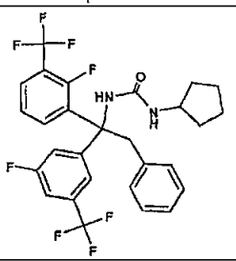
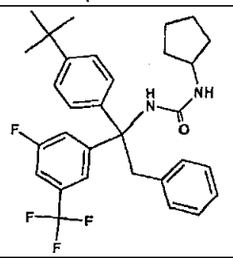
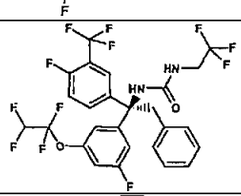
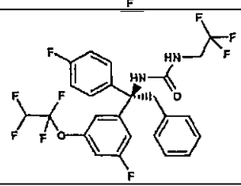
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 6 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.61 LC 489.34 $[M+H]^+$ | Procedure 1 and 2 |
| 7 |  | 1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.30 LC 557.3 $[M+H]^+$ | Procedure 1 and 2 |
| 8 |  | 1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.30 LC 557.3 $[M+H]^+$ | Procedure 1 and 2 |
| 9 |  | (S)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.60 LC 489.33 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |

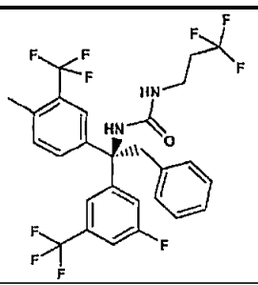
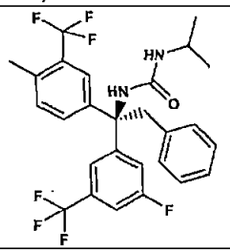
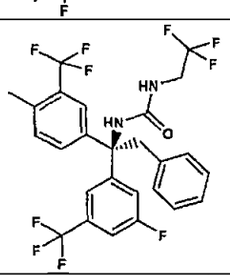
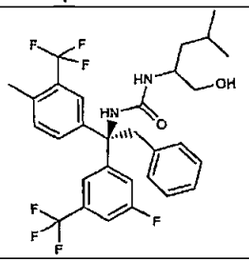
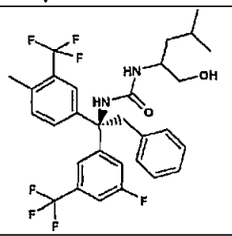
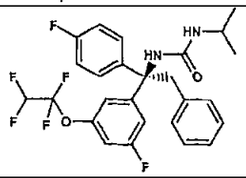
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 10 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.61 LC 489.33 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 11 |  | 1-(1,1-bis(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea | 3.87 LC 557.34 $[M+H]^+$ | Procedure 14 and 2 |
| 12 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)phenyl)ethyl)urea | 4.30 LC 539.38 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 13 |  | (R)-1-cyclopentyl-3-(1-(3,4-difluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 3.64 LC 507.34 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 14 |  | (S)-1-cyclopentyl-3-(1-(3,4-difluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 3.64 LC 507.14 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 15 |  | 2-(4-(3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)phenyl)ethyl)ureido)piperidin-1-yl)acetic acid | 3.75 LC 612.4 $[M+H]^+$ | Procedure 1 and 2 |
| 16 |  | 1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)phenyl)ethyl)-3-(1-(2-hydroxyethyl)piperidin-4-yl)urea | 3.72 LC 598.45 $[M+H]^+$ | Procedure 1 and 2 |

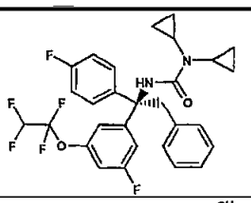
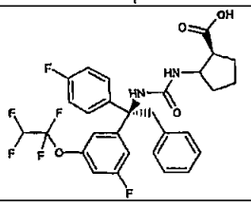
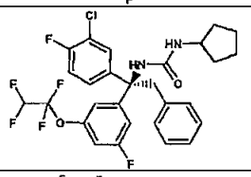
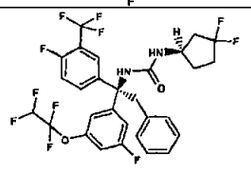
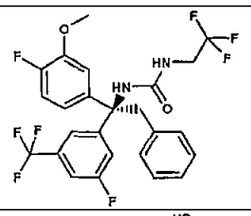
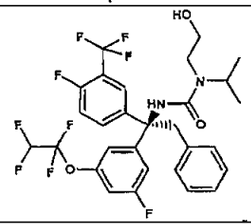
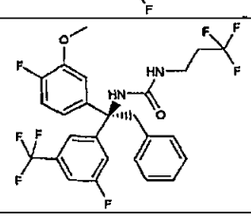
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 17 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methoxy-3-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.22 LC 569.39 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 18 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.42 LC 553.38 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 19 |  | 1-cyclopentyl-3-(2-phenyl-1,1-bis(3-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)urea | 4.13 LC 617.4 $[M+H]^+$ | Procedure 1 and 2 |
| 20 |  | (R)-1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.74 LC 605.37 $[M+H]^+$ | Procedure 1, 3 and 2 |
| 21 |  | (R)-1-cyclopentyl-3-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.17 LC 519.37 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 22 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethoxy)phenyl)ethyl)urea | 4.30 LC 555.40 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 23 |  | (R)-1-cyclobutyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.64 LC 591.39 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 24 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2-methylpyridin-4-yl)urea | 2.64 LC 648.49 $[M+Na]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 25 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2-oxotetrahydrofuran-3-yl)urea | 3.30 LC 621.39 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 26 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.59 LC 633.32 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 27 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-isopropylurea | 3.62 LC 579.34 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 28 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methoxyphenyl)-2-phenylethyl)urea | 4.13 LC 501.3 $[M+H]^+$ | Procedure 1 and 2 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 29 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-(methylthio)phenyl)-2-phenylethyl)urea | 4.24 LC 517.26 $[M+H]^+$ | Procedure 1 and 2 |
| 30 |  | 1-cyclopentyl-3-(1-(4-(difluoromethoxy)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.12 LC 537.27 $[M+H]^+$ | Procedure 1 and 2 |
| 31 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-p-tolylethyl)urea | 4.24 LC 485.32 $[M+H]^+$ | Procedure 1 and 2 |
| 32 |  | 1-(1-(4-chloro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.30 LC 573.23 $[M+H]^+$ | Procedure 1 and 2 |
| 33 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-phenoxyphenyl)-2-phenylethyl)urea | 4.38 LC 563.32 $[M+H]^+$ | Procedure 1 and 2 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 34 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(3-methoxyphenyl)-2-phenylethyl)urea | 4.14 LC 501.32 $[M+H]^+$ | Procedure 1 and 2 |
| 35 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(2-fluorophenyl)-2-phenylethyl)urea | 4.12 LC 489.26 $[M+H]^+$ | Procedure 1 and 2 |
| 36 |  | 1-cyclopentyl-3-(1-(2-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.17 LC 557.26 $[M+H]^+$ | Procedure 1 and 2 |
| 37 |  | 1-(1-(4-tert-butylphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.47 LC 527.33 $[M+H]^+$ | Procedure 1 and 2 |
| 38 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.32 LC 619.31 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 39 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.14 LC 551.21 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 40 |  | (R)-1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 4.37 LC 580.98 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 41 |  | (R)-1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-isopropylurea | 4.36 LC 527.08 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 42 |  | (R)-1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.32 LC 567.04 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 43 |  | 1-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(1-hydroxy-4-methylpentan-2-yl)urea | 4.40 LC 585.13 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 44 |  | 1-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(1-hydroxy-4-methylpentan-2-yl)urea | 4.41 LC 585.13 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 45 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-isopropylurea | 3.95 LC 511.39 $[M+H]^+$ | Procedure 3 4, 5, 6 and 9 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 46 |  | (R)-1,1-dicyclopropyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 4.12 LC 549.32 $[M+H]^+$ | Procedure 3 4, 5, 6 and 9 |
| 47 |  | (1S)-2-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopentanecarboxylic acid | 3.93 LC 581.04 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |
| 48 |  | (S)-1-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea | 3.72 LC 571.36 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 2 |
| 49 |  | 1-((R)-3,3-difluorocyclopentyl)-3-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 4.17 LC 641.3 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 12 |
| 50 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.94 LC 532.98 $[M+H]^+$ | Procedure 4, 5, 6 and 9 |
| 51 |  | (R)-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-1-(2-hydroxyethyl)-1-isopropylurea | 4.09 LC 623.02 $[M+H]^+$ | Procedure 4, 5, 6 and 9 |
| 52 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.49 LC 547.00 $[M+H]^+$ | Procedure 4, 5, 6 and 9 |

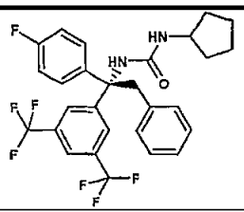
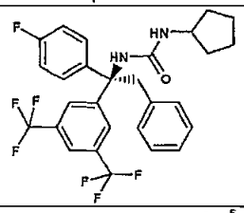
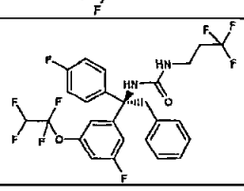
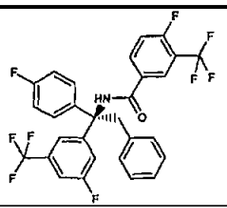
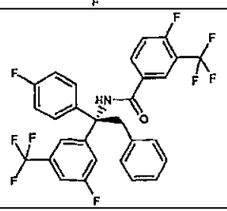
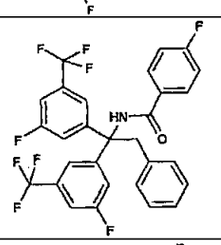
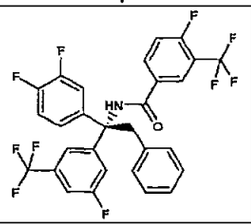
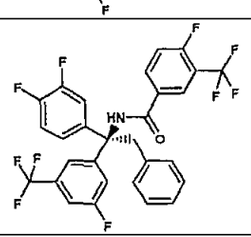
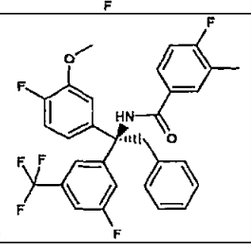
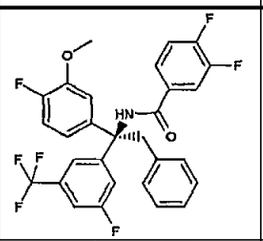
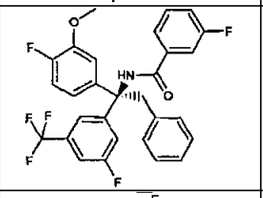
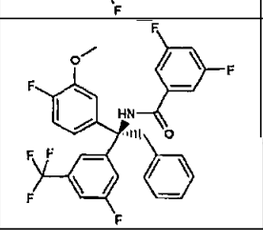
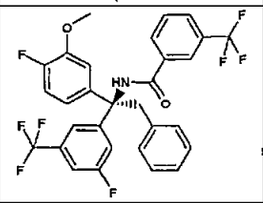
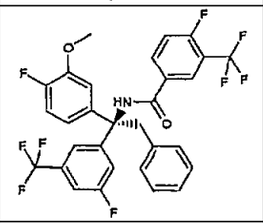
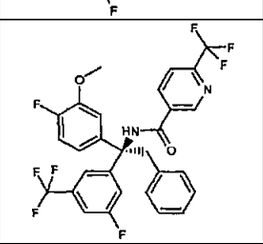
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 53 |  | (S)-1-(1-(3,5-bis(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-cyclopentylurea | 3.82 LC 539.03 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 54 |  | (R)-1-(1-(3,5-bis(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-cyclopentylurea | 3.80 LC 539.03 $[M+H]^+$ | Procedure 4, 5, 6 and 2 |
| 55 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.96 LC 565.36 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 9 |

**TABLE 2**

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 56 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.95 LC 568.30 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 57 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.95 LC 568.24 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 58 |  | N-(1,1-bis(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluorobenzamide | 3.83 LC 568.3 $[M+H]^+$ | Procedure 1 and 7 |
| 59 |  | (S)-N-(1-(3,4-difluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 3.95 LC 586.26 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 60 |  | (R)-N-(1-(3,4-difluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 3.93 LC 497.3 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 61 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-methylbenzamide | 3.79 LC 544.35 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 62 |  | (R)-3,4-difluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)benzamide | 3.73 LC 570.32 $[M+Na]^+$ | Procedure 4, 5, 6 and 7 |
| 63 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)benzamide | 3.67 LC 530.33 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 64 |  | (R)-3,5-difluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)benzamide | 3.75 LC 548.33 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 65 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.86 LC 580.36 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 66 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.90 LC 598.36 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 67 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-6-(trifluoromethyl) nicotinamide | 3.70 LC 581.34 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |

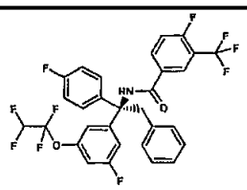
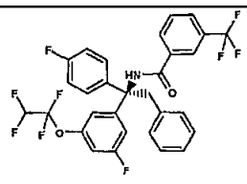
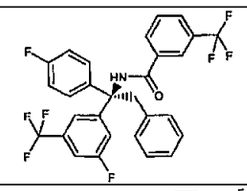
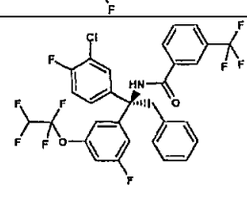
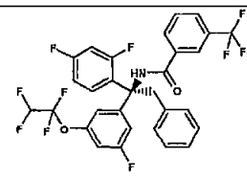
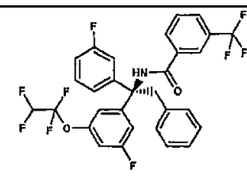
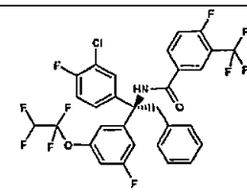
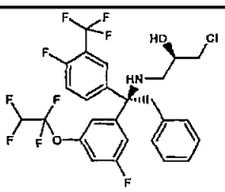
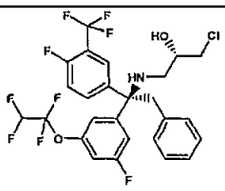
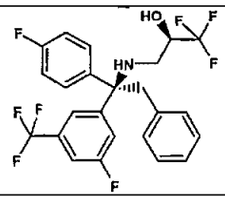
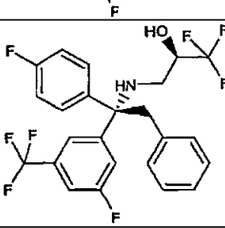
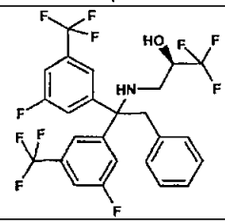
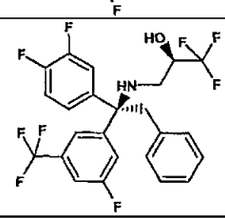
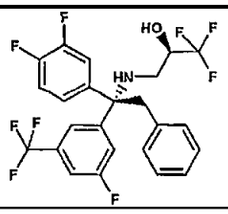
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 68 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.95 LC 616.17 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 69 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.83 LC 598.37 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 70 |  | (R)-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.89 LC 550.36 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 71 |  | (S)-N-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.95 LC 632.32 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 72 |  | (S)-N-(1-(2,4-difluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.86 LC 616.34 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 73 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(3-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.81 LC N.Observed $[M+H]^+$ | Procedure 4, 5, 6 and 7 |
| 74 |  | (S)-N-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.03 LC 650.08 $[M+H]^+$ | Procedure 4, 5, 6 and 7 |

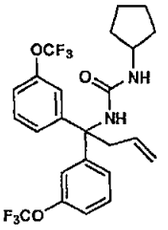
**TABLE 3**

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 75 |  | (R)-1-chloro-3-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino) propan-2-ol | 3.24 LC 586.43 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 8 |
| 76 |  | (S)-1-chloro-3-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino) propan-2-ol | 3.24 LC 586.43 $[M+H]^+$ | Procedure 3, 4, 5, 6 and 8 |
| 77 |  | (R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)propan-2-ol | 3.83 LC No obs $[M+H]^+$ | Procedure 4, 5, 6 and 8 |
| 78 |  | (R)-1,1,1-trifluoro-3-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)propan-2-ol | 3.48 LC No obs $[M+H]^+$ | Procedure 4, 5, 6 and 8 |
| 79 |  | (R)-3-(1,1-bis(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 3.88 LC No obs. $[M+H]^+$ | Procedure 4, 5, 6 and 8 |
| 80 |  | (R)-3-((R)-1-(3,4-difluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 3.63 LC No obs. $[M+H]^+$ | Procedure 4, 5, 6 and 8 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 81 |  | (R)-3-((S)-1-(3,4-difluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 3.64 LC No obs. $[M+H]^+$ | Procedure 4, 5, 6 and 8 |

**[00221]** Additional compounds of the present invention were prepared by procedures analogous to those described above and to the additional procedures described below.

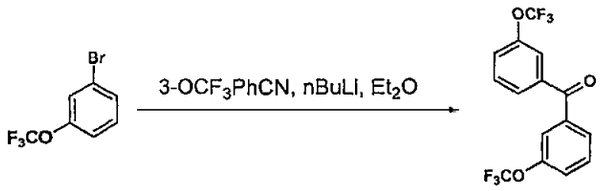
**EXAMPLE 82**



**1-(1,1-bis(3-(trifluoromethoxy)phenyl)but-3-enyl)-3-cyclopentylurea**

**Procedure 11**

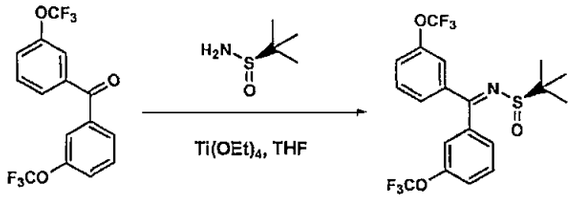
**Bis(3-(trifluoromethoxy)phenyl)methanone**




**[00222]** Using the same procedure as described in Example 2, Procedure 4, bis(3-(trifluoromethoxy)phenyl)methanone was obtained. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.39 - 7.45 (m, 1H), ) 7.36 (m, 1H), 7.25 (d, *J*=15.92 Hz, 1H), 7.15 - 7.20 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ ppm 193.27, 149.29, 138.66, 130.10, 128.27, 125.23,

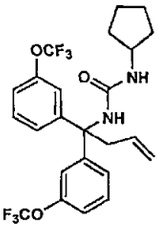
124.26, 122.26, 121.69, 119.13, 116.56; LC-MS (ESI) 351.2 (M+H), retention time = 4.0 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

**(R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide**



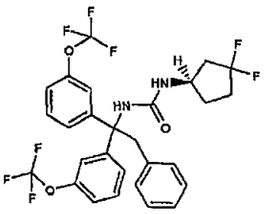

**[00223]** Using the same procedure as that of Procedure 5, (R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide was obtained. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.62- 7.28 (br, m, 8H), ) 1.34 (s, 9H); LC-MS (ESI) 454.28 (M+H), retention time = 4.12 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

**1-(1,1-bis(3-(trifluoromethoxy)phenyl)but-3-enyl)-3-cyclopentylurea**



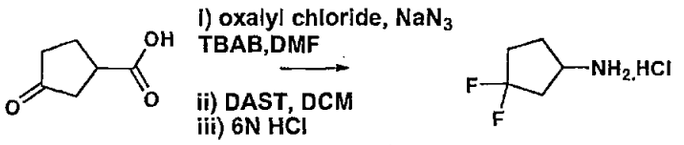

**[00224]** Using similar procedures as Procedure 6, and 2, 1-(1,1-bis(3-(trifluoromethoxy)phenyl)but-3-enyl)-3-cyclopentylurea was obtained. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (t, *J*=7.96 Hz, 2 H), 7.37 - 7.31 (m, 2 H) 7.27 (m, 2 H), 7.18 (d, *J*=8.08 Hz, 2 H), 5.48 - 5.36 (m, 1 H), 5.25 - 5.15 (m, 3 H), 4.10 (s, br, 1 H), 3.86 - 3.96 (m, 1 H), 3.17 (d, *J*=6.82 Hz, 2 H), 1.86 - 1.76 (m, 2 H), 1.53 - 1.42, (m, 4 H) 1.18 - 1.07 (m, 2 H); LC-MS (ESI) 503.33 (M+H), retention time = 4.26 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

## EXAMPLE 83



**(R)-1-(3,3-difluorocyclopentyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea**

### Procedure 12

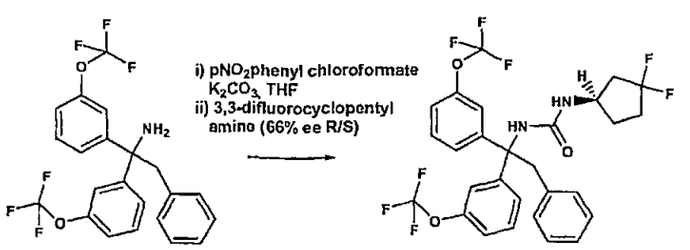



**[00225]** To the solution of 3-oxocyclopentanecarboxylic acid (2.85 g, 22.2 mmol) in dry $CH_2Cl_2$ (4 mL) was added oxalyl chloride (2.0M in dichloromethane, 13 mL) at 0 °C over 15 min followed by DMF (50 mL) After the addition was complete, the reaction mixture was stirred for 2 h (0 °C to rt). Tetrabutylammonium bromide (35 mg) was then added followed by a solution of sodium azide (2.17 g, 26.7 mmol, in the minimum amount of $H_2O$, 9 mL) at 0 °C, and the resulting light brown reaction mixture was stirred for 1 h at rt. The reaction was monitored and upon completion, the organic phase was separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 8 mL). The combined organic phases were washed with brine, dried with sodium sulfate, and filtered through a 2 cm plug of silica. The silica gel plug was washed with $CH_2Cl_2$, twice followed with 10% EtOAc in $CH_2Cl_2$. The resulting pale yellow filtrate was partially concentrated. Benzyl alcohol (25 mL) was added and the remainder of $CH_2Cl_2$ was removed under vacuum. The light brown solution was heated at 100 °C for 3h. After it was cooled to room temperature, the brown solution was vacuum distilled. Benzyl alcohol was collected and the viscous brown oil residue was purified by flash chromatography (120 g $SiO_2$, 0-40% EtOAc/hexane) to provide benzyl 3-oxocyclopentylcarbamate as a pale yellow and colorless oil (2.39 g, 46% yield). $^1H$ NMR ($CDCl_3$, 400 MHz): 7.35 (m, 5H), 5.09 (s, 2H), 4.87 (br, 1H), 4.28 (m, 1H), 2.63 (m, 1H), 2.39-2.15 (m, 4H), 1.86 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 400

MHz): 215.7, 155.8, 136.2, 128.6, 128.3, 128.2, 66.9, 49.3, 45.2, 37.0, 29.9. LC/MS: [M+H] = 234.1.

**[00226]** To a solution of benzyl 3-oxocyclopentylcarbamate (2.32 g, 9.96 mmol) in $CH_2Cl_2$ (10 mL) was added DAST (4.3 mL, 28.9 mmol) at rt. The reaction mixture turned brown while shaken at rt overnight. When the transformation was complete by HPLC, brine was added at 0 °C slowly to quench the reaction [Caution: reacted violently]. $CH_2Cl_2$ was added and the solution was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (40 g $SiO_2$, 0-40% EtOAc/hexane) to furnish benzyl 3,3-difluorocyclopentylcarbamate as an off-white solid (1.5 g, 59%). $^1H$ NMR ($CDCl_3$, 400 MHz): 7.35 (m, 5H), 5.09 (s, 2H), 4.90 (br, 1H), 4.23 (m, 1H), 2.50 (m, 1H), 2.25-1.98 (m, 4H), 1.70 (m, 1H). $^{13}C$ NMR ($CDCl_3$, 400 MHz): 155.6, 136.2, 128.6, 128.3, 128.2, 66.9, 50.86, 49.3, 42.6 (t), 34.2 (t), 30.6. $^{19}F$ NMR ($CDCl_3$, with $CFCl_3$ as standard, 400 MHz): -88.2(m, 1F), -91.4(m, 1F).

**[00227]** Benzyl 3,3-difluorocyclopentylcarbamate (1.5 g, 5.88 mmol) in 6N HCl (6 mL) was heated at 100 °C for 20 h. After the reaction mixture was cooled to rt, the brown solution was extracted with $Et_2O$ (2 x 2 mL) to remove unreacted starting material and toluene. The aqueous phase was dried in the speed vac with heating to give 3,3-difluorocyclopentanamine hydrochloride as a light brown solid (0.79 g, 85% yield). $^1H$ NMR (MeOD-$d_4$, 400 MHz): 4.79 (m, 1H), 2.62 (m, 1H), 2.32 (m, 2H), 2.18 (m, 2H), 1.87 (m, 1H).$^{13}C$ NMR (MeOD-$d_4$, 400 MHz): 131.4 (t), 41.0 (t), 34.8 (t), 28.9. $^{19}F$ NMR (MeOD-$d_4$, with $CFCl_3$ as standard, 400 MHz): -93.0 (m, 2F). LC/MS: [M+H] = 121.9.

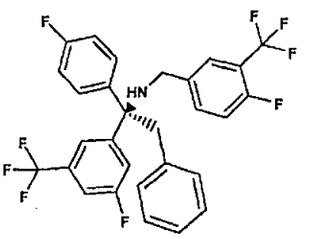



**[00228]** 2-Phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine was prepared according as described for Procedure 6. To a solution of 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine (77 mg, 0.17 mmol) in $CH_2Cl_2$ (1 mL), was

added $K_2CO_3$ (241 mg, 1.7 mmol) followed by 4-nitrophenyl chloroformate (70 mg, 0.35 mmol). The reaction mixture was stirred at rt until the starting material was consumed. The solution was diluted with $CH_2Cl_2$ and washed with $NaHCO_3$. The organic layer were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in anhydrous $CH_2Cl_2$ (1.6 mL) and this mixture was used as a stock solution of the intermediate carbamate (0.11 M in $CH_2Cl_2$).

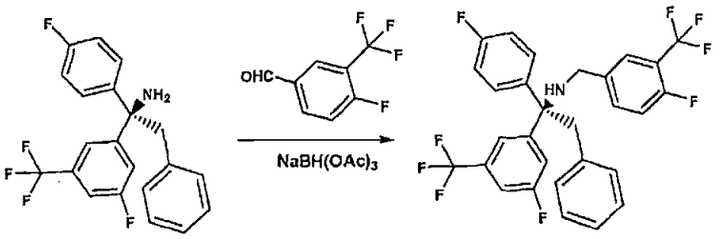
**[00229]** 4-Nitrophenyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethylcarbamate (400 μL of the above stock solution, 0.044 mmol) was added to a vial followed by 3,3-difluorocyclopentanamine hydrochloride (14 mg, 0.087 mmol, 66.4%ee R) and Hunig's base (15 μL, 0.087 mmol). The reaction was monitored for the disappearance of the carbamate. Upon completion, the reaction mixture was diluted with $CH_2Cl_2$, washed with successively with $NaHCO_3$ and 1N NaOH, and extracted with $CH_2Cl_2$ (3x). The combined organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Purification of the residue was accomplished by preparative HPLC (YMC Combiprep ODS-A 30x50 mm; mobile phase: 10% MeOH / 90% $H_2O$ / 0.1% TFA) to provide the desired urea (9.1 mg) as a film. $^1H$ NMR (500 MHz, $CDCl_3$, diastereomeric mixture, ca. 83:17) δ 7.36 (t, $J$ = 7.5 Hz, 2H), 7.22-7.10 (m, 7H), 7.06 (s, 2H), 6.65 (d, $J$ = 5.0 Hz, 2H), 4.89 (s, 1H), 4.33-4.24 (m, 1H), 4.23-4.14 (m, 1H), 3.76 (s, 2H), 2.42-2.30 (m, 1H), 2.13-1.93 (m, 3H), 1.77-1.67 (m, 1H), 1.48-1.41 (m, 1H); LC/MS (MeOH/$H_2O$/$NH_4OAc$ mobile phase) rt = 4.26 min; [M+H] = 589.3.

## EXAMPLE 84




**(R)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine**

**Procedure 13**




**[00230]** (R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (21.5 mg, 0.057 mmol) in dichloroethane (0.5 mL) in a two drum vial was added 4-fluoro-3-(trifluoromethyl)benzaldehyde (21.9 mg, 0.114 mmol) followed by a drop of acetic acid. The reaction mixture was shaken for 20 minutes at room temperature before $NaBH(OAc)_3$ (36.3 mg, 0.171 mmol) was added. The reaction was stirred at room temperature overnight. The solvents were removed and the residue was purified by preparative HPLC (phenominex C18 column, 21x100 mm, 5 μ) using $MeOH/H_2O$ (with 0.1%TFA) to give (R)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine as a colorless oil (17.5 mg, 46% yield). LCMS: 4.32 min (4 min gradient, $MeOH/H_2O$ 0.1%TFA); 1H NMR (400 MHz, $CDCl_3$) δ ppm 3.78 - 3.91 (m, 4 H), 6.60 (d, *J*=7.47 Hz, 2 H), 7.14 - 7.27 (m, 7 H), 7.35 - 7.48 (m, 6 H).

**TABLE 4**

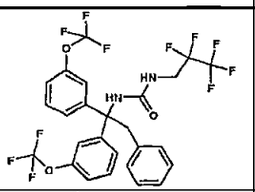
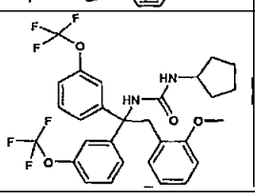
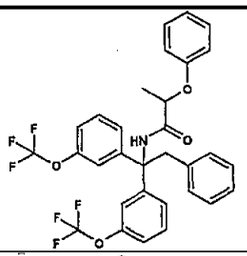
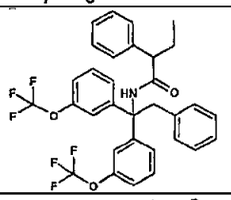
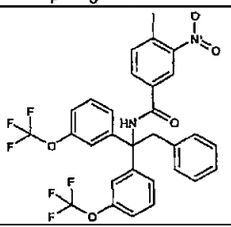
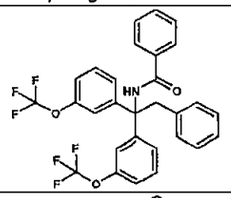
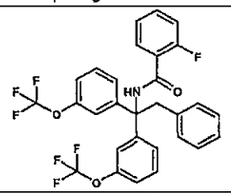
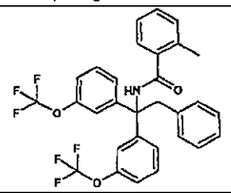
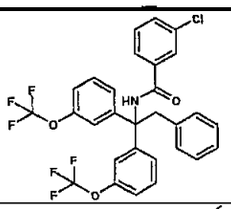
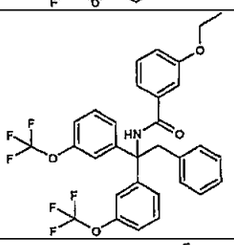
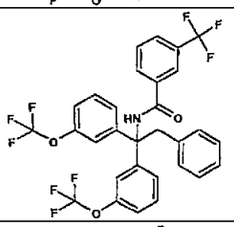
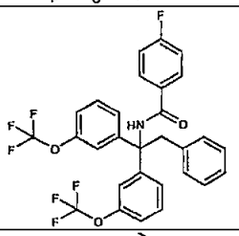
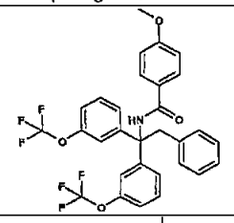
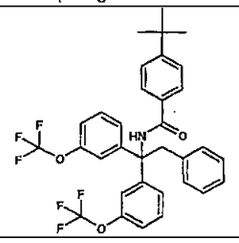
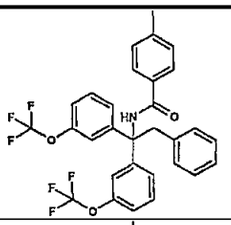
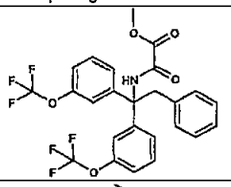
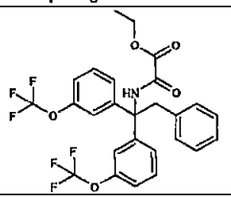
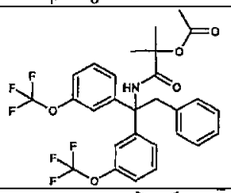
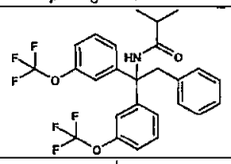
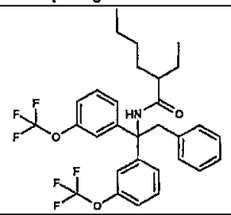
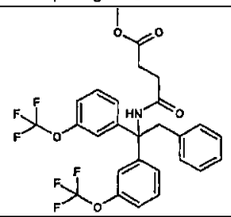
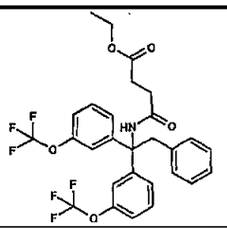
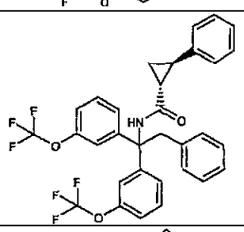
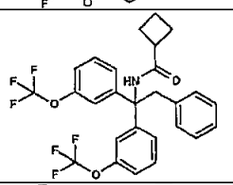
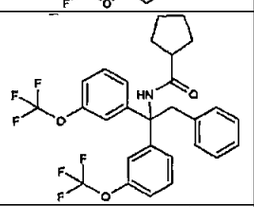
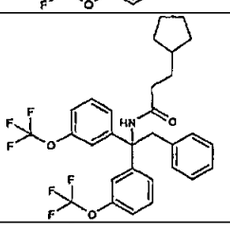
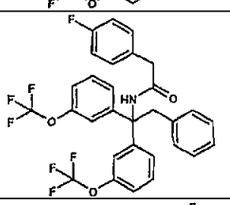
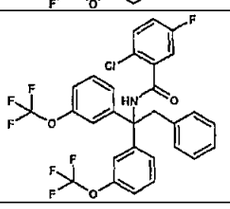
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| 86 |  | 1-cyclopentyl-3-(2-(2-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.92 LC 583.03 $[M+H]^+$ | Procedure 11 and 2 |

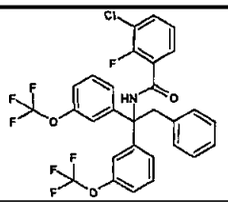
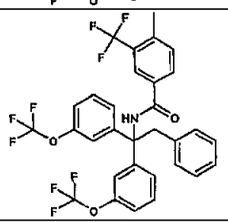
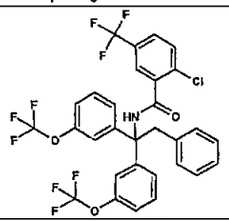
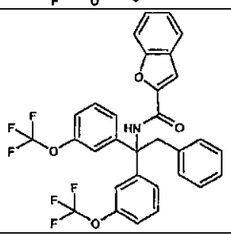
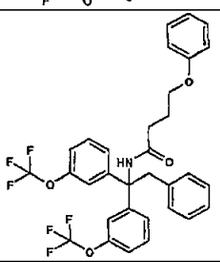
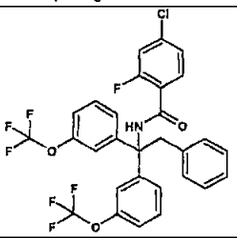
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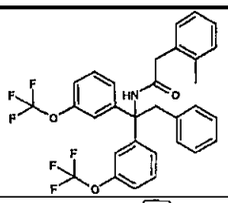
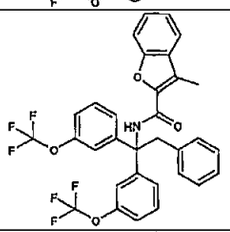
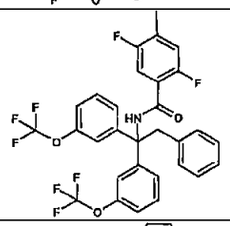
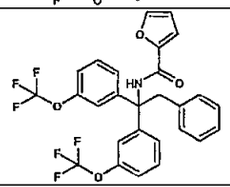
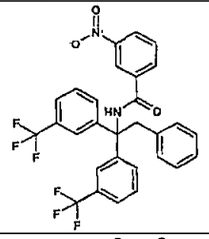
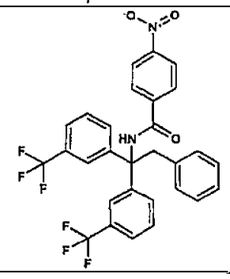
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 87 |  | 2-phenoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)propanamide | 4.37 LC 590.16 $[M+H]^+$ | Procedure 11 and 7 |
| 88 |  | 2-phenyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)butanamide | 4.39 LC 588.22 $[M+H]^+$ | Procedure 11 and 7 |
| 89 |  | 4-methyl-3-nitro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)benzamide | 4.31 LC 605.15 $[M+H]^+$ | Procedure 11 and 7 |
| 90 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.24 LC 546.14 $[M+H]^+$ | Procedure 11 and 7 |
| 91 |  | 2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.27 LC 564.09 $[M+H]^+$ | Procedure 11 and 7 |
| 92 |  | 2-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.26 LC 560.14 $[M+H]^+$ | Procedure 11 and 7 |

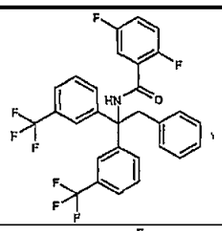
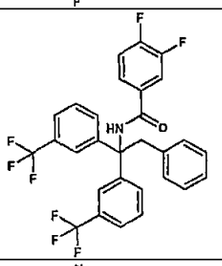
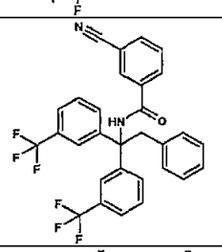
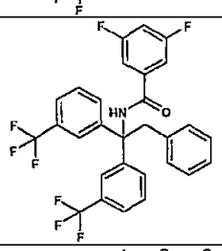
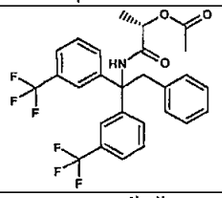
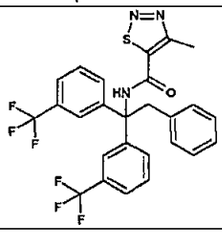
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 93 |  | 3-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.36 LC 580.09 $[M+H]^+$ | Procedure 11 and 7 |
| 94 |  | 3-ethoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.32 LC 590.16 $[M+H]^+$ | Procedure 11 and 7 |
| 95 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) -3-(trifluoromethyl)benzamide | 4.36 LC 614.1 $[M+H]^+$ | Procedure 11 and 7 |
| 96 |  | 4-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.28 LC 564.12 $[M+H]^+$ | Procedure 11 and 7 |
| 97 |  | 4-methoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)benzamide | 4.26 LC 576.15 $[M+H]^+$ | Procedure 11 and 7 |
| 98 |  | 4-tert-butyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)benzamide | 4.51 LC 602.16 $[M+H]^+$ | Procedure 11 and 7 |

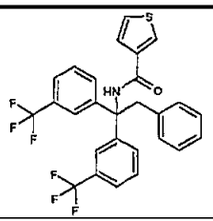
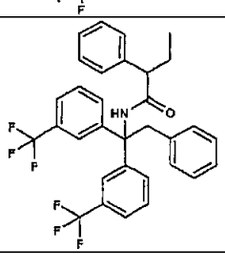
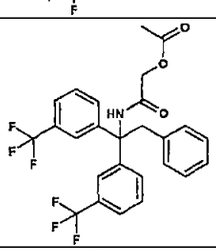
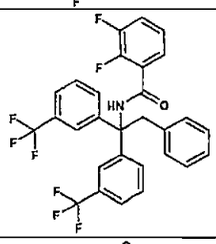
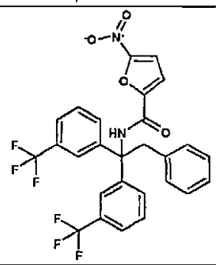
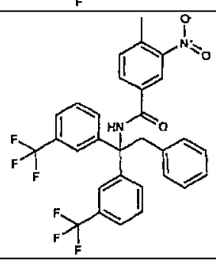
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 99 |  | 4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.30 LC 560.14 $[M+H]^+$ | Procedure 11 and 7 |
| 100 |  | methyl 2-oxo-2-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)acetate | 4.13 LC 528.08 $[M+H]^+$ | Procedure 11 and 7 |
| 101 |  | ethyl 2-oxo-2-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)acetate | 4.18 LC 542.14 $[M+H]^+$ | Procedure 11 and 7 |
| 102 |  | 2-methyl-1-oxo-1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)propan-2-yl acetate | 4.19 LC 570.15 $[M+H]^+$ | Procedure 11 and 7 |
| 103 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) isobutyramide | 4.22 LC 512.14 $[M+H]^+$ | Procedure 11 and 7 |
| 104 |  | 2-ethyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) hexanamide | 4.45 LC 568.21 $[M+H]^+$ | Procedure 11 and 7 |
| 105 |  | methyl 4-oxo-4-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)butanoate | 4.17 LC 556.13 $[M+H]^+$ | Procedure 11 and 7 |

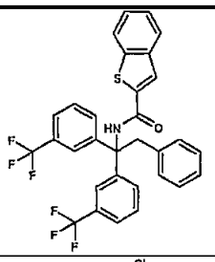
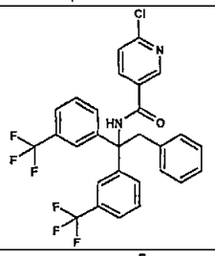
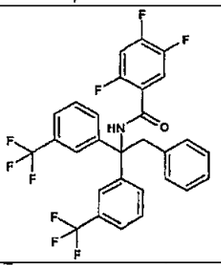
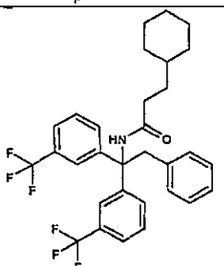
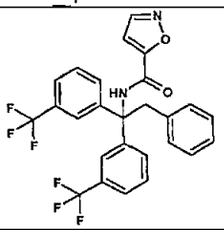
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 106 |  | ethyl 4-oxo-4-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)butanoate | 4.21 LC 570.15 $[M+H]^+$ | Procedure 11 and 7 |
| 107 |  | (1R,2R)-2-phenyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl) cyclopropanecarboxamide | 4.37 LC 586.15 $[M+H]^+$ | Procedure 11 and 7 |
| 108 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) cyclobutanecarboxamide | 4.27 LC 524.13 $[M+H]^+$ | Procedure 11 and 7 |
| 109 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) cyclopentanecarboxamide | 4.32 LC 538.14 $[M+H]^+$ | Procedure 11 and 7 |
| 110 |  | 3-cyclopentyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)propanamide | 4.48 LC 566.17 $[M+H]^+$ | Procedure 11 and 7 |
| 111 |  | 2-(4-fluorophenyl)-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)acetamide | 4.29 LC 578.1 $[M+H]^+$ | Procedure 11 and 7 |
| 112 |  | 2-chloro-5-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)benzamide | 4.27 LC 598.06 $[M+H]^+$ | Procedure 11 and 7 |

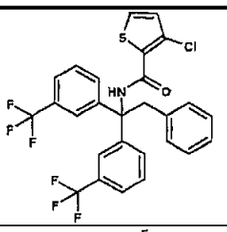
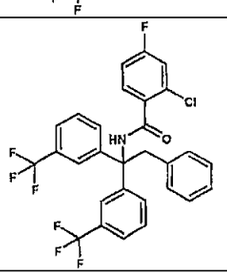
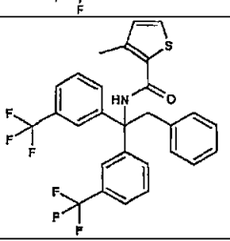
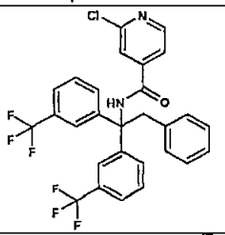
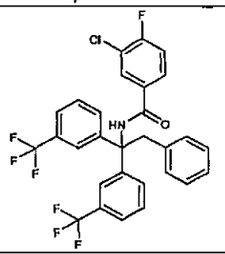
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 113 |  | 3-chloro-2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)benzamide | 4.35 LC 598.04 $[M+H]^+$ | Procedure 11 and 7 |
| 114 |  | 4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) -3-(trifluoromethyl)benzamide | 4.43 LC 628.11 $[M+H]^+$ | Procedure 11 and 7 |
| 115 |  | 2-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) -5-(trifluoromethyl)benzamide | 4.36 LC 648.05 $[M+H]^+$ | Procedure 11 and 7 |
| 116 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzofuran-2-carboxamide | 4.39 LC 586.12 $[M+H]^+$ | Procedure 11 and 7 |
| 117 |  | 4-phenoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)butanamide | 4.39 LC 604.16 $[M+H]^+$ | Procedure 11 and 7 |
| 118 |  | 4-chloro-2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)benzamide | 4.39 LC 598.1 $[M+H]^+$ | Procedure 11 and 7 |

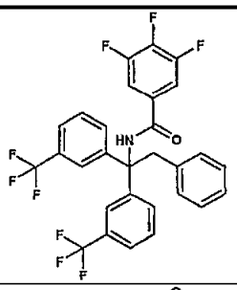
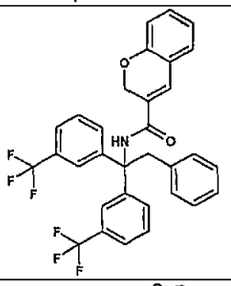
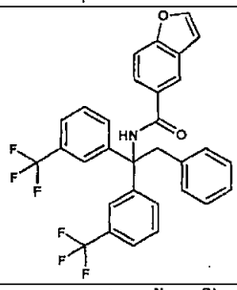
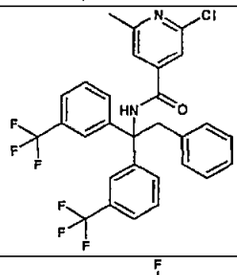
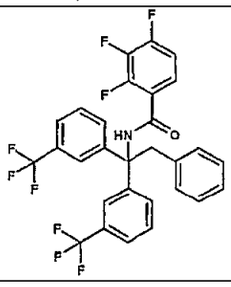
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 119 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-2-o-tolylacetamide | 4.35 LC 574.15 $[M+H]^+$ | Procedure 11 and 7 |
| 120 |  | 3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzofuran-2-carboxamide | 4.57 LC 600.14 $[M+H]^+$ | Procedure 11 and 7 |
| 121 |  | 2,5-difluoro-4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) benzamide | 4.40 LC 596.1 $[M+H]^+$ | Procedure 11 and 7 |
| 122 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl) furan-2-carboxamide | 4.19 LC 536.13 $[M+H]^+$ | Procedure 11 and 7 |
| 127 |  | 3-nitro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.19 LC 559.22 $[M+H]^+$ | Procedure 11 and 7 |
| 128 |  | 4-nitro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.19 LC 559.21 $[M+H]^+$ | Procedure 11 and 7 |

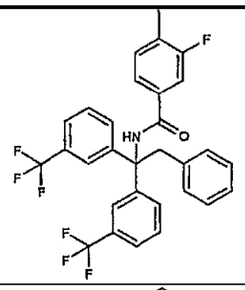
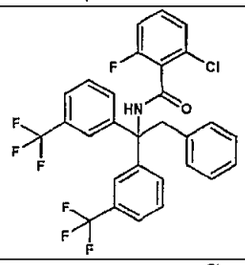
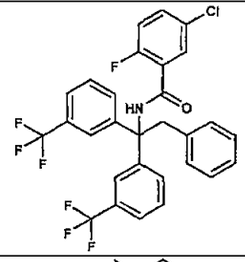
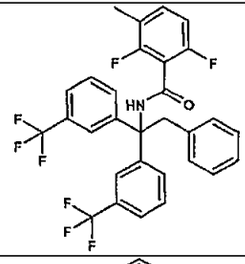
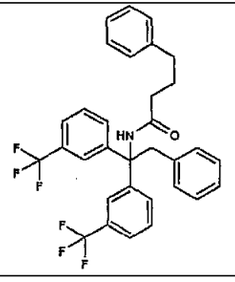
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 129 |  | 2,5-difluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.19 LC 550.21 $[M+H]^+$ | Procedure 11 and 7 |
| 130 |  | 3,4-difluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.22 LC 550.2 $[M+H]^+$ | Procedure 11 and 7 |
| 131 |  | 3-cyano-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.10 LC 539.2 $[M+H]^+$ | Procedure 11 and 7 |
| 132 |  | 3,5-difluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.24 LC 550.21 $[M+H]^+$ | Procedure 11 and 7 |
| 133 |  | (S)-1-oxo-1-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethylamino)propan-2-yl acetate | 4.04 LC 524.23 $[M+H]^+$ | Procedure 11 and 7 |
| 134 |  | 4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-1,2,3-thiadiazole-5-carboxamide | 4.14 LC 536.2 $[M+H]^+$ | Procedure 11 and 7 |

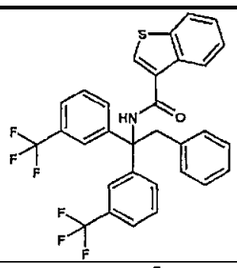
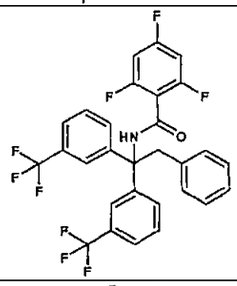
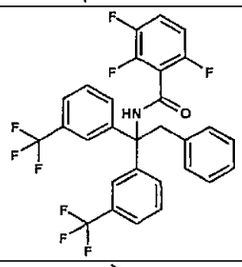
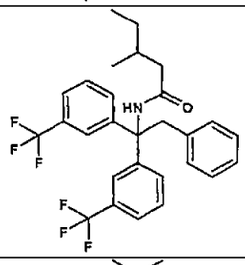
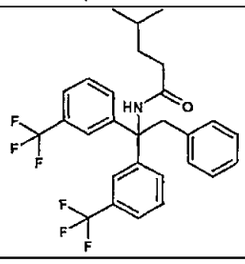
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 135 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) thiophene-3-carboxamide | 4.10 LC 520.17 $[M+H]^+$ | Procedure 11 and 7 |
| 136 |  | 2-phenyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) butanamide | 4.29 LC 556.26 $[M+H]^+$ | Procedure 11 and 7 |
| 137 |  | 2-oxo-2-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethylamino)ethyl acetate | 4.00 LC 510.2 $[M+H]^+$ | Procedure 11 and 7 |
| 138 |  | 2,3-difluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.16 LC 550.14 $[M+H]^+$ | Procedure 11 and 7 |
| 139 |  | 5-nitro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) furan-2-carboxamide | 4.11 LC 549.16 $[M+H]^+$ | Procedure 11 and 7 |
| 140 |  | 4-methyl-3-nitro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.23 LC 573.21 $[M+H]^+$ | Procedure 11 and 7 |

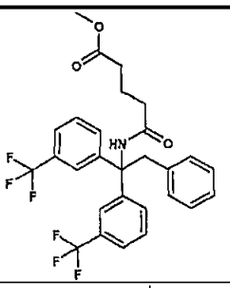
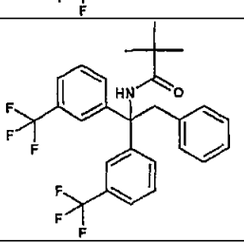
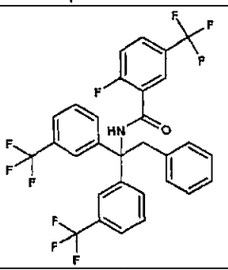
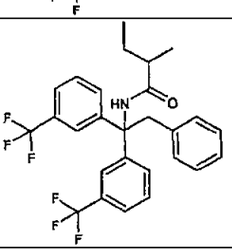
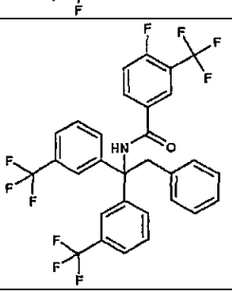
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 141 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzo[b]thiophene-2-carboxamide | 4.29 LC 570.17 $[M+H]^+$ | Procedure 11 and 7 |
| 142 |  | 6-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) nicotinamide | 4.15 LC 549.17 $[M+H]^+$ | Procedure 11 and 7 |
| 143 |  | 2,4,5-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.24 LC 568.2 $[M+H]^+$ | Procedure 11 and 7 |
| 144 |  | 3-cyclohexyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)propanamide | 4.44 LC 548.27 $[M+H]^+$ | Procedure 11 and 7 |
| 145 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) isoxazole-5-carboxamide | 4.00 LC 505.18 $[M+H]^+$ | Procedure 11 and 7 |

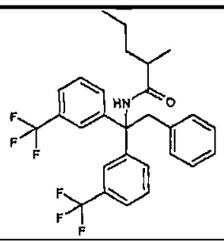
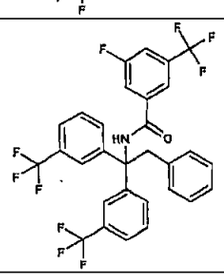
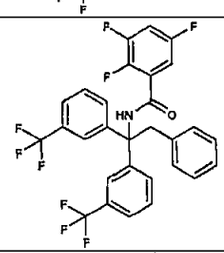
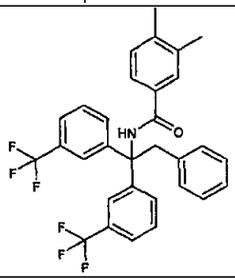
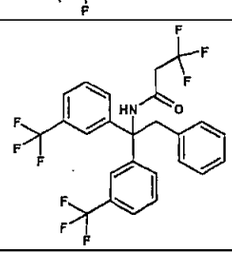
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 146 |  | 3-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) thiophene-2-carboxamide | 4.22 LC 554.12 $[M+H]^+$ | Procedure 11 and 7 |
| 147 |  | 2-chloro-4-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.18 LC 566.15 $[M+H]^+$ | Procedure 11 and 7 |
| 148 |  | 3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) thiophene-2-carboxamide | 4.15 LC 534.19 $[M+H]^+$ | Procedure 11 and 7 |
| 149 |  | 2-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) isonicotinamide | 4.17 LC 549.17 $[M+H]^+$ | Procedure 11 and 7 |
| 150 |  | 3-chloro-4-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.30 LC 566.15 $[M+H]^+$ | Procedure 11 and 7 |

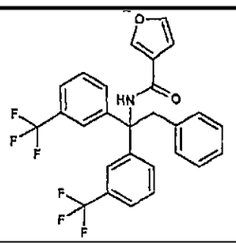
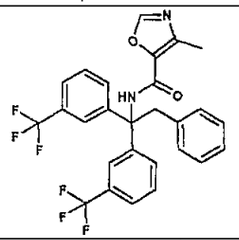
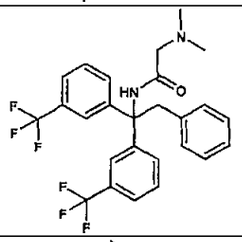
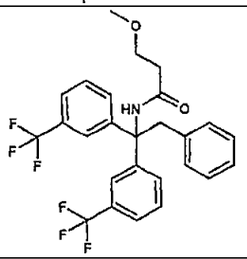
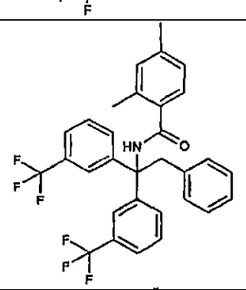
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 151 |  | 3,4,5-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.33 LC 568.15 $[M+H]^+$ | Procedure 11 and 7 |
| 152 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-2H-chromene-3-carboxamide | 4.31 LC 568.17 $[M+H]^+$ | Procedure 11 and 7 |
| 153 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzofuran-5-carboxamide | 4.17 LC 554.16 $[M+H]^+$ | Procedure 11 and 7 |
| 154 |  | 2-chloro-6-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)isonicotinamide | 4.23 LC 563.15 $[M+H]^+$ | Procedure 11 and 7 |
| 155 |  | 2,3,4-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.23 LC 568.12 $[M+H]^+$ | Procedure 11 and 7 |

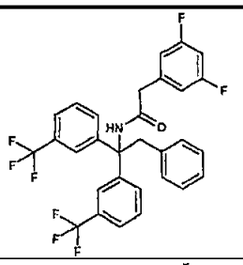
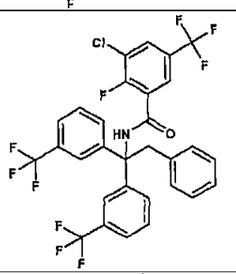
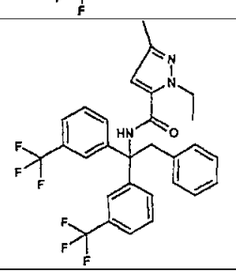
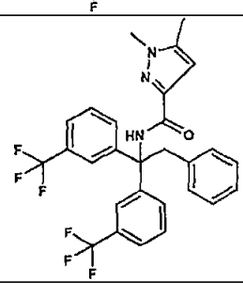
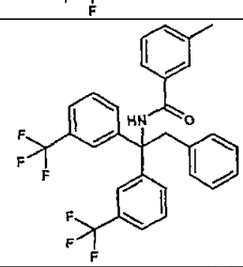
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 156 |  | 3-fluoro-4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.24 LC 546.15 $[M+H]^+$ | Procedure 11 and 7 |
| 157 |  | 2-chloro-6-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.11 LC 566.13 $[M+H]^+$ | Procedure 11 and 7 |
| 158 |  | 5-chloro-2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.27 LC 566.09 $[M+H]^+$ | Procedure 11 and 7 |
| 159 |  | 2,6-difluoro-3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.13 LC 564.15 $[M+H]^+$ | Procedure 11 and 7 |
| 160 |  | 4-phenyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) butanamide | 4.30 LC 556.21 $[M+H]^+$ | Procedure 11 and 7 |

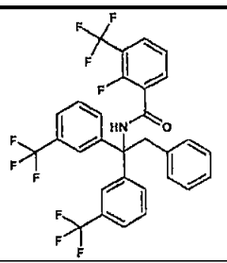
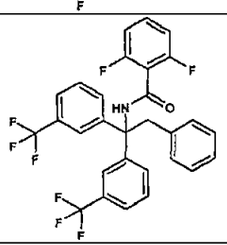
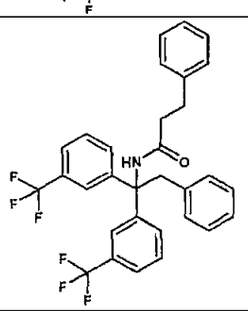
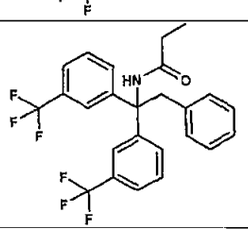
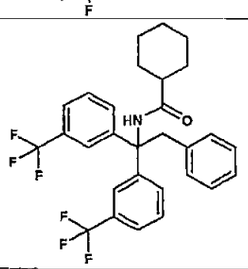
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 161 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzo[b]thiophene-3-carboxamide | 4.28 LC 570.12 $[M+H]^+$ | Procedure 11 and 7 |
| 162 |  | 2,4,6-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.12 LC 568.11 $[M+H]^+$ | Procedure 11 and 7 |
| 163 |  | 2,3,6-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.11 LC 568.15 $[M+H]^+$ | Procedure 11 and 7 |
| 164 |  | 3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) pentanamide | 4.24 LC 508.26 $[M+H]^+$ | Procedure 11 and 7 |
| 165 |  | 4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) pentanamide | 4.25 LC 508.19 $[M+H]^+$ | Procedure 11 and 7 |

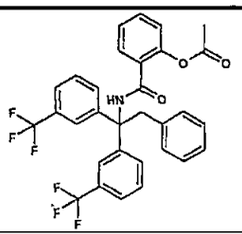
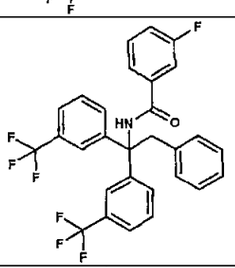
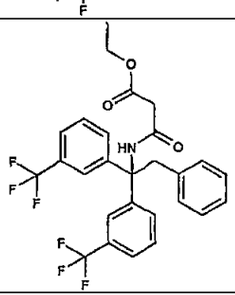
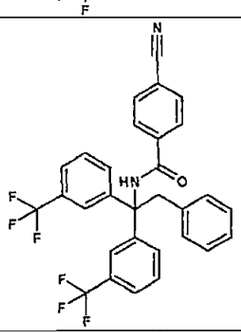
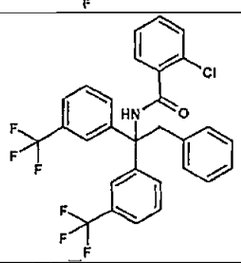
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 166 |  | methyl 5-oxo-5-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethylamino)pentanoate | 4.06 LC 538.2 $[M+H]^+$ | Procedure 11 and 7 |
| 167 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) pivalamide | 4.18 LC 494.19 $[M+H]^+$ | Procedure 11 and 7 |
| 168 |  | 2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-5-(trifluoromethyl)benzamide | 4.26 LC 600.1 $[M+H]^+$ | Procedure 11 and 7 |
| 169 |  | 2-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) butanamide | 4.16 LC 494.19 $[M+H]^+$ | Procedure 11 and 7 |
| 170 |  | 4-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.30 LC 600.12 $[M+H]^+$ | Procedure 11 and 7 |

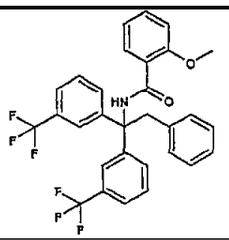
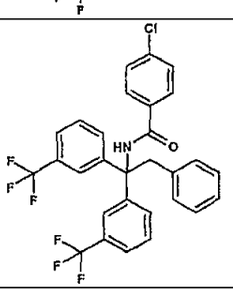
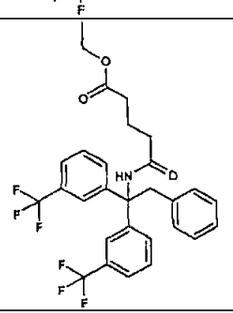
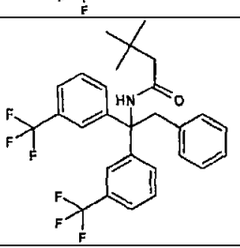
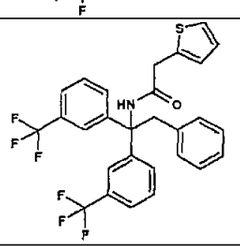
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 171 |  | 2-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) pentanamide | 4.22 LC 508.26 $[M+H]^+$ | Procedure 11 and 7 |
| 172 |  | 3-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-5-(trifluoromethyl)benzamide | 4.35 LC 600.2 $[M+H]^+$ | Procedure 11 and 7 |
| 173 |  | 2,3,5-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.22 LC 568.11 $[M+H]^+$ | Procedure 11 and 7 |
| 174 |  | 3,4-dimethyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.26 LC 542.2 $[M+H]^+$ | Procedure 11 and 7 |
| 175 |  | 3,3,3-trifluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)propanamide | 4.07 LC 520.14 $[M+H]^+$ | Procedure 11 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 176 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) furan-3-carboxamide | 4.06 LC 504.15 $[M+H]^+$ | Procedure 11 and 7 |
| 177 |  | 4-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) oxazole-5-carboxamide | 4.06 LC 504.15 $[M+H]^+$ | Procedure 11 and 7 |
| 178 |  | 2-(dimethylamino)-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)acetamide | 3.50 LC 495.22 $[M+H]^+$ | Procedure 11 and 7 |
| 179 |  | 3-methoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)propanamide | 4.06 LC 496.19 $[M+H]^+$ | Procedure 11 and 7 |
| 180 |  | 2,4-dimethyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethyl)benzamide | 4.23 LC 542.19 $[M+H]^+$ | Procedure 11 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 181 |  | 2-(3,5-difluorophenyl)-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) acetamide | 4.21 LC 564.15 $[M+H]^+$ | Procedure 11 and 7 |
| 182 |  | 3-chloro-2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)-5-(trifluoromethyl)benzamide | 4.38 LC 634.17 $[M+H]^+$ | Procedure 11 and 7 |
| 183 |  | 1-ethyl-3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)-1H-pyrazole-5-carboxamide | 4.17 LC 546.27 $[M+H]^+$ | Procedure 11 and 7 |
| 184 |  | 1,5-dimethyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)-1H-pyrazole-3-carboxamide | 4.09 LC 532.27 $[M+H]^+$ | Procedure 11 and 7 |
| 185 |  | 3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.20 LC 528.26 $[M+H]^+$ | Procedure 11 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 186 |  | 2-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.23 LC 600.17 $[M+H]^+$ | Procedure 11 and 7 |
| 187 |  | 2,6-difluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.07 LC 550.17 $[M+H]^+$ | Procedure 11 and 7 |
| 188 |  | 3-phenyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) propanamide | 4.25 LC 542.26 $[M+H]^+$ | Procedure 11 and 7 |
| 189 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) propionamide | 4.06 LC 466.25 $[M+H]^+$ | Procedure 11 and 7 |
| 190 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) cyclohexanecarboxamide | 4.26 LC 520.26 $[M+H]^+$ | Procedure 11 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 191 |  | 2-((2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) carbamoyl)phenyl acetate | 4.07 LC 572.22 $[M+H]^+$ | Procedure 11 and 7 |
| 192 |  | 3-fluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.17 LC 532.21 $[M+H]^+$ | Procedure 11 and 7 |
| 193 |  | ethyl 3-oxo-3-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethylamino)propanoate | 4.10 LC 539.2 $[M+H]^+$ | Procedure 11 and 7 |
| 194 |  | 4-cyano-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.10 LC 539.2 $[M+H]^+$ | Procedure 11 and 7 |
| 195 |  | 2-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.13 LC 548.17 $[M+H]^+$ | Procedure 11 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 196 |  | 2-methoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.21 LC 544.2 $[M+H]^+$ | Procedure 11 and 7 |
| 197 |  | 4-chloro-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) benzamide | 4.25 LC 548.16 $[M+H]^+$ | Procedure 11 and 7 |
| 198 |  | ethyl 5-oxo-5-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl) ethylamino)pentanoate | 4.11 LC 552.26 $[M+H]^+$ | Procedure 11 and 7 |
| 199 |  | 3,3-dimethyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)butanamide | 4.23 LC 508.26 $[M+H]^+$ | Procedure 11 and 7 |
| 200 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl)-2-(thiophen-2-yl)acetamide | 4.14 LC 534.18 $[M+H]^+$ | Procedure 11 and 7 |

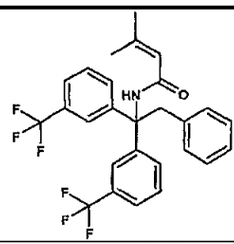
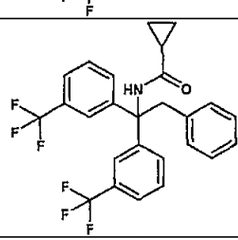
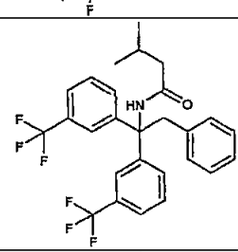
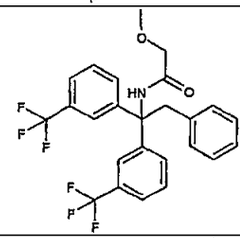
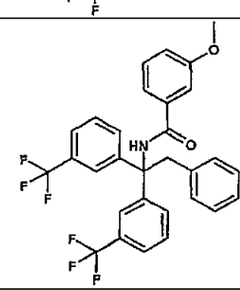
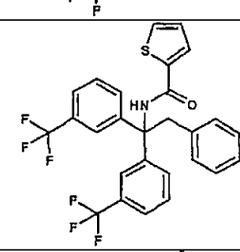
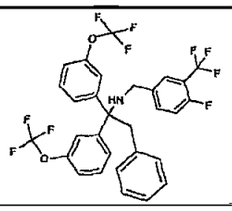
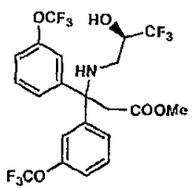
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 201 |  | 3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) but-2-enamide | 4.14 LC 492.26 $[M+H]^+$ | Procedure 11 and 7 |
| 202 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) cyclopropanecarboxamide | 4.07 LC 478.23 $[M+H]^+$ | Procedure 11 and 7 |
| 203 |  | 3-methyl-N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) butanamide | 4.17 LC 494.26 $[M+H]^+$ | Procedure 11 and 7 |
| 204 |  | 2-methoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)acetamide | 4.03 LC 482.25 $[M+H]^+$ | Procedure 11 and 7 |
| 205 |  | 3-methoxy-N-(2-phenyl-1,1-bis(3-(trifluoromethyl) phenyl)ethyl)benzamide | 4.15 LC 544.27 $[M+H]^+$ | Procedure 11 and 7 |
| 206 |  | N-(2-phenyl-1,1-bis(3-(trifluoromethyl)phenyl)ethyl) thiophene-2-carboxamide | 4.09 LC 520.2 $[M+H]^+$ | Procedure 11 and 7 |

**TABLE 6**

| Ex. No | Compound Structure | Compound Name | Retention Time Min./ Molecular Mass | Procedure of Ex. |
|---|---|---|---|---|
| 207 |  | N-(4-fluoro-3-(trifluoromethyl)benzyl)-2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethanamine | 4.51 LC No obs. $[M+H]^+$ | Procedure 11 and 13 |

**[00231]** Additional compounds of the present invention were prepared by the general procedures analogous to those described above and to the additional general procedures described below.

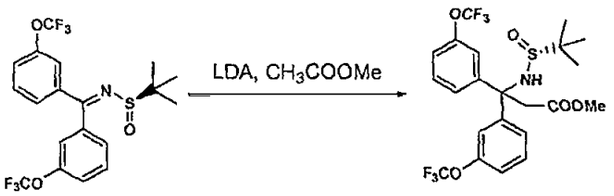
**EXAMPLE 208**



**(R)-methyl 3-(3,3,3-trifluoro-2-hydroxypropylamino)-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate**

**Procedure 14**

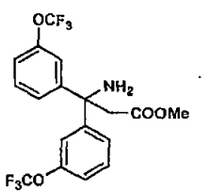
**(R)-methyl 3-(2-methylpropan-2-ylsulfinamido)-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate**




**[00232]** (R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide was prepared as described for Procedure 11. Under an argon atmosphere,

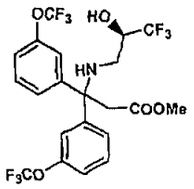
$CH_3COOMe$ (0.70 mL, 8.83 mmol, 2.0 eq) was stirred in anhydrous $Et_2O$ (50 mL) in an oven-dried round bottomed flask at -78°C. LDA (2.0 M, 4.4 mL, 8.8 mmol, 2.0 eq) was added dropwise. The resulting mixture was stirred at -78°C for 30 min. (R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (2.0 g, 4.42 mmol) in $Et_2O$ (10 mL) was added dropwise to the above stirred solution. The reaction mixture was stirred at -78°C for 1.5 h. Saturated $NH_4Cl$ was added, followed by the addition of EtOAc. The organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0 to 100%) to give N-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl)-ethyl)-2-methylpropane-2-sulfinamide as light tan oil (1.96 g, yield: 84.1%). LC-MS (ESI) 528.34 (M+H), retention time = 4.00 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.36 (d, J=8.0 Hz, 2H), 7.31 (t, J=8.0 Hz, 1H), 7.25 - 7.18 (m, 2H), 7.14 - 7.05 (m, 3H), 6.14 (s, 1H), 3.93 (d, *J*=16.1 Hz, 1H), 3.54 (d, *J*=15.9 Hz, 1H), 3.86 (m, 2 H), 3.49 (s, 3H), 1.26 (s, 9H). $^{13}C$ NMR (400 MHz, $CDCl_3$) □ ppm 22.71, 43.84, 51.68, 56.41, 63.69, 118.63, 119.52, 120.49, 121.35, 124.27, 125.73, 129.81, 129.92, 143.83, 147.52, 149.33, 171.93.

**Methyl 3-amino-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate**



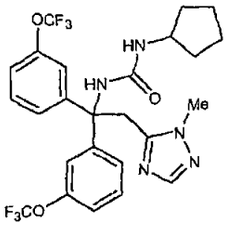

**[00233]** Using the same procedure as that of Procedure 6, methyl 3-amino-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate was obtained. LC-MS (ESI) 407.16 (M-$NH_3$+H) , retention time = 3.18 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.18 - 7.27 (m, 6 H), 7.02 (d, *J*=8.07 Hz, 2 H), 3.47 (s, 3H), 3.17 (s, 2H).

**(R)-methyl 3-(3,3,3-trifluoro-2-hydroxypropylamino)-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate**



**[00234]** Using a similar procedure to that described in Procedure 8, (R)-methyl 3-(3,3,3-trifluoro-2-hydroxypropylamino)-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate was obtained. LC-MS (ESI) 536.29 (M+H), retention time = 3.93 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.38-7.35 (m, 2H), 7.24 - 7.19 (m, 2H), 7.13 (m, 4H), 3.44 (s, 3H), 3.22-3.35 (m, 2H), 2.57-2.74 (m, 2H).

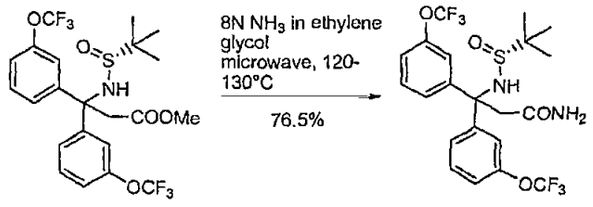
**EXAMPLE 209**



**1-cyclopentyl-3-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea**

**Procedure 15**

**(R)-3-(2-methylpropan-2-ylsulfinamido)-3,3-bis(3-(trifluoromethoxy)phenyl)propanamide**

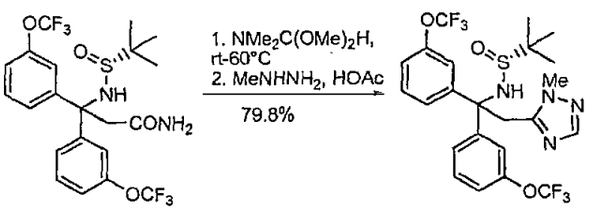



**[00235]** (R)-methyl-3-(2-methylpropan-2-ylsulfinamido)-3,3-bis(3-(trifluoromethoxy)phenyl)propanoate (prepared as described for Procedure 11, 0.70 g,

1.33 mmol) was dissolved in 8N $NH_3$ in ethylene glycol (6 mL) at room temperature in a microwave vial. The reaction mixture was heated at 120°C for 1200sec, and then at 130°C for 1200sec under microwave irradiation. After cooling, the cap was removed, and $H_2O$ was added. The mixture was extracted with EtOAc (3x), washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc, then 10%MeOH in EtOAc) to give 3-(2-methylpropan-2-ylsulfinamido)-3,3-bis(3-(trifluoromethoxy)phenyl)-propanamide as white solid (0.52 g, yield: 76%) LCMS: 3.88 min [M+1] 513.28 (4min gradient, MeOH/$H_2O$ 0.1%TFA); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.29 (m, 3 H), 7.22 - 7.12 (m, 3 H), 7.11- 7.02 (m, 2 H), 6.29 (m, 2 H), 5.40 (s, br, 1 H), 3.78 (d, *J*=14.50 Hz, 1 H), 3.71 (s, 2 H), 3.35 (d, *J*=14.50 Hz, 1 H), 1.21 - 1.28 (m, 9 H).

**Procedure 16**

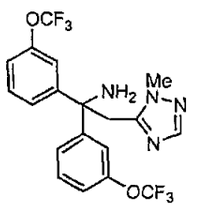
**(R)-2-methyl-N-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide**




**[00236]** (R)-3-(2-methylpropan-2-ylsulfinamido)-3,3-bis(3-(trifluoromethoxy)phenyl)propanamide (Procedure 15, 0.21 g, 0.41 mmol) was stirred in N,N-dimethylformamide dimethylacetal (6 mL) at room temperature for 1.5 h, then 60°C for 20 min. The solvent was evaporated to give crude N-(5-(dimethylamino)-3-oxo-1,1-bis(3-(trifluoromethoxy)phenyl)pent-4-enyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI) 568.4 (M+H), retention time = 3.60 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run). This brownish residue was dissolved in HOAc (2 mL), and methyl hydrazine (0.4 mL) was added. The resulting reaction mixture was heated at 60°C for 1.5 h. After cooling, $H_2O$ was added. It was extracted with EtOAc (2x), washed with sat'd $NaHCO_3$, $H_2O$ and brine, dried over $Na_2SO_4$, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica

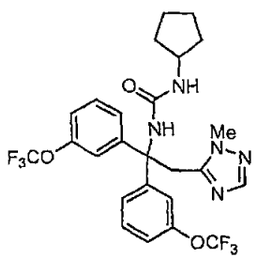
gel, hexanes/EtOAc) to give 2-methyl-N-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide (0.18g, yield: 79.8%). LC-MS (ESI) 551.35 (M+H), retention time = 3.99 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run);

**2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)-ethanamine**



**[00237]** Using the same procedure as that described in Procedure 6, 2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine was obtained. LC-MS (ESI) 447.24 (M+H), retention time = 2.90 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run);

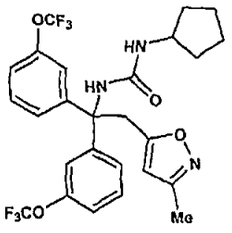
**1-cyclopentyl-3-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea**



**[00238]** Using the same procedure as described for Procedure 2, 1-cyclopentyl-3-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea was obtained. LC-MS (ESI) 558.43 (M+H), retention time = 3.81 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ ppm 7.44 (s, 1H), 7.32 (t, *J*=8.0Hz, 2H), 7.26 (m, 2H), 7.18 (m, 2H), 7.11 (d, J= 8.0Hz, 2H), 6.96 (br, s, 1H), 4.56 (m, 1H), 3.87 (m, 1H), 3.73 (s, 2H), 3.35 (s, 3H), 1.92-1.85 (m, 2H), 1.61-1.49 (m, 4H), 1.29-1.22 (m, 2H).

286

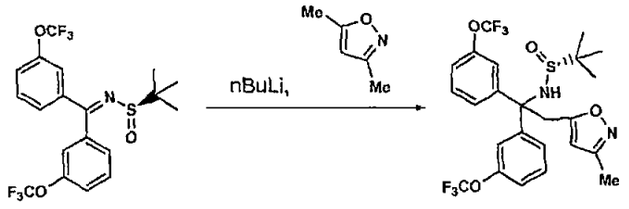
**EXAMPLE 210**



**1-cyclopentyl-3-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea**

**Procedure 17**

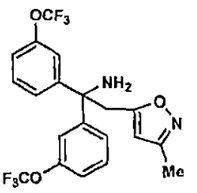
**(R)-2-methyl-N-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide**



**[00239]** (R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide was prepared as described for Procedure 11. Under an Argon atmosphere, 3,5-dimethylisoxazole (0.20 mL) was stirred in anhydrous THF in an oven-dried round bottomed flask at -78°C. nBuLi (2.5 M in hexanes, 0.84 mL, 2.1mmol) was added dropwise. The resulting yellowish solution was stirred at -78°C for 2h. N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (0.81g, 1.8mmol) in THF (2 mL) was added dropwise to the above stirred solution. The reaction mixture was stirred at -78°C for 5h, then slowly warmed up to room temperature overnight. Saturated $NH_4Cl$ was added, followed by the addition of EtOAc. The organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0 to 100%, came out at 100% EtOAc) to give 2-methyl-N-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide as light tan viscous oil (0.14g, yield: 13.5% with 0.55 g recovery of the starting material). LC-MS (ESI) 551.38

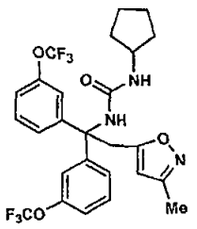
(M+H), retention time = 3.98 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.49 - 7.40 (m, 2H), 7.37 - 7.28(m, 1H), 7.19 (d, *J*=6.57 Hz, 1 H), 7.05 - 7.14 (m, 4 H), 5.70 (s, 1H), 4.61 (s, 1H), 4.14 (d, *J*=14.40 Hz, 1H), 3.88 (d, *J*=14.40 Hz, 1H), 2.26 (s, 2 H), 2.13 (s, 3H), 1.26 (s, 9H).

**2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine**



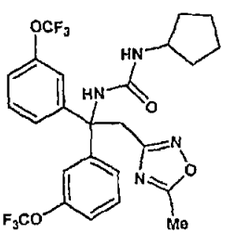

**[00240]** Using the same procedure as that described for Procedure 6, the titled compound was obtained. LC-MS (ESI) 447.35 (M+H), retention time = 3.16 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run).

**1-cyclopentyl-3-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)-phenyl)ethyl)urea**




**[00241]** Using the same procedure as that described for Procedure 2, the titled compound was obtained. LC-MS (ESI) 558.41 (M+H), retention time = 3.98 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.39-7.35 (m, 2H), 7.28 - 7.26 (m, 2H), 7.15 - 7.13 (m, 4H), 5.57 (s, 1H), 5.29 (m, 1H), 4.04 (s, 2H), 3.93 (m, 1H), 2.19 (s, 3H), 1.92-1.89 (m, 2H), 1.64-1.59 (m, 4H), 1.35 – 1.26 (m, 2H).

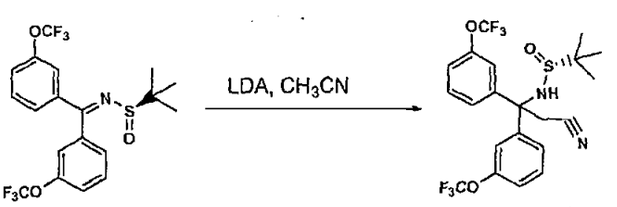
## EXAMPLE 211



**1-cyclopentyl-3-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea**

### Procedure 18

**(R)-N-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide**

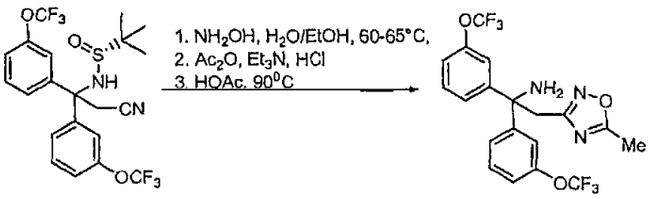



**[00242]** (R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide was prepared as described for Procedure 11. Under an argon atmosphere, acetonitrile (0.46 mL, 8.84 mmol, 2.0 eq) was stirred in anhydrous $Et_2O$ (40 mL) in an oven-dried round bottomed flask at -78°C. LDA (2.0 M, 4.42 mL, 8.84 mmol, 2.0 eq) was added dropwise. The resulting mixture was stirred at -78°C for 30 min. (R)-N-(bis(3-(trifluoromethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (2.0 g, 4.42 mmol) in $Et_2O$ (10 mL) was added dropwise to the above stirred solution. The reaction mixture was stirred at -78°C for 4h. Sat'd $NH_4Cl$ was added, followed by the addition of EtOAc. The organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0 to 100%) to give (R)-N-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide as light tan oil (1.15g, yield: 52.7% with 0.85 g recovery of the starting material). LC-MS (ESI) 495.26 (M+H), retention time = 3.84 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.40-7.35 (m, 2H), 7.29 (d, J = 8Hz,

1H), 7.21 - 7.16 (m, 4H), 7.08 (m, 1H), 4.53 (s, 1H), 3.75 (d, J=16 Hz, 1H) 3.56 (d, J=16 Hz, 1H), 1.21 (s, 9 H).

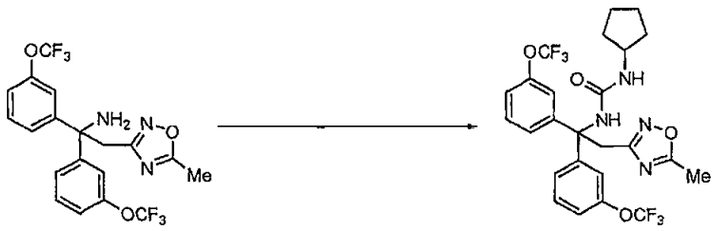
**Procedure 19**

**2-methyl-N-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide**



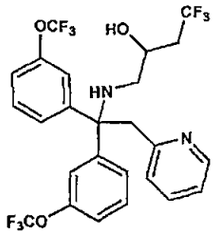

**[00243]** (R)-*N*-(2-Cyano-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (140 mg, 0.28 mmol) was stirred in EtOH (3 mL) and $NH_2OH$ in $H_2O$ (3 mL) in a capped microwave tube. The mixture was heated in an oil bath at 60-65°C for 2 h. LC-MS (ESI) 528.42 (M+H), retention time = 3.46 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run). The cap was removed and the solvents were concentrated. The residue was dissolved in $CH_2Cl_2$, washed with $H_2O$, dried over $MgSO_4$, filtered, and concentrated to give crude *N'*-hydroxy-3-(2-methylpropan-2-ylsulfinamido)-3,3-bis(3-(trifluoromethoxy)phenyl)propanamidine. After drying under vacuum for 2 h, the residue was dissolved in $CH_2Cl_2$ (5 mL). $Et_3N$ (0.25 mL, mmol, eq) was added followed by the addition of $Ac_2O$ (0.1 mL). The resulting mixture was stirred at room temperature for 24 h. LC-MS (ESI) 570.49 (M+H), 592.49 (M+Na), retention time = 3.92 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run). $CH_2Cl_2$ (5 mL) was added. The organic layer was washed with $H_2O$, dried over $MgSO_4$, filtered, and concentrated to dryness to give colorless film (0.255g). This residue was dissolved in HOAc (5 mL) and was heated at 90°C for 4 h. After cooling, $H_2O$ was added. The mixture was extracted with $CH_2Cl_2$ (2x) and the combined organic portion washed with sat'd $NaHCO_3$ (2x), $H_2O$ and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0 to 100%) to give 2-methyl-*N*-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide as colorless oil (52 mg, total yield for 3 steps: 41%). LC-MS (ESI)

441.29 (M-$NH_2$), retention time = 3.14 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.26 - 7.19 (m, 5H), 7.00 (m, 3H), 3.57 (s, 2H), 2.39 (s, 3H).



**[00244]** Using the same procedure described for Procedure 2, 1-cyclopentyl-3-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)urea was obtained after purification using reverse phase HPLC (30-90% MeOH in $H_2O$ with 0.1% TFA in a 10min gradient, came out 17.53-18.00 min). LC-MS (ESI) 559.25 (M+H), retention time = 4.06 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.36-7.28 (m, 4H), 7.20 (m, 2H), 7.10 (m, 2H), 3.93 (m, 1H), 3.84 (s, 2H), 2.46 (s, 3H), 1.89 (m, 2H), 1.56 (m, 4H), 1.28 (m, 2H).

## EXAMPLE 219

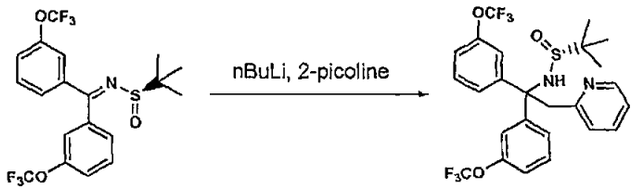


**4,4,4-trifluoro-1-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethylamino)butan-2-ol**

**Procedure 20**

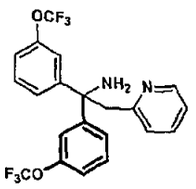
**(R)-2-methyl-N-(2-(pyridin-2-yl)-1,1-bis(3-**

**(trifluoromethoxy)phenyl)ethyl)propane-2-sulfinamide**




**[00245]** 2-Picoline (0.20 mL, 2.0 mmol) was stirred in anhydrous $Et_2O$ (20 mL) at 0°C under Argon. nBuLi (2.5 M in hexanes, 0.84 mL, mmol) was added dropwise. The reaction mixture turned to dark brown, and stirred at 0°C for 20 min, then at room temperature for 1 h. It was cooled back to 0°C, and (R)-N-(bis(3-(trifluoromethoxy)phenyl)-methylene)-2-methylpropane-2-sulfinamide (prepared as described in Example 82, Procedure 11) (0.906g, 2.0 mmol) in $Et_2O$ (4.0 mL) was added dropwise. The mixture was stirred at 0°C for 1h. then at room temperature for 1h. The reaction was quenched by addition of sat'd $NH_4Cl$. EtOAc was added; the organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 0 to 100%) to give 2-methyl-N-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)-ethyl)propane-2-sulfinamide as light tan solids (0.19g with recovery of 0.59 g of starting material, yield:48% based on recovery of the starting material). LC-MS (ESI) 547.38 (M+H), retention time = 3.90 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 8.36 - 8.44 (m, 1H), 7.90 (m, 1H), 7.51 (d, *J*=8.59 Hz, 1H), 7.37 (td, *J*=7.83, 2.27 Hz, 2H), 7.19 - 7.24 (m, 2H), 7.11 - 7.17 (m, 3 H), 6.98 - 7.07 (m, 2H), 6.75 (d, *J*=7.83 Hz, 1H), 4.15 (d, *J*=13.90 Hz, 1H), 3.81 (d, *J*=13.90 Hz, 1H), 1.25 - 1.33 (m, 9H)

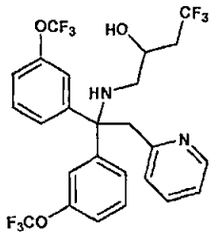
**2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine**




**[00246]** Using the same procedure described for Procedure 6, 2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine was obtained. LC-MS (ESI) 444.38

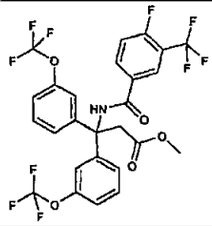
(M+H), retention time = 3.10 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run);

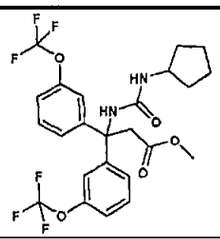
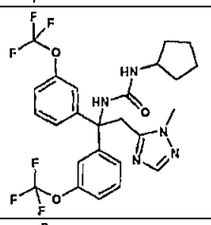
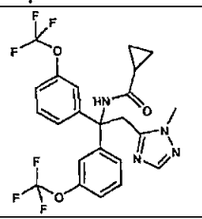
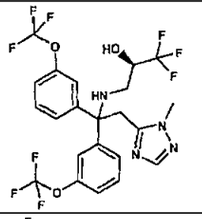
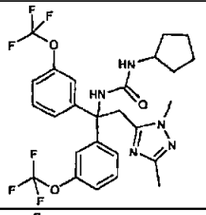
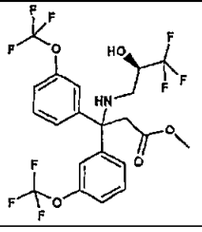
**4,4,4-trifluoro-1-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethylamino)butan-2-ol**

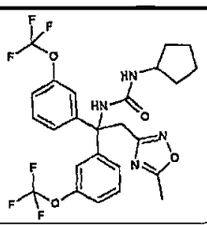
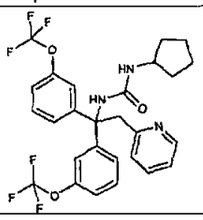
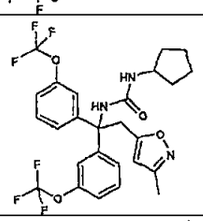
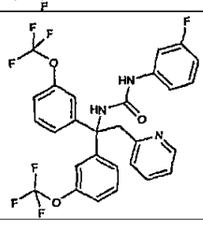
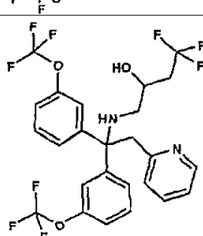
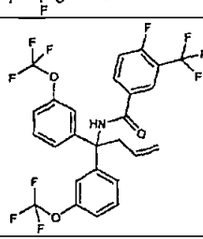



**[00247]** Using the procedure described for Procedure 8, 4,4,4-trifluoro-1-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethylamino)butan-2-ol was obtained after purification via reverse phase HPLC to give pure (+/-)-4,4,4-trifluoro-1-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethylamino)butan-2-ol as a TFA salt. LC-MS (ESI) 569.31 (M+H), retention time = 3.21 min (10-90% MeOH in $H_2O$ with 0.1% TFA in a 4-min run); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 8.65 (d, *J*=4.39 Hz, 1H), 7.63 - 7.70 (m, 1H), 7.41 - 7.47 (m, 1H), 7.34 - 7.38 (m, 2H), 7.30-7.14 (m, 5H), 6.98 (m, 1H), 6.81 (d, *J*=7.91 Hz, 1H), 4.47 - 4.53 (m, 1 H), 3.86 (m, 2 H), 2.84 (dd, *J*=12.08, 9.89 Hz, 1 H), 2.67 (dd, *J*=11.86, 2.64 Hz, 1 H), 2.46 (m, 1 H), 2.22 (m, 1H).

**TABLE 7**

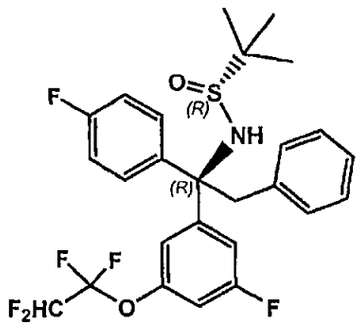
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 220 |  | methyl 3-(4-fluoro-3-(trifluoromethyl)benzamido)-3,3-bis(3-(trifluoromethoxy)phenyl) propanoate | 4.10 LC 614.36 $[M+H]^+$ | Procedures 11, 14 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 221 |  | methyl 3-(3-cyclopentylureido)-3,3-bis(3-(trifluoromethoxy) phenyl)propanoate | 4.02 LC 535.38 $[M+H]^+$ | Procedures 11, 14 and 2 |
| 222 |  | 1-cyclopentyl-3-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.81 LC 558.43 $[M+H]^+$ | Procedures 15,16 and 2 |
| 223 |  | N-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl) cyclopropanecarboxamide | 3.61 LC 515.33 $[M+H]^+$ | Procedures 15,16 and 7 |
| 224 |  | (R)-1,1,1-trifluoro-3-(2-(2-methyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)propan-2-ol | 3.73 LC 559.4 $[M+H]^+$ | Procedures 15,16 and 8 |
| 225 |  | 1-cyclopentyl-3-(2-(2,5-dimethyl-2H-1,2,4-triazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.73 LC 572.48 $[M+H]^+$ | Procedures 15,16 and 2 |
| 226 |  | (R)-methyl 3-(3,3,3-trifluoro-2-hydroxypropylamino)-3,3-bis(3-(trifluoromethoxy) phenyl)propanoate | 3.93 LC 536.29 $[M+H]^+$ | Procedures 14 and 8 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 227 |  | 1-cyclopentyl-3-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.06 LC 559.25 $[M+H]^+$ | Procedures 18,19 and 2 |
| 228 |  | 1-cyclopentyl-3-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.43 LC 554.4 $[M+H]^+$ | Procedures 20 and 2 |
| 229 |  | 1-cyclopentyl-3-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 3.98 LC 558.41 $[M+H]^+$ | Procedures 17 and 2 |
| 230 |  | 1-(3-fluorophenyl)-3-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.56 LC 580.33 $[M+H]^+$ | Procedures 20 and 2 |
| 231 |  | 4,4,4-trifluoro-1-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)butan-2-ol | 3.21 LC 569.31 $[M+H]^+$ | Procedures 20 and 8 |
| 232 |  | N-(1,1-bis(3-(trifluoromethoxy)phenyl) but-3-enyl)-4-fluoro-3-(trifluoromethyl)benzamide | 581.402 | Procedures 11 and 7 |

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## EXAMPLE 233




**(R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide**

### Procedure 21

**[00248]** (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was prepared by analogous procedures described in Procedure 3, 4 and 5. The material was crystallized from $CDCl_3$ and an X-ray structure obtained.

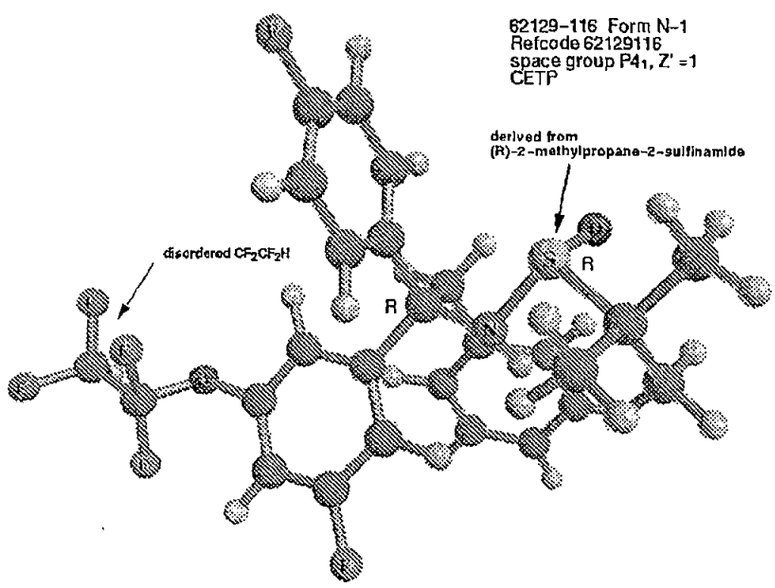
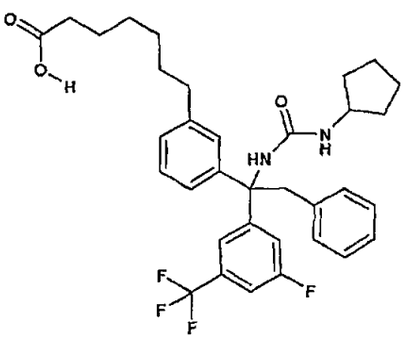


**Table 1. Properties of Crystal Forms**

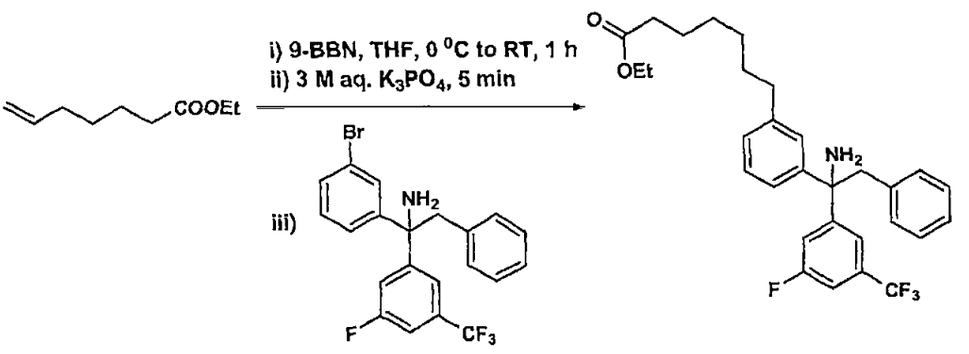
| CSD Refcode | FORM | Solvent Sites | % Solvent ideal(w/w) | HOT STAGE (°C) | $D_{calc}$ (g/cc) | Z | V/Z | sg | T (°C) |
|---|---|---|---|---|---|---|---|---|---|
| 62129116 | N-1 | None | - | 127-31 | 1.384 | 4 | 635 | $P4_1$ | -50 |

**EXAMPLE 234**



**7-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)phenyl)heptanoic**

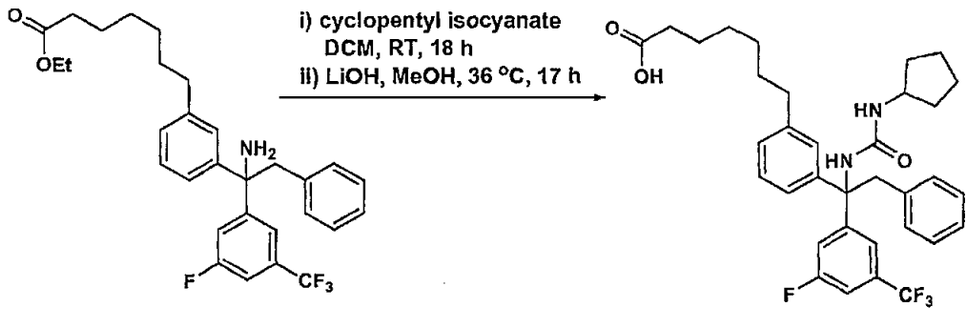
**Procedure 22**




**[00249]** To a solution of ethyl hept-6-enoate (156 mg, 1 mmol) in dry THF (4 mL) cooled in an ice water bath was added a solution of 9-BBN (0.5 M in THF, 2.0 mL, 1 mmol). The cooling bath was removed and the reaction mixture was stirred for 1 h at room temperature. To the reaction mixture was added an aqueous solution of potassium phosphate (3 M, 0.66 mL, 2 mmol) and stirred for an additional 5 min. To the reaction mixture was added a solution of 1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethanamine, prepared as described in Procedure 1, (0.2 M in THF, 3 mL, 0.6 mmol), followed by tris-(dibenzylideneacetone)

dipalladium(0) (45 mg, 0.04 mmol). The resulting yellow solution was heated under reflux for 20 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was extracted between water (10 mL) and ether (10 mL). The ether layer was washed twice with water, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (2% to 10 % EtOAc in Heptane) to yield ethyl 7-(3-(1-amino-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)phenyl)heptanoate (169 mg, 54 % yield). LCMS: RT = 3.61 min, Purity 84% [M+H] 516.3 (Sunfire-S5-C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

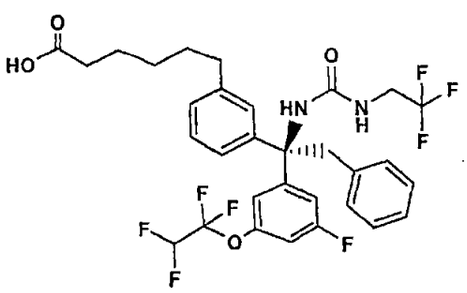
**Procedure 23**




**[00250]** To a solution of ethyl 7-(3-(1-amino-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)phenyl)heptanoate (169 mg, 0.33 mmol) in anhydrous DCM (1 mL) was added cyclopentyl isocyanate (22 mg, 0.2 mmol). The reaction mixture was stirred at rt for 18 h. To the reaction mixture was added anhydrous THF (1 mL) and the mixture was stirred at room temperature for additional 1 h. The solvents were evaporated on a rotary evaporator and the residue was dissolved in methanol and purified by preparative HPLC (RT = 11.3 min, Waters Sunfire C18 OBD, 19 X 100 mm eluting with 26-90% MeCN/$H_2O$ containing 0.1% TFA over 9 min and hold at 90% for 7 more minutes; 40 mL/min, monitoring at 220 nm). The resulting solid was dissolved in methanol (1 mL) followed by the addition of aqueous lithium hydroxide (1 N, 0.25 mL, 0.25 mmol). The reaction mixture was heated at 36 °C for 18 h. The crude product was purified by preparative HPLC (RT = 10.7 min, Waters Sunfire C18 OBD, 19 X 100 mm eluting with 18-90% MeCN/$H_2O$

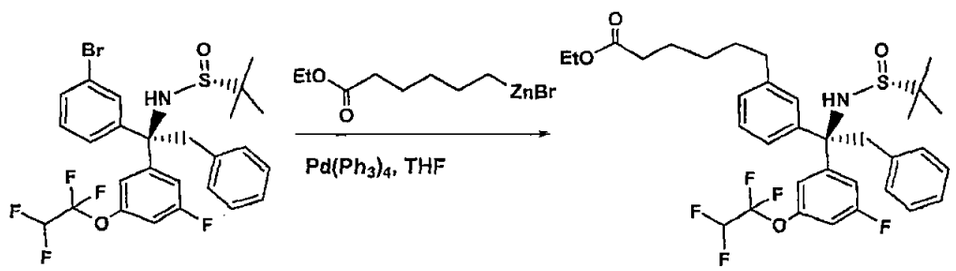
over 10 min and hold at 90% for 6 additional minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to yield 7-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)phenyl)heptanoic acid (Example 234, 32 mg, 53 % yield for 2 steps). LCMS: RT = 4.33 min, Purity >95%, [M+H] 599.4 (Sunfire-S5-C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) 7.36 ppm, 1 H, s; 7.16-7.24 ppm, 4 H, m; 7.10-7.13 ppm, 3 H, m; 6.97 ppm, 1 H, d, J = 7.7 Hz; 6.94 ppm, 1 H, s; 6.67 ppm, 2 H, d, J=7.1 Hz; 5.58 ppm, 1 H, brd, s; 3.87 ppm, 1 H, d, J=12.6 Hz; 3.83 ppm, 1 H, m; 3.65 ppm, 1 H, d, J=12.7 Hz; 2.54, 2 H, t, J=7.5 Hz; 2.29 ppm, 2 H, t, J=7.4 Hz; 1.73-1.84 ppm, 2 H, m; 1.50-1.60 ppm, 8 H, m; 1.15-1.36 ppm, 6 H, m.

**EXAMPLE 235**



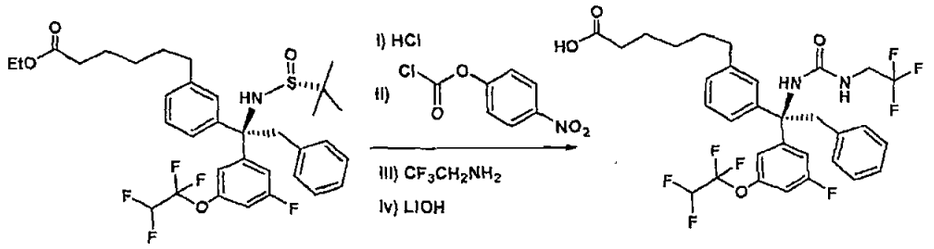
**(R)-6-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl)phenyl)hexanoic acid**

**Procedure 24**




**[00251]** To a solution of (R)-N-((S)-1-(3-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (236 mg, 0.4 mmol), prepared as described in Procedure 3, 4, 5 and 6 (67% yield), in

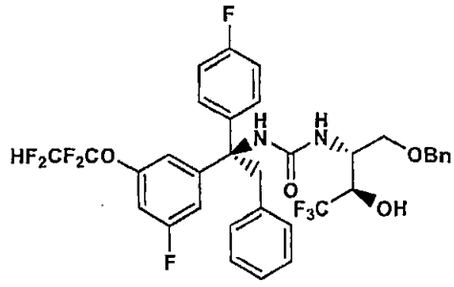
anhydrous THF (1 mL) was added (6-ethoxy-6-oxohexyl)zinc(II) bromide (2.4 ml, 1.2 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol). Under Ar atmosphere, the reaction mixture was heated to 130 °C under microwave irradiation for 15 min. The residue was diluted with EtOAc (10 mL) and washed with sat. $NH_4Cl$ (2 x 5 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was dissolved in methanol and purified by preparative HPLC (Waters Sunfire C18 19 x 50 mm column eluting with 10-90% MeOH/$H_2O$ over 7 min; 20 mL/min, monitoring at 220 nm) to give ethyl 6-(3-((R)-1-((R)-1,1-dimethylethylsulfinamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)phenyl)hexanoate (60 mg, 23% yield). LCMS: RT = 3.97 min [M+H] 654.52 (4 min YMC-ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 7.24 - 7.33 (2 H, m), 7.11 - 7.19 (5 H, m), 6.89 - 6.94 (2 H, m), 6.82 (1 H, d, *J*=8.52 Hz), 6.67 - 6.73 (2 H, m), 5.85 (1 H, ttt, *J*=53.06, 2.61 Hz), 4.25 (1 H, s), 4.11 (2 H, q, *J*=7.15 Hz), 4.03 (1 H, d, *J*=12.65 Hz), 3.60 (1 H, d, *J*=12.65 Hz), 2.59 (2 H, dd), 2.26 (2 H, t, *J*=7.56 Hz), 1.61 (4 H, tt, *J*=15.77, 7.87 Hz), 1.28 - 1.34 (2 H, m), 1.22 - 1.27 (3 H, m), 1.20 (9 H, s).




**[00252]** (R)-6-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl)phenyl)hexanoic acid (Example 235, 13 mg, 50% yield) was prepared as described in Procedure 6, 12 and 23. LCMS: RT = 4.10 min [M+H] 647.30 (Sunfire-S5-C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 1.17 - 1.26 (m, 2 H), 1.53 - 1.63 (m, 4 H), 2.23 - 2.32 (m, 2 H), 2.56 (t, *J*=7.15 Hz, 2 H), 3.60 (ddd, *J*=15.05, 9.14, 5.77 Hz, 1 H), 3.66 (d, *J*=12.92 Hz, 1 H), 3.83 (ddd, *J*=15.67, 8.80, 7.15 Hz, 1 H), 3.93 (d, *J*=12.92 Hz, 1

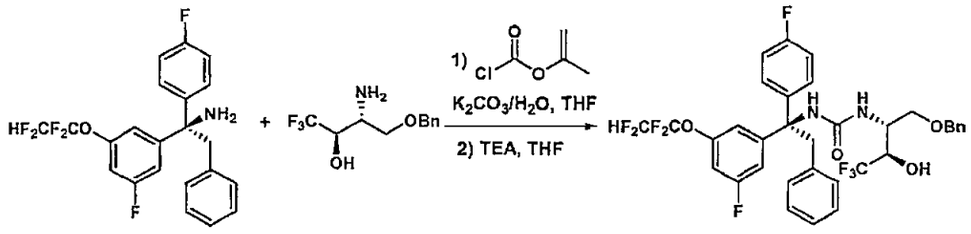
H), 5.09 (t, *J*=5.91 Hz, 1 H), 5.64 (s, 1 H), 5.86 (ttt, *J*=53.06, 2.61 Hz, 1 H), 6.69 (d, *J*=7.15 Hz, 2 H), 6.87 (d, *J*=8.80 Hz, 1 H), 6.90 (s, 1 H), 6.96 (d, *J*=7.97 Hz, 1 H), 6.99 - 7.02 (m, 2 H), 7.06 - 7.12 (m, 3 H), 7.16 (t, *J*=7.29 Hz, 1 H), 7.22 (t, *J*=7.70 Hz, 1 H), 7.26 (s, 1 H).

**EXAMPLE 236**



**1-((2R,3R)-1-(benzyloxy)-4,4,4-trifluoro-3-hydroxybutan-2-yl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

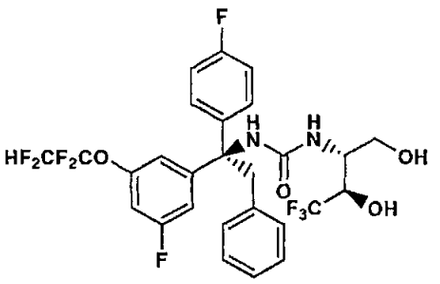
**Procedure 25**



**[00253]** To a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (20 mg, 0.047 mmol), prepared as described in Procedure 3, 4, 5 and 6, in THF (0.5 mL) was added $K_2CO_3$ in $H_2O$ (10 mg, 2 M in $H_2O$, 0.071 mmol), followed by the addition of prop-1-en-2-yl carbonochloridate (6 µL, 0.052 mmol). The reaction mixture was stirred at rt for 2 h, diluted with EtOAc (25 mL), washed with saturated NaCl (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. To the residue was added (2R,3R)-3-amino-4-(benzyloxy)-1,1,1-trifluorobutan-2-ol (23 mg, 0.094 mmol), prepared according to the procedure described in J. Org. Chem., 68(19):7545 (2003), TEA (20 µL, 0.14 mmol) in THF (0.5 mL). The reaction mixture was heated at 70 °C for 18 h. The reaction

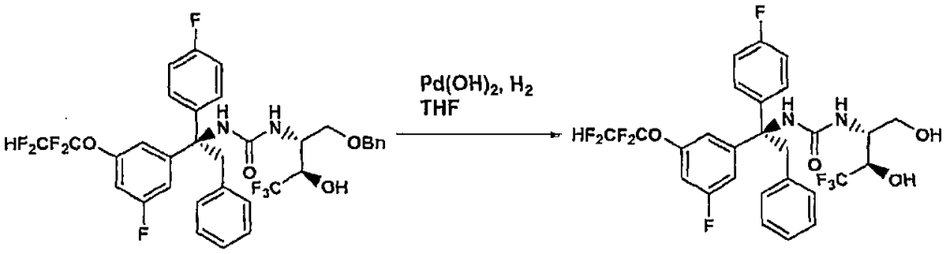
solution was concentrated under reduced pressure and purified by ISCO chromatography (12 g column) using hexane/EtOAc (0-30% over 20 min) to give 1-((2R,3R)-1-(benzyloxy)-4,4,4-trifluoro-3-hydroxybutan-2-yl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 236) as a white solid at a retention time of 17 min (19 mg, 59% yield). LCMS: RT = 2.138 min [M+H] 701.29 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.335 min, Purity 94% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.37 ppm, 3 H, m; 7.25 ppm, 3 H, m; 7.20 ppm, 1 H, t, *J*=7.03 Hz; 7.13 ppm, 4 H, m; 6.97 ppm, 2 H, t, *J*=8.35 Hz; 6.89 ppm, 3 H, m; 6.69 ppm, 2 H, d, *J*=7.47 Hz; 5.86 ppm, 1 H, m; 5.18 ppm, 1 H, d, *J*=8.35 Hz; 5.13 ppm, 1 H, s; 4.44 ppm, 2 H, m; 4.26 ppm, 1 H, d, *J*=9.67 Hz; 4.14 ppm, 1 H, dd, *J*=8.13, 3.30 Hz; 3.99 ppm, 1 H, m; 3.81 ppm, 2 H, m; 3.71 ppm, 1 H, m; 3.59 ppm, 1 H, m.

**EXAMPLE 237**



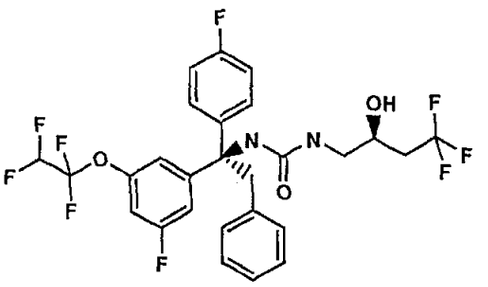

**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((2R,3R)-4,4,4-trifluoro-1,3-dihydroxybutan-2-yl)urea**

**Procedure 26**



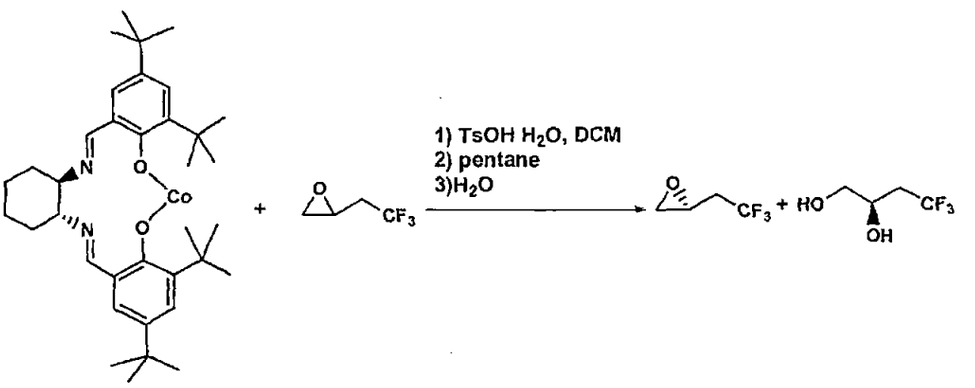

**[00254]** To a solution of 1-((2R,3R)-1-(benzyloxy)-4,4,4-trifluoro-3-hydroxybutan-2-yl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 236, 17 mg, 0.024 mmol) in THF (1 mL) was added 20% $Pd(OH)_2/C$ (8 mg) and the slurry was subjected to balloon hydrogenation for 18 h. The reaction mixture was filtered and the filtrate was concentrated and purified by preparative HPLC (Shimadzu-YMC-ODS-A 5μ column, 30 × 100 mm eluting with 30-100% MeOH (90% in $H_2O$, 0.1%TFA) gradient over 12 min with flow rate 40 mL/min and UV detection at 220 nm) to yield 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((2R,3R)-4,4,4-trifluoro-1,3-dihydroxybutan-2-yl)urea (Example 237) eluting at a retention time of 11.54 min as a clear oil (11 mg, yield 78%). LCMS: RT = 1.983 min [M+H] 611.26 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.081 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.20 ppm, 1 H, s; 7.16 ppm, 5 H, m; 6.99 ppm, 2 H, m; 6.91 ppm, 3 H, m; 6.70 ppm, 2 H, d, *J*=7.47 Hz; 5.87 ppm, 1 H, m; 5.38 ppm, 1 H, d, *J*=7.47 Hz; 5.35 ppm, 1 H, s; 4.28 ppm, 1 H, d, *J*=5.71 Hz; 4.11 ppm, 2 H, m; 3.94 ppm, 2 H, d, *J*=7.91 Hz; 3.82 ppm, 1 H, m; 3.73 ppm, 1 H, m; 3.67 ppm, 1 H, d, *J*=8.35 Hz.

## EXAMPLE 238



**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((S)-4,4,4-trifluoro-2-hydroxybutyl)urea**

### Procedure 27

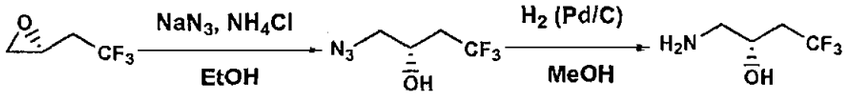



**[00255]** To a solution of (R,R)-(-)-N'N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclo-hexanediamine (0.92 g, 1.53 mmol) in DCM (35 mL) was added TsOH $H_2O$ (308 mg, 1.62 mmol) and the reaction mixture was stirred at room temperature while open to air for 1 h. The reaction mixture was concentrated under reduced pressure and pentane was added to the residue. The resulting solid was filtered, rinsed with pentane once, diluted with DCM and transferred to the reaction flask. DCM was then removed under reduced pressure and 2-(2,2,2-trifluoroethyl)oxirane (37 g, 294 mmol) was added to the resulting solid. The mixture was cooled to 0 °C and $H_2O$ (3.7 mL, 206 mmol) was added dropwise. After addition was finished, the reaction mixture was stirred at room temperature for 72 h. (S)-2-(2,2,2-trifluoroethyl)oxirane was isolated as a clear oil (10 g, 28%) by vacuum distillation from the reaction mixture into a cooled (-78 °C) receiving flask. NMR: 400MHz $^1H$ ($CDCl_3$) 3.16 ppm, 1 H, m;

2.87 ppm, 1 H, t, *J*=4.39 Hz; 2.59 ppm, 1 H, dd, *J*=4.61, 2.42 Hz; 2.39 ppm, 1 H, m; 2.29 ppm, 1 H, m, *J*=10.44, 10.44, 5.05, 4.83 Hz.

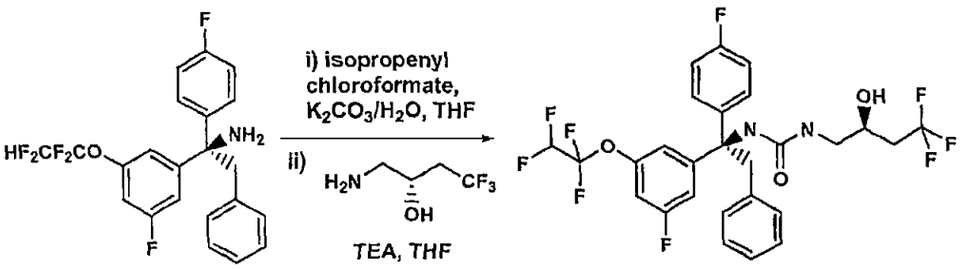
**[00256]** The recovered epoxide was determined to be >99% ee according to the procedure used by Jacobsen (J. Am. Chem. Soc., 124(7):1307-1315 (2004)). (Chiral HPLC analysis of the 2-napthylsulfide derivative (obtained by ring opening with 2-napthalenethiol in MeOH using 1 equiv TEA and direct analysis of the product obtained, Chiralcel® AD, 95:5 hexanes:*i*-PrOH, 1 mL / min, 254 nm, RT (minor) = 16.52 min, RT (major) = 19.28 min).

**Procedure 28**



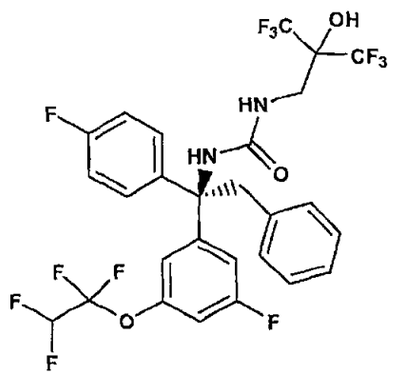

**[00257]** To a solution of (S)-2-(2,2,2-trifluoroethyl)oxirane (2.00 g, 16.0 mmol) in a mixture of EtOH (16 mL) and $H_2O$ (4 mL) were added $NaN_3$ (2.06 g, 32.0 mmol) and $NH_4Cl$ (1.70 g, 32.0 mmol). After stirring at room temperature for 18 h, the reaction mixture was diluted with $H_2O$ (50 mL), extracted with $Et_2O$ (2 × 75 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated to give (S)-1-azido-4,4,4-trifluorobutan-2-ol as an oil (2.26 g, 83% yield). NMR: 400MHz $^1H$ ($CDCl_3$) 4.17 ppm, 1 H, ddd, *J*=6.81, 3.74, 3.52 Hz; 3.48 ppm, 1 H, m; 3.37 ppm, 1 H, m; 2.35 ppm, 2 H, m.

**[00258]** The crude (S)-1-azido-4,4,4-trifluorobutan-2-ol (2.26 g, 13.0 mmol) was subjected to balloon hydrogenation for 18 h. After the filtration, the filtrate was concentrated to give (S)-1-amino-4,4,4-trifluorobutan-2-ol (1.02 g, 45% yield). NMR: 400MHz $^1H$ ($CDCl_3$) 3.88 ppm, 1 H, m, *J*=7.85, 7.85, 3.84, 3.74 Hz; 2.93 ppm, 1 H, dd, *J*=12.74, 3.52 Hz; 2.61 ppm, 1 H, dd, *J*=12.52, 8.13 Hz; 2.34 ppm, 1 H, m; 2.21 ppm, 1 H, m; 1.91 ppm, 3 H, s.



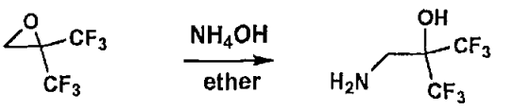

**[00259]** 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((S)-4,4,4-trifluoro-2-hydroxybutyl)urea (Example 238) was prepared as described in Procedure 25 (27 mg, 65% yield). LCMS: RT = 2.02 min [M+H] 595.28 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.165 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 ppm, 5 H, m; 6.94 ppm, 5 H, m; 6.69 ppm, 2 H, d, *J*=7.03 Hz; 5.73 ppm, 1 H, m; 4.10 ppm, 2 H, m; 3.93 ppm, 1 H, s; 3.84 ppm, 1 H, m; 3.73 ppm, 1 H, m; 3.52 ppm, 1 H, s; 3.29 ppm, 1 H, m; 3.04 ppm, 1 H, m; 2.17 ppm, 2 H, m.

**EXAMPLE 239**

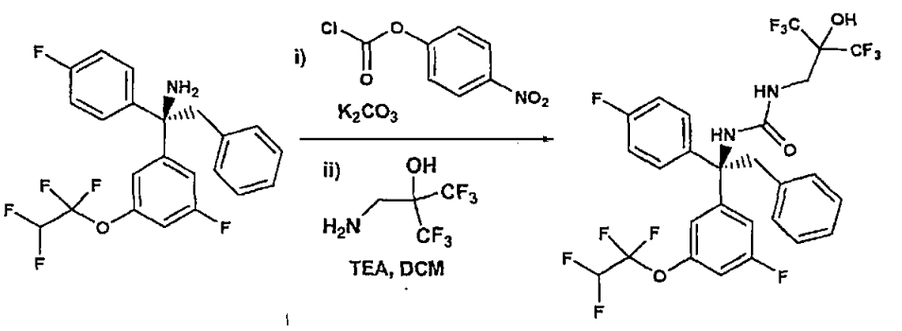



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl)urea**

**Procedure 29**



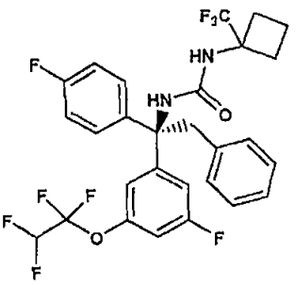

**[00260]** To a 1:1 mixture of ether (1.85 mL) and 30% ammonium hydroxide (1.85 mL) was added drop-wise 2,2-bis(trifluoromethyl)oxirane (1.00 g, 5.5 mmol). The reaction mixture was stirred for 2 h at rt, then diluted with ether and $H_2O$. The aqueous layer was extracted twice with ether and the combined ether layer was dried over $MgSO_4$, filtered and concentrated to give 2-(aminomethyl)-1,1,1,3,3,3-hexafluoropropan-2-ol as a semi solid (0.87 g, 81% yield). $^1$H NMR (400 MHz, $CDCl_3$) ppm 3.14 (s, 2 H), 3.25 (s, 1 H).




**[00261]** (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl)urea was prepared as described in Procedure 12. The product was purified by ISCO chromatography (4 g column) using hexane/EtOAc (0-20% over 12 min) to give the (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl)urea (Example 239) as a colorless oil (24 mg, 65% yield). LCMS: RT = 4.11 min [M+H] 649.10 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 3.60 - 3.90 (m, 4 H), 5.13 (t, $J$ = 5.81 Hz, 1 H), 5.50 (s, 1 H), 5.69 - 6.05 (t, $J$ = 56 Hz, 1 H), 6.68 (d, $J$ = 6.82 Hz, 2 H), 6.81 - 6.95 (m, 3 H), 6.96 - 7.05 (m, 3 H), 7.06 - 7.24 (m, 5 H).

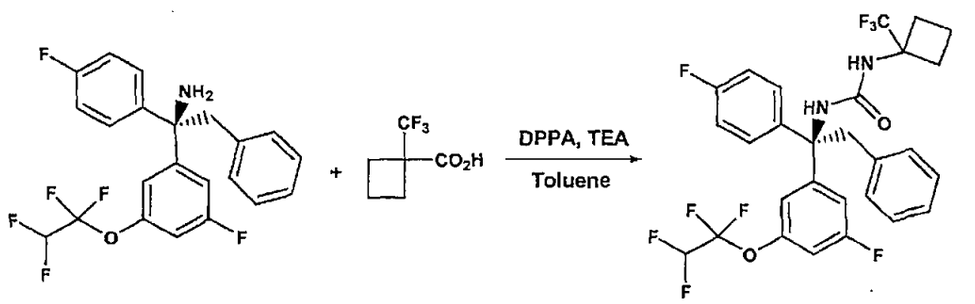
307

## EXAMPLE 240



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclobutyl)urea**

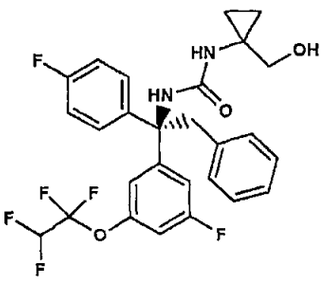
**Procedure 30**



**[00262]** To a solution of 1-(trifluoromethyl)cyclobutanecarboxylic acid (54 mg, 0.354 mmol) in toluene (0.9 mL) was added TEA (36 mg, 0.354 mmol), followed by DPPA (76.4 uL, 0.354 mmol). The reaction mixture was heated at 90 °C for 2 h, then allowed to cool to rt. (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (50 mg, 0.117 mmol), prepared as described in Procedure 3, 4, 5 and 6, was added and the reaction mixture was stirred at rt for 4.5 h. The reaction mixture was concentrated under reduced pressure and purified by ISCO chromatography (12 g column, eluting with 0-30% hexane/EtOAc over 18 min). The product was further purified by preparative HPLC (Phenomenex AXIA Luna column, 30 x 100 mm, flow rate 40 mL/min, eluting with 40-100% ACN/$H_2O$/0.1% TFA over 10 min) to yield (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclobutyl)urea (Example 240) as a white solid (45 mg, 65% yield). LCMS: RT = 4.13 min [M+H] 519.18 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over

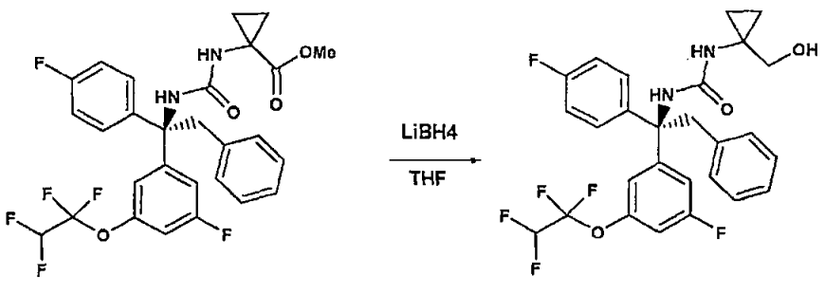
4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 1.83 - 2.06 (m, 2 H), 2.16 - 2.33 (m, 2 H), 2.33 - 2.51 (m, 2 H), 3.78 (qt, $J$ = 13 Hz, 2 H), 4.71 (s, 1 H), 5.02 (s, 1 H), 5.85 (t, $J$ = 52 Hz, 1 H), 6.65 - 6.75 (m, 2 H), 6.83 - 7.06 (m, 5 H), 7.05 - 7.23 (m, 5 H).

**EXAMPLE 241**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-(hydroxymethyl)cyclopropyl)urea**

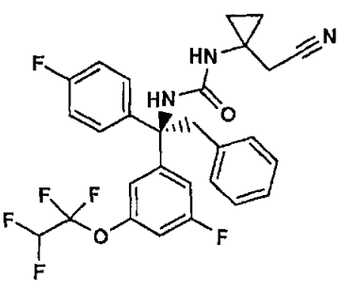
**Procedure 31**




**[00263]** To a solution of (R)-methyl 1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)-cyclopropanecarboxylate (112 mg, 0.2 mmol), prepared by the method described in Procedure 30, in THF (0.2 mL) was added $LiBH_4$ (0.2 mL, 2 M in THF, 0.4 mmol) at room temperature. The reaction mixture was stirred for 14 h, then cooled to 0 °C and 1 N HCl was added. The reaction mixture was diluted with ether. The organic layer was washed with $H_2O$ and sat. NaCl, dried over $MgSO_4$, filtered and concentrated to give a colorless oil. The resulting oil was purified by ISCO chromatography (4 g column, eluting with 0-100% hexane/EtOAc over 16 min) to yield (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-

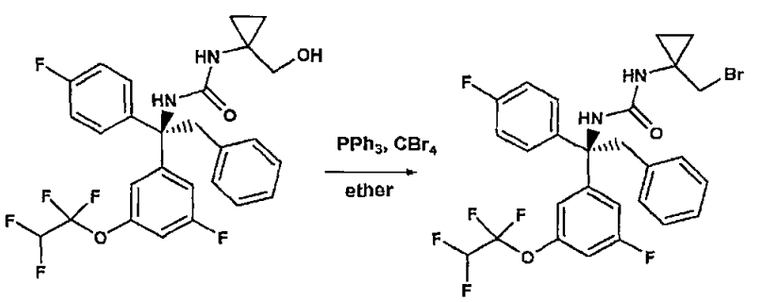
(hydroxymethyl)cyclopropyl)urea (Example 241) as a white foam (91 mg, 84% yield). LCMS: RT = 2.97 min [M+H] 539.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% $CH_3CN/H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) ppm 0.61 - 0.81 (m, 4 H), 2.50 (brs, 1 H), 3.31 - 3.50 (m, 2 H), 3.84 (qt, $J$ = 12 Hz, 2 H), 4.93 (s, 1 H), 5.84 (t, $J$ = 53 Hz, 1 H), 6.53 - 7.05 (m, 8 H), 7.05 - 7.24 (m, 5 H).

**EXAMPLE 242**



**(R)-1-(1-(cyanomethyl)cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

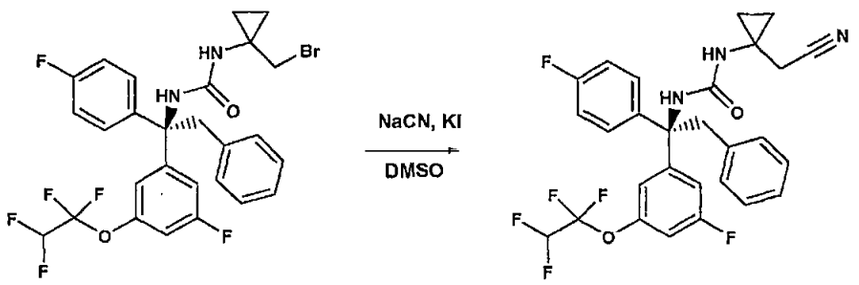
**Procedure 32**




**[00264]** To a solution of (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-(hydroxymethyl)cyclopropyl)urea (Example 241, 43 mg, 0.08 mmol) in ether (0.4 mL) was added $PPh_3$ (48 mg, 0.18 mmol) and $CBr_4$ (58 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred for 14 h and concentrated under reduced pressure and purified by ISCO chromatography (4 g column, eluting with 0-15% hexane/EtOAc over 14 min) to yield (R)-1-(1-(bromomethyl)cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea as a white solid (8 mg, 17% yield). LCMS: RT =

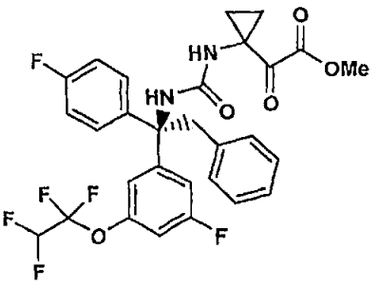
4.06 min [M+H] 601.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 0.82 - 1.03 (m, 4 H), 3.47 (qt, $J$ = 12 Hz, 2 H), 3.81 (ABqt, $J$ = 12 Hz, 2 H), 5.01 (s, 1 H), 5.39 (s, 1 H), 5.86 (t, $J$ = 53 Hz, 1 H), 6.61 - 6.78 (m, 2 H), 6.80 - 7.25 (m, 10 H).

**Procedure 33**



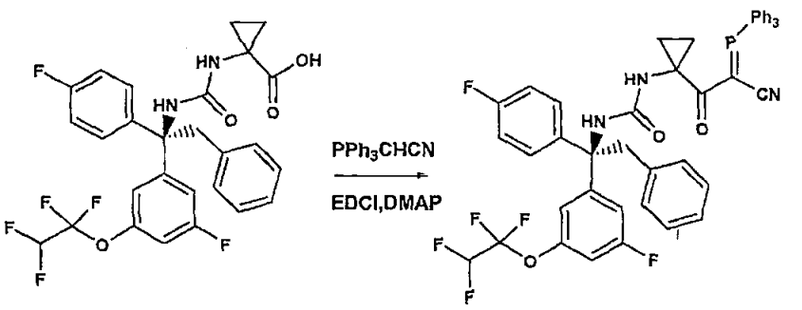

**[00265]** To a solution of (R)-1-(1-(bromomethyl)cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (8 mg, 0.013 mmol) in DMSO (0.3 mL) was added NaCN (18 mg, 0.37 mmol) and KI (20 mg, 0.12 mmol). The reaction mixture was stirred at rt for 3 days. The reaction mixture was concentrated under reduced pressure and purified by preparative HPLC (Phenomenex AXIA Luna column, 30x100 mm, flow rate 40 mL/min, 30-100% ACN/$H_2O$/0.1% TFA over 12 min) to yield (R)-1-(1-(cyanomethyl)cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 242, 5 mg, 63% yield). LCMS: RT = 3.88 min [M+H] 548.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 0.76 - 0.91 (m, 4 H), 2.58 (qt, $J$ = 17 Hz, 2 H), 3.78 (qt, $J$ = 12 Hz, 2 H), 5.49 (s, 1 H), 5.52 (s, 1 H), 5.87 (t, $J$ = 53 Hz, 1 H), 6.66 (d, $J$ = 6.6 Hz, 2 H), 6.84 - 6.95 (m, 3 H), 6.96 - 7.07 (m, 2 H), 7.07 - 7.26 (m, 5 H).

## EXAMPLE 243



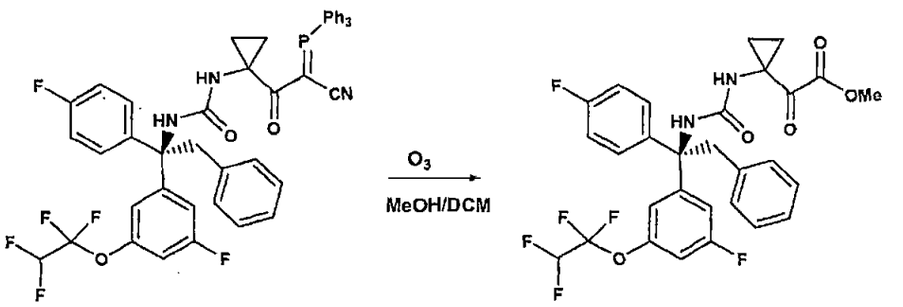
**(R)-methyl 2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopropyl)-2-oxoacetate**

**Procedure 34**



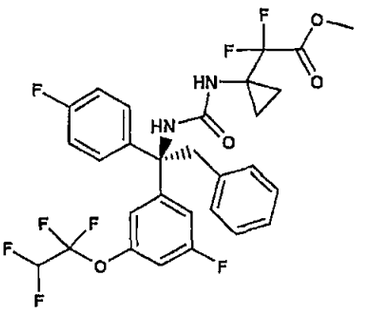

**[00266]** To a solution of (R)-1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)-cyclopropanecarboxylic acid (84 mg, 0.153 mmol), prepared by the method described in Procedure 30, in DCM (0.5 mL) was added 2-(phenylphosphinylidene)acetonitrile compound with biphenyl (1:1) (51 mg, 0.168 mmol), EDCI (32 mg, 0.168 mmol) and DMAP (3 mg, 0.024 mmol). The reaction mixture was stirred at room temperature for 4.5 h, concentrated under reduced pressure and purified by ISCO chromatography (12 g column, eluting with 0-100% hexane/EtOAc) to yield (R)-1-(1-(2-cyano-2-(phenylphosphinylidene)acetyl)cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea compound with biphenyl (1:1) as a white solid (53 mg, 42% yield). LCMS: RT = 3.49 min [M+H] 836.4 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 50-100% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) ppm 0.78 - 1.00 (m, 2 H), 1.34 - 1.49 (m, 2 H), 3.79 -

3.95 (m, 2 H), 5.62 - 5.98 (m, 3 H), 6.67 - 6.94 (m, 7 H), 6.98 - 7.20 (m, 5 H), 7.37 - 7.66 (m, 15 H).



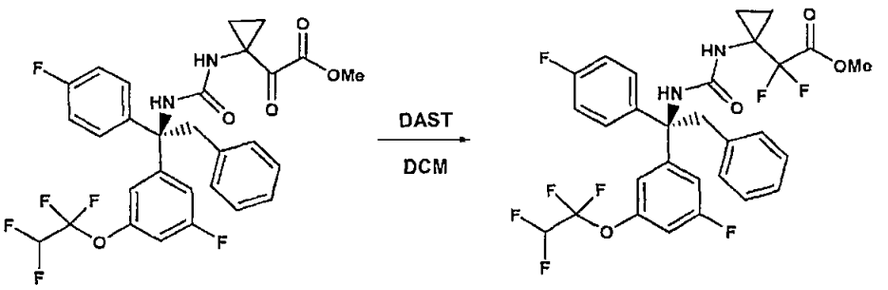

**[00267]** A solution of (R)-1-(1-(2-cyano-2-(phenylphosphinylidene)acetyl)cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea with biphenyl (1:1) (53 mg, 0.063 mmol) in DCM/MeOH (0.7 mL/0.3 mL) was cooled to -78 °C. $O_3$ was bubbled into the solution until the solution became light blue. The reaction mixture was warmed to room temperature and concentrated under reduced pressure. The resulting residue was purified by ISCO chromatography (4 g column) using hexane/EtOAc (0-100%) to give (R)-methyl 2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopropyl)-2-oxoacetate (Example 243) as a white solid (33 mg, 86% yield). LCMS: RT = 2.99 min [M+H] 595.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 50-100% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 0.81 - 0.95 (m, 2 H), 1.04 - 1.18 (m, 2 H), 3.63 - 3.88 (m, 5 H), 5.48 (s, 2 H), 5.86 (t, $J$ = 53 Hz, 1 H), 6.60 - 6.69 (m, 2 H), 6.80 - 7.02 (m, 5 H), 7.05 - 7.24 (m, 5 H).

**EXAMPLE 244**



**(R)-methyl 2,2-difluoro-2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopropyl)acetate**

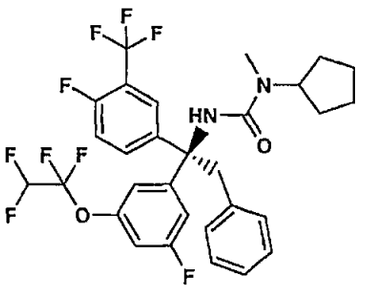
**Procedure 35**




**[00268]** To a solution of (R)-methyl 2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopropyl)-2-oxoacetate (Example 243, 24 mg, 0.040 mmol) in DCM (0.5 mL) at 0 °C was added DAST (40 mg, 0.24 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched by addition of sat. $NaHCO_3$ (0.5 mL), concentrated under reduced pressure and purified by preparative HPLC (Phenomenex Axia column, 30 x 100 mm, flow rate 40 mL/min, 30-100% $CH_3CN/H_2O$/0.1% TFA over 13 min) to yield (R)-methyl 2,2-difluoro-2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopropyl)acetate (Example 244) as a white solid (3 mg, 12% yield). LCMS: RT = 2.12 min [M+H] 617.5 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) ppm 0.81 - 0.98 (m, 2

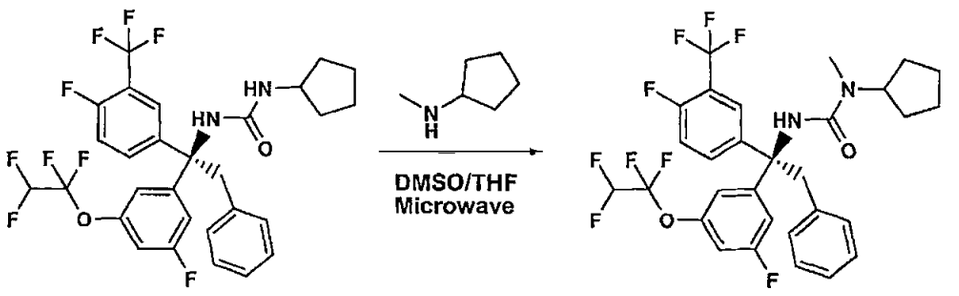
H), 1.21 - 1.35 (m, 2 H), 3.62 - 3.94 (m, 5 H), 4.96 (s, 1 H), 5.57 - 6.08 (m, 2 H), 6.61 - 6.72 (m, 2 H), 6.84 - 7.25 (m, 21 H).

**EXAMPLE 245**



**(R)-1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-1-methylurea**

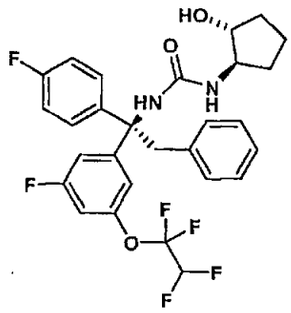
**Procedure 36**




**[00269]** To a solution of (R)-1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea (20 mg, 0.033 mmol), prepared as described in Procedure 3, 4, 5, 6 and 2, in DMSO/THF (0.1 mL /0.1 mL) was added N-methylcyclopentanamine (32 mg, 0.33 mmol). The resulting solution was stirred at 120 °C under microwave irradiation for 1800 sec. The reaction mixture was filtered and the solid was washed with EtOAc. The filtrate was then washed with $H_2O$, sat. NaCl and dried over $Na_2SO_4$. The organic solvent was evaporated under reduced pressure and the resulting residue was purified by prep HPLC (Phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford (R)-1-cyclopentyl-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-

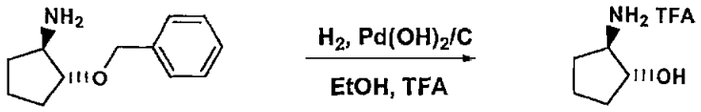
(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-1-methylurea (Example 246) as white lyophillate (13 mg, 65% yield). LCMS: [M+H] 619.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 246**

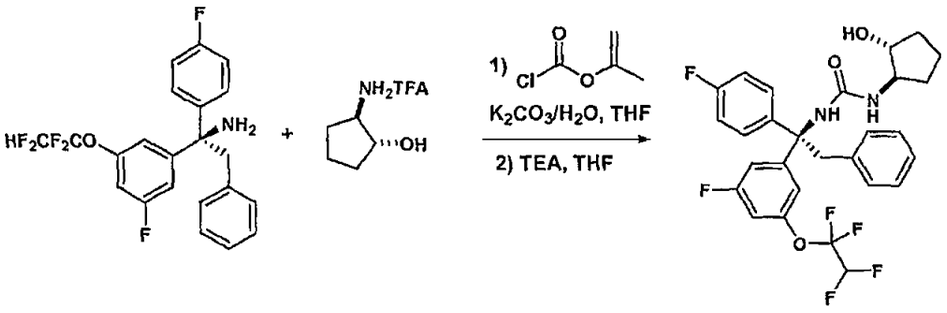


**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1R,2R)-2-hydroxycyclopentyl)urea**

**Procedure 37**

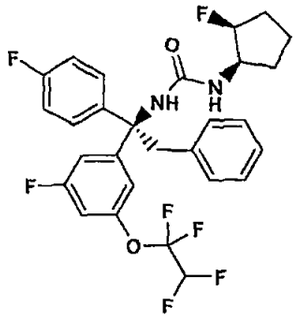



**[00270]** To a solution of (1R,2R)-2-(benzyloxy)cyclopentanamine (3.5 g, 18.3 mmol) in EtOH (20 mL) was added TFA (1.6 mL, 21.5 mmol), followed by $Pd(OH)_2/C$ (20% wt, 627 mg). The reaction mixture was degassed with Ar and stirred at rt under $H_2$ atmosphere for 3 days. The resulting solid was filtered and rinsed with EtOH. The filtrate was concentrated to yield (1R,2R)-2-aminocyclopentanol TFA salt (4.3 g, 100% yield) as a yellow oil. $^1H$ NMR (400 MHz, DMSO-D6) ppm 1.00 - 1.13 (m, 1 H), 1.39 - 1.57 (m, 2 H), 1.56 - 1.76 (m, 2 H), 1.79 - 1.94 (m, 1 H), 1.94 - 2.10 (m, 1 H), 3.06 - 3.23 (m, 1 H), 3.88 - 4.02 (m, 1 H), 7.84 - 8.07 (m, 2 H).



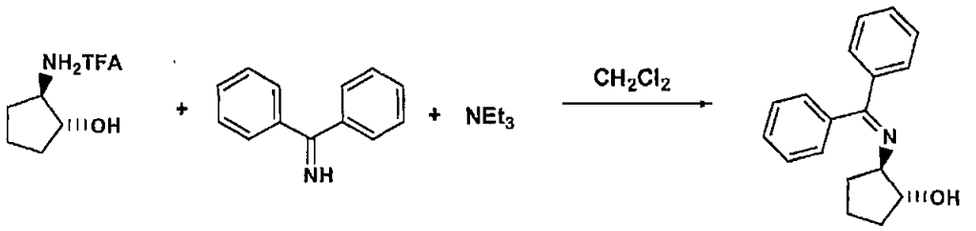

**[00271]** 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1R,2R)-2-hydroxycyclopentyl)urea (Example 246) was prepared as described in Procedure 25. HPLC: RT = 3.94 min [M+H] 553.08 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 1.07 - 1.35 (m, 1 H), 1.43 - 1.78 (m, 3 H), 1.80 - 1.98 (m, 2 H), 3.42 - 3.60 (m, 1 H), 3.61 - 3.73 (m, 1 H), 3.74 - 3.83 (m, 1 H), 3.83 - 3.96 (m, 1 H), 4.52 - 4.92 (m, 1 H), 5.66 - 6.03 (m, 2 H), 6.64 - 6.77 (m, 2 H), 6.80 - 6.89 (m, 1 H), 6.89 - 7.04 (m, 4 H), 7.04 - 7.22 (m, 4 H).

**EXAMPLE 247**

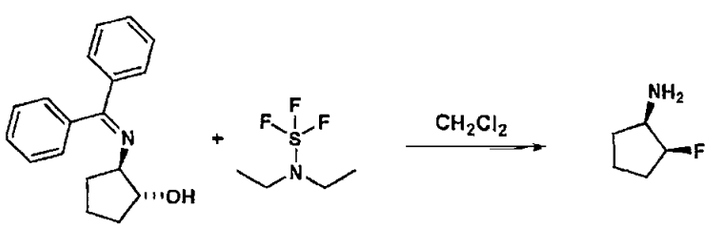



**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1R,2S)-2-fluorocyclopentyl)urea**

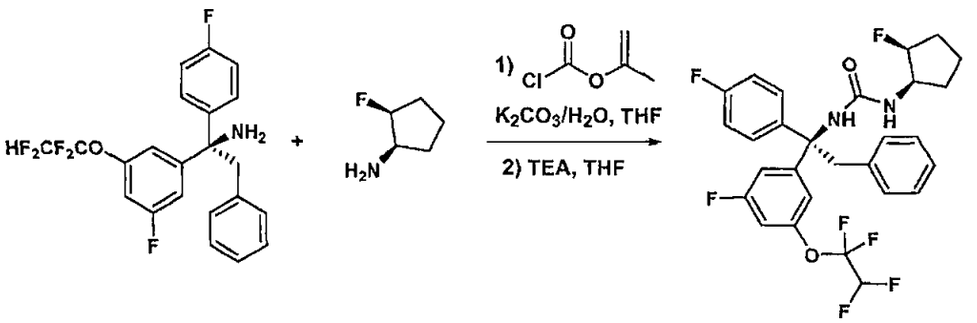
**Procedure 38**




**[00272]** To a solution of (1R,2R)-2-aminocyclopentanol TFA salt (630 mg, 2.93 mmol) was added diphenylmethanimine (490 uL, 2.93 mmol) and TEA (0.5 mL, 3.58 mmol) in $CH_2Cl_2$ (3 mL). The reaction mixture was stirred at rt for 2 h and concentrated under reduced pressure and purified by ISCO flash chromatography using EtOAc and hexane as eluting solvent to yield (1R,2R)-2-(diphenylmethyleneamino)cyclopentanol (697 mg, 90% yield) as a colorless gum. HPLC: RT = 1.96 min [M+H] 266.13 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 1.49 - 1.64 (m, 2 H), 1.66 - 1.91 (m, 3 H), 2.08 - 2.24 (m, 1 H), 3.55 - 3.71 (m, 1 H), 4.31 - 4.47 (m, 1 H), 7.15 - 7.25 (m, 2 H), 7.29 - 7.53 (m, 6 H), 7.61 - 7.67 (m, 2 H).

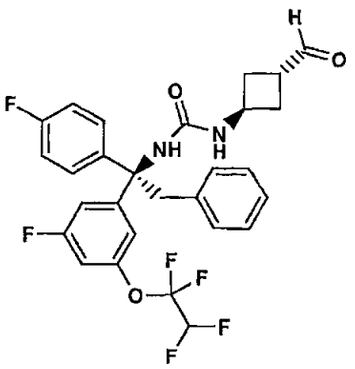



**[00273]** To a solution of (1R,2R)-2-(diphenylmethyleneamino)cyclopentanol (112 mg, 0.42 mmol) in $CH_2Cl_2$ (1 mL) at -20 °C was added dropwise DAST (67 uL, 0.5 mmol). The reaction mixture was allowed to warm up rt and stirred for 16 h. The solution was concentrated under reduced pressure to yield crude (1*R*,2*R*)-2-fluorocyclopentanamine (120 mg) which was used to next step without further purification.



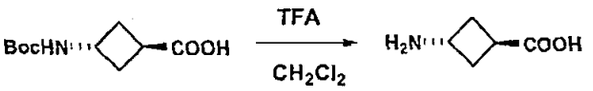

**[00274]** 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1R,2S)-2-fluorocyclopentyl)urea (Example 247) was prepared as described in Procedure 25. LCMS: RT = 4.07 min [M+H] 555.20 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CD_3CN$) δ ppm 1.02 - 1.12 (m, 6 H), 3.15 - 3.33 (m, 2 H), 3.89 (dd, 2 H), 5.10 - 5.24 (m, 1 H), 6.22 (t, 1 H), 6.71 - 6.82 (m, 2 H), 6.93 - 7.00 (m, 1 H), 7.01 - 7.33 (m, 9 H).

**EXAMPLE 248**

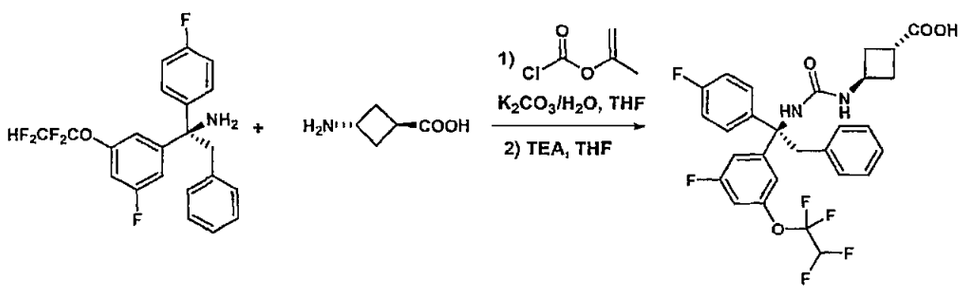



**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1r,3R)-3-formylcyclobutyl)urea**

**Procedure 39**

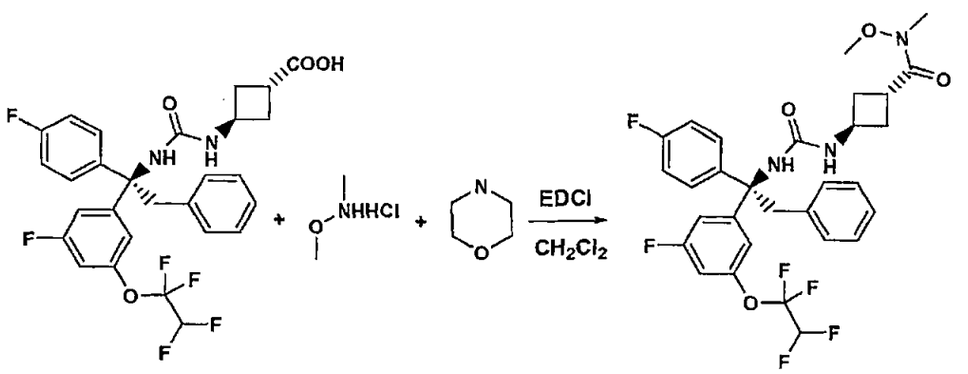


**[00275]** To a suspension of (1*r*,3*r*)-3-(tert-butoxycarbonylamino)cyclobutanecarboxylic acid (217 mg, 1 mmol) in $CH_2Cl_2$ (5 ml) at ambient temperature was added TFA (0.37 mL, 2.7 mmol) in one portion, and the reaction mixture was stirred at ambient temperature for 16 h, then concentrated to yield (1*r*,3*r*)-3-aminocyclobutanecarboxylic acid (227 mg, 100% yield) as a colorless oil. $^1$H NMR (500 MHz, DMSO-D6) δ ppm 2.21 - 2.34 (m, 2 H), 2.35 - 2.46 (m, 2 H), 3.01 - 3.17 (m, 1 H), 3.65 - 3.85 (m, 1 H), 7.90 - 8.13 (m, 3 H).




**[00276]** Using the method described in Procedure 25, (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclobutanecarboxylic acid was prepared as a white solid (372 mg, 66% yield). HPLC: RT = 3.90 min [M+H] 567.69 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

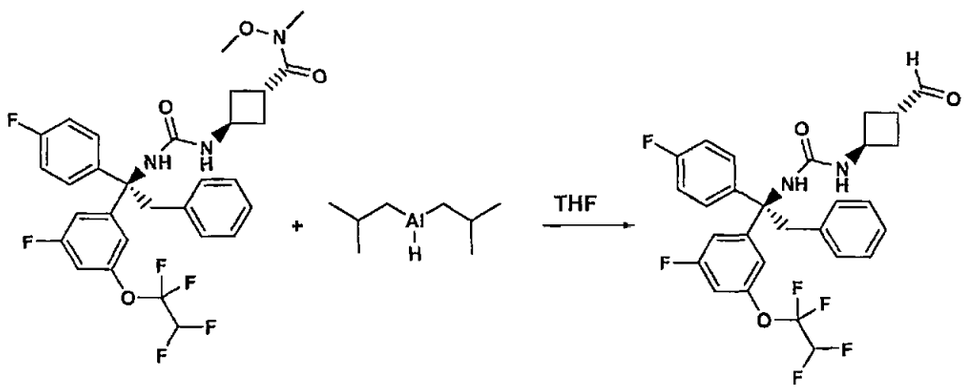
**Procedure 40**




**[00277]** To a solution of (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-

phenylethyl)ureido)cyclobutanecarboxylic acid (180 mg, 0.32 mmol) in $CH_2Cl_2$ (5 mL) was added N,O-dimethylhydroxyamine HCl (31 mg, 0.32 mmol) and N-methylmorpholine (32 mg, 0.37 mmol). The reaction mixture was cooled to -10 °C under Ar. After 5 min, EDCI (61 mg, 0.39 mmol) was added and the reaction mixture was allowed to reach rt and stirred for 15 min. The reaction mixture was concentrated and purified by ISCO flash chromatography to yield (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)-*N*-methoxy-*N*-methylcyclobutanecarboxamide as a white solid (194 mg, 100% yield). HPLC: RT = 3.94 min [M+H] 610.72 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, DMSO) ppm 2.55 - 2.63 (m, 2 H), 2.94 - 3.10 (m, 2 H), 3.61 - 3.71 (m, 3 H), 3.84 - 4.02 (m, 1 H), 4.13 - 4.21 (m, 3 H), 4.41 (dd, 2 H), 4.58 - 4.75 (m, 1 H), 5.92 - 6.05 (m, 2 H), 6.75 (t, 1 H), 7.24 - 7.33 (m, 2 H), 7.43 - 7.52 (m, 2 H), 7.54 - 7.64 (m, 3 H), 7.64 - 7.83 (m, 5 H).

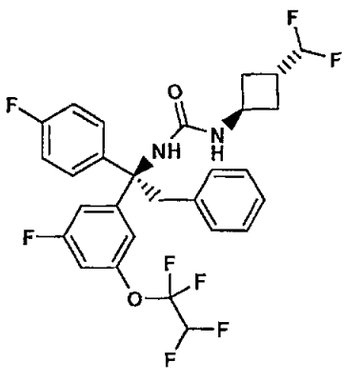
**Procedure 41**




**[00278]** To a solution of (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)-*N*-methoxy-*N*-methylcyclobutanecarboxamide (182 mg, 0.3 mmol) in THF (2 mL) at -78 °C under Ar was added dropwise DIBAL-*H* (1.0 M in hexane, 0.75 mL). The reaction mixture was stirred at -78 °C for 20 min. Acetone (1 mL) was added, followed by saturated aqueous potassium sodium tartrate (5 mL) and ether (2 mL). The resulting reaction mixture was stirred at rt for 16 h. The aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated

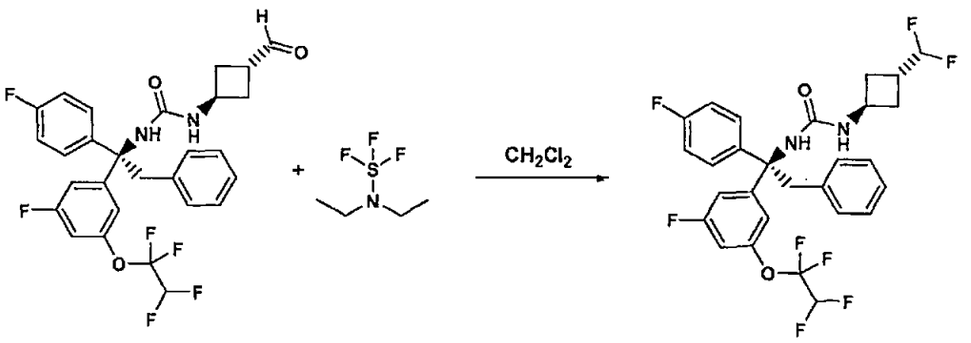
under reduced pressure. The resulting residue was purified by ISCO flash chromatography using EtOAc and hexane as eluting solvent to yield 1-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1*r*,3*R*)-formylcyclobutyl)urea (Example 248) as a white solid (122 mg, 74% yield). HPLC: RT = 3.89 min [M+H] 551.10 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 1.73 - 1.88 (m, 2 H), 2.35 - 2.49 (m, 2 H), 2.80 - 2.94 (m, 1 H), 3.64 (dd, 2 H), 3.81 - 3.98 (m, 1 H), 4.95 (d, 1 H), 5.20 - 5.29 (m, 1 H), 5.79 (t, 1 H), 6.56 (d, 2 H), 6.71 - 6.92 (m, 4 H), 6.92 - 7.16 (m, 5 H), 9.58 - 9.70 (m, 1 H).

**EXAMPLE 249**



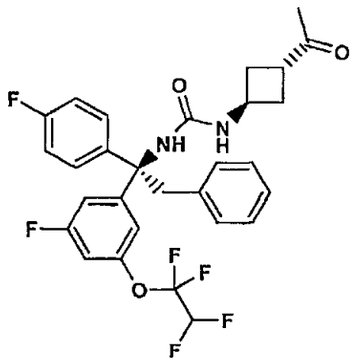
**1-((1r,3R)-3-(difluoromethyl)cyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

**Procedure 42**



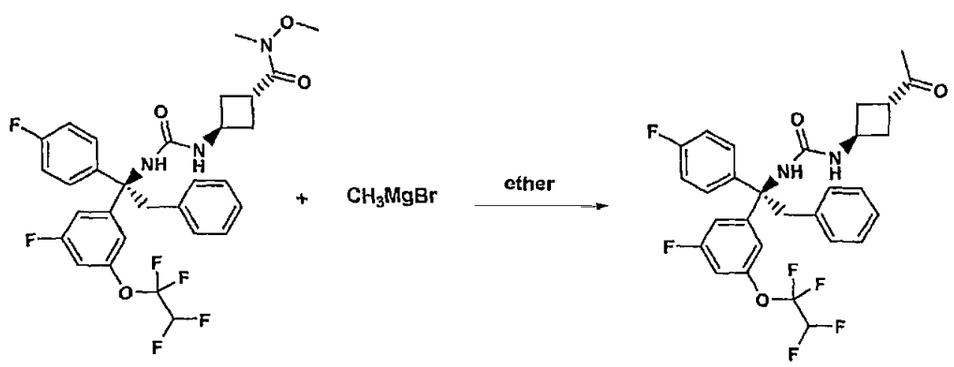
**[00279]** To a solution of 1-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1*r*,3*R*)-formylcyclobutyl)urea (Example 248, 43 mg, 0.078 mmol) in $CH_2Cl_2$ (0.5 ml) at rt was added DAST (30 uL , 0.23 mmol) dropwise. The reaction mixture was stirred at rt for 16 h, concentrated under reduced pressure and purified by prep HPLC (phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm). The product was further purified by ISCO flash chromatography to yield 1-((1r,3*R*)-3-(difluoromethyl)cyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 249) as a white solid (18 mg, 40% yield). HPLC: RT = 4.03 min [M+H] 573.69 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (500 MHz, $CD_3CN$) δ ppm 1.98 - 2.08 (m, 2 H), 2.24 - 2.39 (m, 2 H), 2.46 - 2.65 (m, 1 H), 3.85 (dd, 2 H), 4.08 - 4.22 (m, 1 H), 5.45 - 5.56 (m, 1 H), 5.96 (t, 1 H), 6.19 (t, 1 H), 6.65 - 6.78 (m, 2 H), 6.88 - 6.97 (m, 2 H).

**EXAMPLE 250**



**1-((1r,3R)-3-acetylcyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

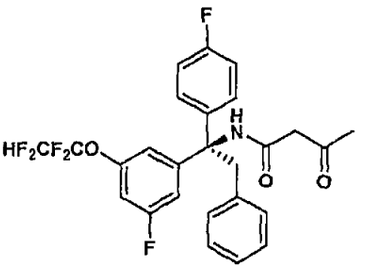
**Procedure 43**




**[00280]** To a solution of (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)-*N*-methoxy-*N*-methylcyclobutanecarboxamide, prepared as described in Procedure 40, (160 mg, 0.26 mmol) in ether (5 mL) at - 40 °C, was added dropwise $CH_3MgBr$ (3 M in ether, 0.2 mL). Then the reaction mixture was stirred at 0 °C for 4 h. The reaction was quenched with sat. NaCl and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified by ISCO flash chromatography using EtOAc and hexane as eluting solvent to yield 1-((1r,3*R*)-3-acetylcyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 250) as a white solid (32 mg, 22% yield). HPLC: RT = 3.90 min [M+H] 565.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CD_3CN$) δ ppm 2.03 - 2.09 (m, 2 H), 2.08 - 2.12 (m, 3 H), 2.41 - 2.54 (m, 2 H), 3.10 - 3.23 (m, 1 H), 3.88 (dd, 2 H), 3.98 - 4.07 (m, 1 H), 5.41 - 5.51 (m, 2 H), 6.21 (t, 1 H), 6.73 - 6.80 (m, 2 H), 6.93 - 7.00 (m, 2 H), 7.02 - 7.10 (m, 3 H), 7.12 - 7.30 (m, 6 H).

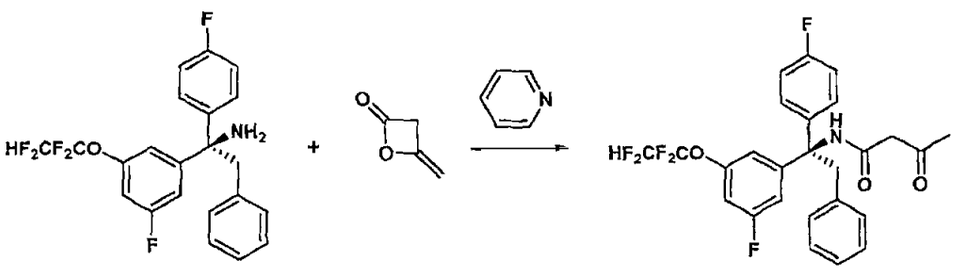
324

## EXAMPLE 251



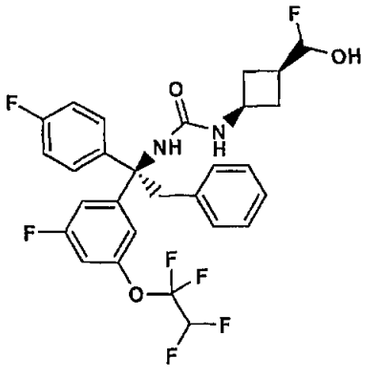
**(R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-oxobutanamide**

**Procedure 44**



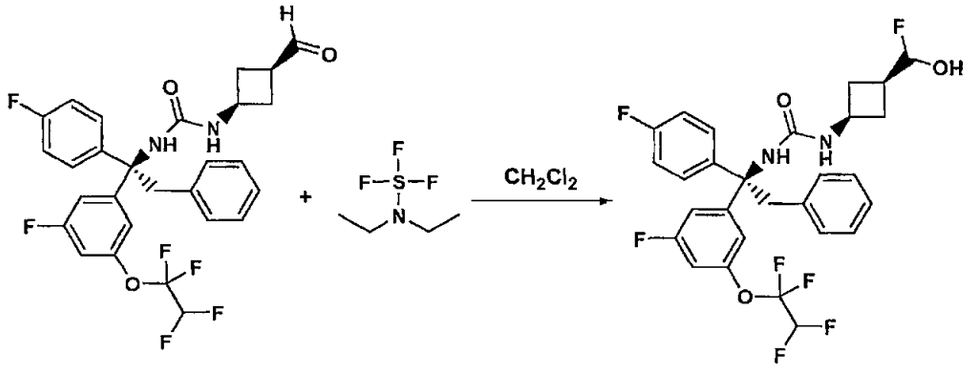
**[00281]** To a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (28 mg, 0.07 mmol), prepared as described in Procedure 3, 4, 5 and 6, in DCM (1 mL) was added pyridine (0.01 mL, 0.12 mmol). The reaction was cooled to 0 °C, followed by the addition of 4-methyleneoxetan-2-one (0.01 mL, 0.13 mmol). The reaction mixture was stirred at rt for 2 h and concentrated. The residue was purified by preparative HPLC (Axia luna column, 30 x 75 mm, 40-100% ACN/$H_2O$ with 0.1% TFA over 10 min, flow rate 40 mL/min, monitoring at 220 nm) to yield (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-oxobutanamide (Example 251) as colorless oil (23 mg, 58% yield). LCMS: RT = 3.71 min [M+H] 510.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 8.23 (1 H, s), 7.04 - 7.20 (5 H, m), 6.96 - 7.02 (2 H, m), 6.87 - 6.92 (3 H, m), 6.61 (2 H, d, *J*=7.07 Hz), 5.87 (1 H, t, *J*=2.78 Hz), 3.94 (1 H, d, *J*=12.88 Hz), 3.71 (1 H, d, *J*=12.88 Hz), 3.43 (2 H, s), 2.24 (3 H, s).

**EXAMPLE 252**



**1-((1R,3S)-3-((S)-fluoro(hydroxy)methyl)cyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

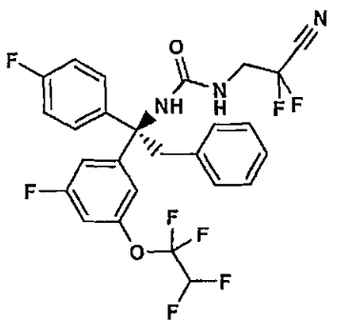
**Procedure 45**



**[00282]** To a solution of 1-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1s,3S)-3-formylcyclobutyl)urea (Example 248, 35 mg , 0.064 mmol) in $CH_2Cl_2$ (0.5 ml) was added DAST (50 uL, 0.37 mmol). The reaction mixture was stirred at rt for 3 days, then concentrated and purified by prep HPLC to yield 1-((1R,3S)-3-((S)-fluoro(hydroxy)methyl)cyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 252) as a light yellow solid (20 mg, 56% yield). LCMS: RT = 1.79 min [M+H] 553.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% $MeOH/H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 1.59 - 1.79 (m, 1 H), 1.95 - 2.15 (m, 1 H), 2.52 -

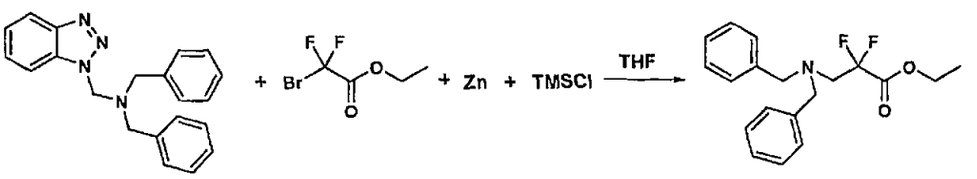
2.77 (m, 2 H), 2.90 - 3.07 (m, 1 H), 3.65 - 3.76 (m, 2 H), 3.99 - 4.16 (m, 1 H), 4.60 - 5.11 (m, 1 H), 5.56 - 6.07 (m, 2 H), 6.57 - 6.67 (m, 2 H), 6.78 - 7.32 (m, 12 H), 10.13 - 10.41 (m, 1 H).

**EXAMPLE 253**



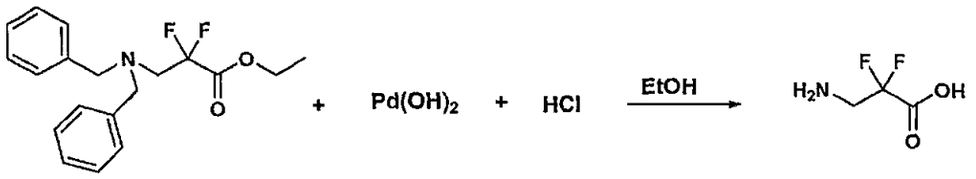
**(R)-1-(2-cyano-2,2-difluoroethyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

**Procedure 46**

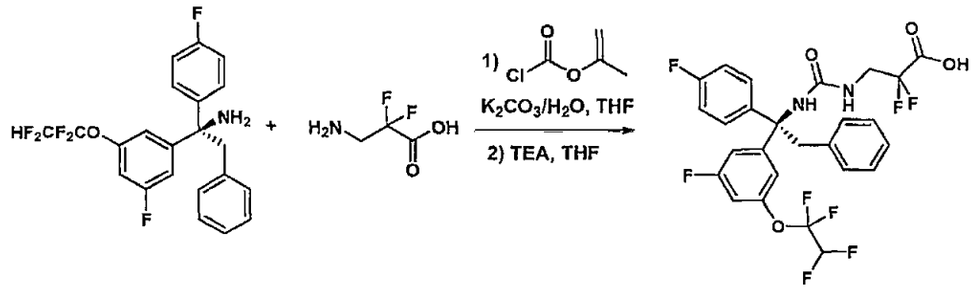



**[00283]** To a suspension of zinec dust (238 mg, 3.66 mmol) in THF (3 ml) under Ar was added TMSCl (234 uL, 1.83 mmol). The reaction mixture was stirred at rt for 10 min followed by addition of ethyl bromodifluoroacetate (260 uL, 2.0 mmol) dropwise. After 10 min, *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-*N*-benzyl-1-phenylmethanaime (600 mg, 1.83 mmol) in THF (3 ml) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with 5% $NaHCO_3$ in $H_2O$ (10 mL). The resulting solid was filtered and washed with EtOAc. The filtrate was extracted with EtOAc and the combined EtOAc layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by ISCO flash chromatography by using EtOAc and hexane as eluting solvent to yield ethyl 3-(dibenzylamino)-2,2-difluoropropanoate as a colorless oil (577 mg, 56% yield). LCMS: RT = 4.09 min [M+H] 334.28 (Phenomenex Luna

C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

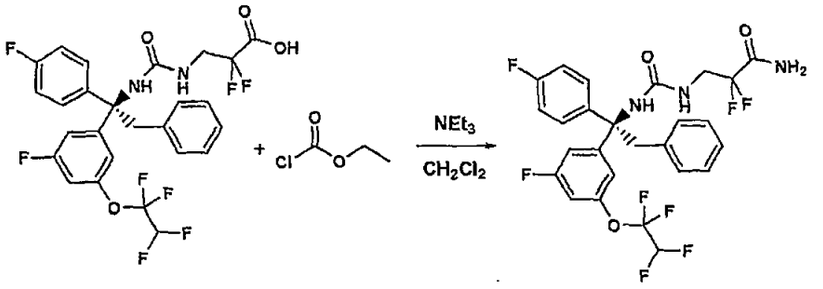



**[00284]** To a solution of ethyl 3-(dibenzylamino)-2,2-difluoropropanoate (517 mg, 1.55 mmol) in EtOH (1 mL) was added 0.5 N HCl (1 mL) and $Pd(OH)_2/C$ (20%, 50 mg). The reaction mixture was stirred at room temperature under $H_2$ atmosphere for 3 days. The reaction mixture was filtered and the solid was rinsed with water and ether. The aqueous layer was separated from the ether layer and lyophilized to yield ethyl 3-amino-2,2-difluoropropanoic acid as a white solid (210 mg, 100 % yield). $^1H$ NMR (400 MHz, DMSO) ppm 3.27 - 3.46 (m, 2 H), 8.06 - 8.64 (m, 3 H).



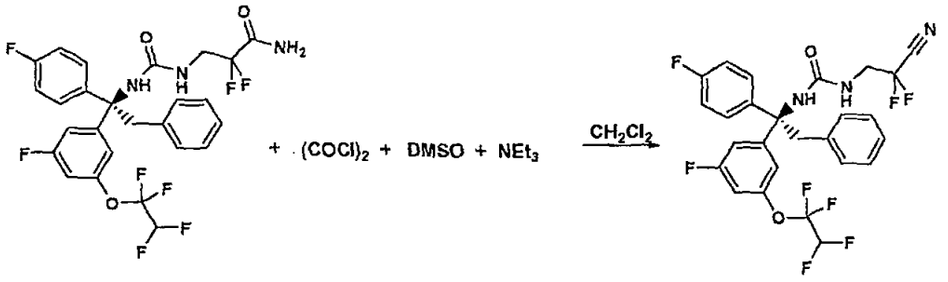

**[00285]** Using the method described in Procedure 25, (*R*)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)propanoic acid (60 mg, 0.1 mmol) was prepared as a white solid (62 mg, 54% yield). LCMS: RT = 1.97 min [M+H] 577.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**Procedure 47**



**[00286]** To a solution of (*R*)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)propanoic acid (60 mg, 0.1 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C was added ethyl carbonochloridate (10 uL, 0.1 mmol), followed by $NEt_3$ (0.021 mL, 0.15 mmol) and $NH_3 \cdot H_2O$ (0.1 mL, 2.6 mmol). The reaction mixture was stirred at rt for 30 min, then concentrated under reduced pressure and purified by prep HPLC (Phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to yield (*R*)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4- fluorophenyl)-2-phenylethyl)ureido)propanamide as a white solid (12 mg, 21% yield). LCMS: RT = 3.85 min [M+H] 576.1 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

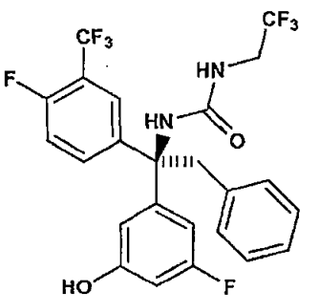
**Procedure 48**



**[00287]** To a solution of (*R*)-2,2-difluoro-3-(3-(1-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)propanamide (12 mg, 0.02 mmol) in $CH_2Cl_2$ (0.5 mL) at -78 °C was added DMSO (10 uL, 0.14 mmol), followed by addition of $(COCl)_2$ (2 M in $CH_2Cl_2$, 0.05 mmol). The reaction mixture

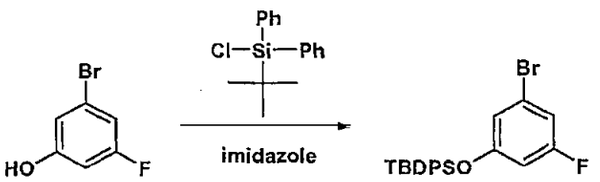
was stirred at -78 °C for 15 min, then $NEt_3$ (0.03 mL, 0.2 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep HPLC (Phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to yield (*R*)-1-(2-cyano-2,2-difluoroethyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 253) as a white solid (7 mg, 62% yield). LCMS: RT = 4.03 min [M+H] 558.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 3.71 (d, 2 H), 3.76 - 3.99 (m, 3 H), 4.75 - 4.84 (m, 1 H), 5.13 - 5.27 (m, 1 H), 5.86 (t, 1 H), 6.64 - 6.76 (m, 2 H), 6.86 - 6.96 (m, 3 H), 6.97 - 7.06 (m, 2 H), 7.07 - 7.23 (m, 5 H).

**EXAMPLE 254**



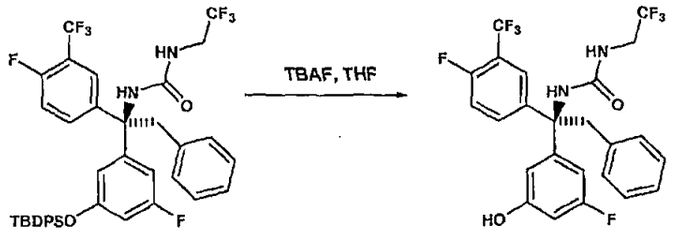

**(*R*)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-hydroxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea**

**Procedure 49**




**[00288]** To a solution of 3-bromo-5-fluorophenol (5.7 g, 30 mmol), prepared as described in Procedure 3, and imidazole (4.0 g, 60 mmol, 2 eq) in anhydrous THF (100 mL) at 0 °C was added tert-butyldiphenyl-silyl chloride (9.6 mL, 1.3 eq). The

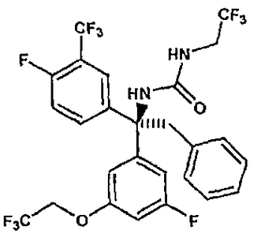
resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water and extracted with hexane/EtOAc (1:1). The combined organic layers were washed with $H_2O$ (2 x) and sat. NaCl (2 x), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexanes/EtOAc) to give (3-bromo-5-fluorophenoxy)(tert-butyl)diphenylsilane as colorless oil (7.5 g, yield 58 %).




**[00289]** (R)-1-(1-(3-(tert-butyldiphenylsilyloxy)-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea was prepared as described in Procedure 4, 5, 6 and 10 (85 mg, 37 % overall yield). LCMS: RT = 2.71 min [M+H] 757.3 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

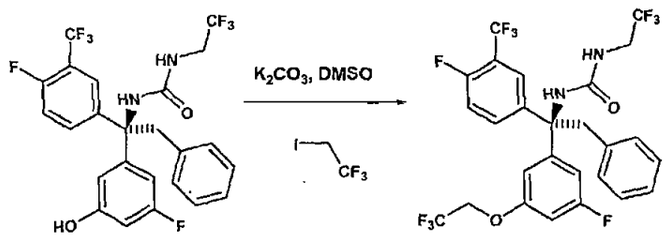
**[00290]** To a solution of (R)-1-(1-(3-(tert-butyldiphenylsilyloxy)-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (85 mg, 0.11 mmol) in THF (1.5 mL) was added TBAF (1.0 M in THF, 0.12 mL, 0.12 mmol). The resulting mixture was stirred at room temperature for 45 min. The reaction was diluted with $CH_2Cl_2$ and washed with sat. $NH_4Cl$, $H_2O$ and sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give (*R*)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-hydroxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 254, 45 mg, yield 77 %). LCMS: RT = 2.0 min [M+H] 519.1 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.20 - 7.27 (3 H, m), 7.09 - 7.18 (3 H, m), 6.72 (1 H, d, *J*=9.60 Hz), 6.66 (3 H, d, *J*=7.07 Hz), 6.57 (1 H, s), 3.73 - 3.78 (1 H, m), 3.65 - 3.71 (1 H, m), 3.63 (1 H, d, *J*=8.59 Hz), 3.47 - 3.58 (1 H, m).

## EXAMPLE 255



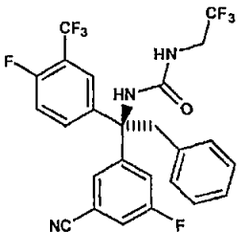
**(*R*)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea**

**Procedure 50**



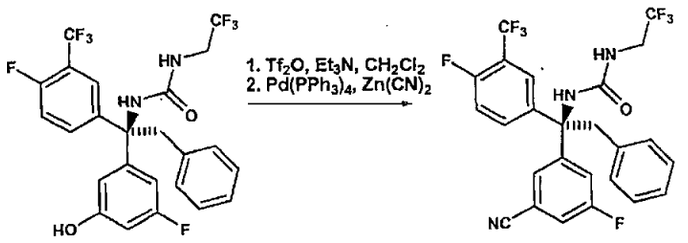

**[00291]** To a solution of (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-hydroxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 254, 15 mg, 0.03 mmol) in DMSO (0.15 mL) was added $ICH_2CF_3$ (0.02 mL) and $K_2CO_3$ (20 mg, 0.2 mmol). The reaction mixture was heated at 70 °C overnight. The reaction was cooled to rt and diluted with $CH_3CN$, filtered and purified by prep HPLC (phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to give (*R*)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 255) as white solid (10 mg, yield 58%). LCMS: RT = 2.18 min [M+H] 601.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.33 - 7.43 (2 H, m), 7.21 (1 H, d, *J*=6.60 Hz), 7.12 - 7.19 (2 H, m), 6.68 (2 H, d, *J*=7.70 Hz), 6.54 - 6.63 (3 H, m), 4.19 - 4.30 (2 H, m), 3.73 - 3.84 (4 H, m).

## EXAMPLE 256



**(*R*)-1-(1-(3-cyano-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea**

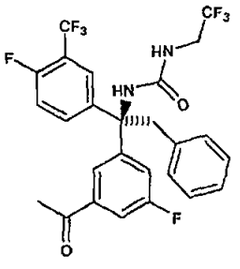
### Procedure 51




**[00292]** To a solution of (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-hydroxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 254, 0.12 g, 0.23 mmol) in anhydrous $CH_2Cl_2$ (2 mL) at 0 °C under argon was added $Et_3N$ (0.05 mL, 0.4 mmol) followed by dropwise addition of trifluoroacetic anhydride (0.05 mL). The reaction mixture was stirred at 0 °C for 30 min the diluted with $CH_2Cl_2$ (10 mL). The organic layer was washed with $H_2O$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give (R)-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl)phenyl trifluoromethanesulfonate (65 mg). LCMS: RT = 2.34 min [M+H] 651.4 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). To a solution of (R)-3-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl)phenyl trifluoromethanesulfonate (65 mg, 0.1 mmol) in DMF (0.4 mL) was added $Zn(CN)_2$ (70 mg) and $Pd(PPh_3)_4$ (catalytic amount). The reaction mixture was heated to 105 °C in a sealed vial for 2 h. After cooling to rt, the reaction solution was filtered and the solid was rinsed with EtOAc. The filtrate was

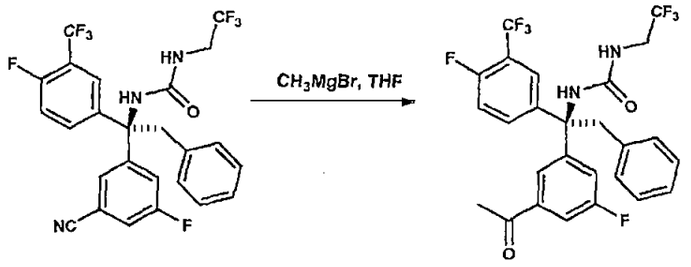
washed with sat. $NaHCO_3$, $H_2O$, and sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give (R)-1-(1-(3-cyano-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 256, 37 mg, 30% yield for 2 steps). LCMS: RT = 3.88 min [M+H] 528.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% $MeOH/H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.31 (m, 2 H), 7.26-7.13 (m, 4 H), 7.02-6.93 (m, 3 H), 6.66 (d, *J*=7.7 Hz, 2 H), 5.24 (s, br, 1H), 5.05 (t, *J*=6.0 Hz, 1 H), 3.80 (AB, *J*=12.6 Hz, 2 H), 3.74 (m, 2 H).

**EXAMPLE 257**



**(*R*)-1-(1-(3-acetyl-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea**

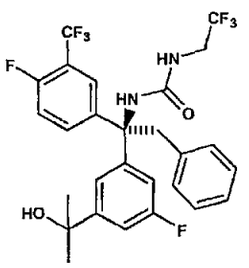
**Procedure 52**




**[00293]** To a solution of (S)-1-(1-(3-cyanophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 256, 30 mg, 0.06 mmol) in THF (1 mL) at rt was added $CH_3MgBr$ (3.0 M in $Et_2O$, 0.1 mL). The reaction mixture was heated at 48 °C - 55 °C for 2.5 h. After cooling, 1N

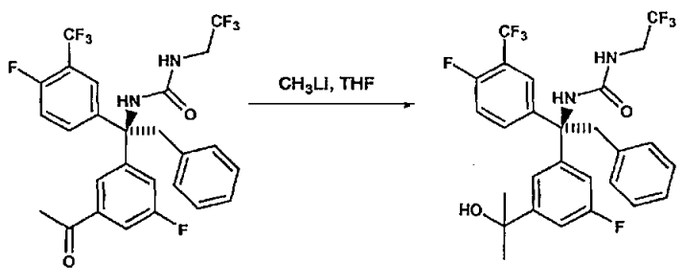
HCl was added and the reaction mixture was stirred for 10 min at rt. The reaction mixture was extracted with EtOAc, washed with $H_2O$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give pure (*R*)-1-(1-(3-acetyl-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 257, 26 mg, yield: 84%). LCMS: RT = 3.90 min [M+H] 545.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.58 (m, 1 H), 7.53 (m, 1 H), 7.36 (m, 2 H), 7.23 (m, 1 H), 7.16 (m, 4 H), 6.68 (d, J=6.8 Hz, 2 H), 5.43 (s, br, 1 H), 5.17 (m, 1 H), 3.88 (dd, J=23.2, 12.9 Hz, 2 H), 3.78 (m, 2 H), 3.03 (s, 3 H).

**EXAMPLE 258**



**(*R*)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(2-hydroxypropan-2-yl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea**

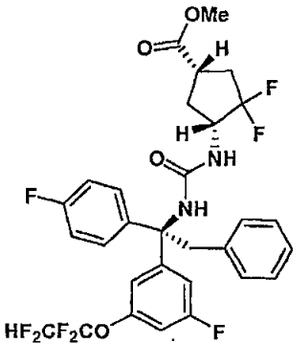
**Procedure 53**




**[00294]** To a solution of (R)-1-(1-(3-acetyl-5-fluorophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 257, 20 mg, 0.037 mmol) in THF (1 mL) at 0 °C under argon was added dropwise $CH_3Li$ (1.4 M in $Et_2O$, 0.04 mL, 0.056 mmoL). The reaction mixture was stirred at room

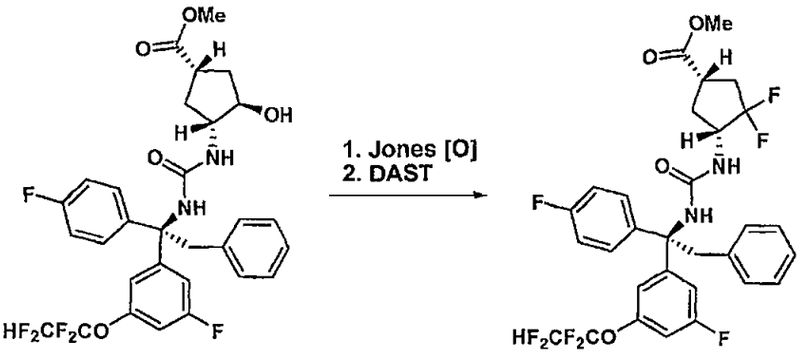
temperature for 2 h, then quenched with sat. $NH_4Cl$ and 0.5 N HCl and the aqueous layer was extracted with EtOAc. The combined organic portions were washed with $H_2O$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes /EtOAc) to give (*R*)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(2-hydroxypropan-2-yl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 258, 8 mg, yield 39%). LCMS: RT = 3.89 min [M+H] 559.4 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% $NH_4Cl$; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) ppm 7.51-7.45 (m, 2 H), 7.21-6.96 (m, 6 H), 6.68 (d, *J*=6.8 Hz, 2 H), 6.61 (d, J= 9.9 Hz, 1 H), 5.43 (s, br, 1 H), 5.17 (m, 1 H), 4.01 (d, *J*= 13.2 Hz, 1 H), 3.85-3.62 (m, 3 H), 1.46 (s, 3 H), 1.44 (s, 3 H).

**EXAMPLE 259**




**(1S,4R)-methyl 3,3-difluoro-4-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetra-fluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-)ureido)cyclopentanecarboxylate**

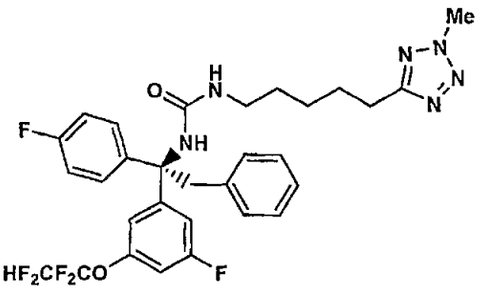
**Procedure 54**




**[00295]** To a solution of (1S,3R,4R)-methyl 3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)-4-hydroxycyclopentanecarboxylate, prepared as described Procedure 12, (11 mg, 0.017 mmol) in acetone (430 μL) was added a solution of Jones reagent (17 μL, 1 M solution). The reaction mixture was stirred at rt for 1.5 h, then filtered through a celite pad. The pad was washed with acetone and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with $H_2O$. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (17 mL) and DAST (6.5 mL) was added at rt. The reaction mixture was stirred overnight, then quenched with sat. NaCl. The aqueous layer was extracted with $CH_2Cl_2$ (3 x). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenoma Luna AXIA 10A, C18, eluting with MeCN / $H_2O$ containing 0.1% TFA, monitoring at 220 nm) to provide (1S,4R)-methyl 3,3-difluoro-4-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetra-fluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-)ureido)cyclopentanecarboxylate (Example 259, 9 mg, 85% yield) as a film. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.16-7.07 (m, 6 H), 7.00-6.83 (m, 6 H), 6.62 (d, $J$ = 10 Hz, 2 H), 5.93-5.68 (m, 1 H), 5.37 (s, 1 H), 3.77 (d, $J$ = 10 Hz, 1 H), 3.64 (s, 3 H), 3.68-5.58 (m, 2 H), 2.90-2.84 (m, 1 H), 2.47-2.26 (m, 3 H), 1.60-1.53 (m, 1 H); LC/MS: RT = 3.97 min [M+H] 631.4 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-

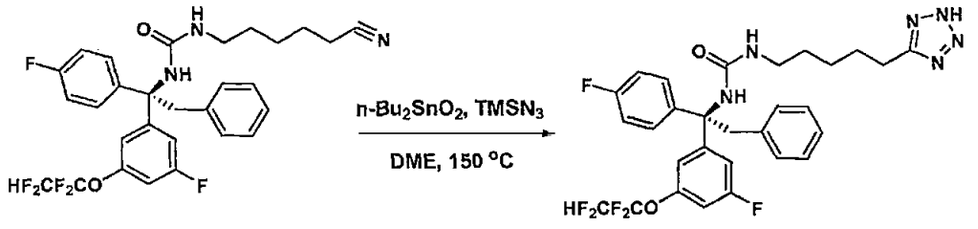
90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 260**



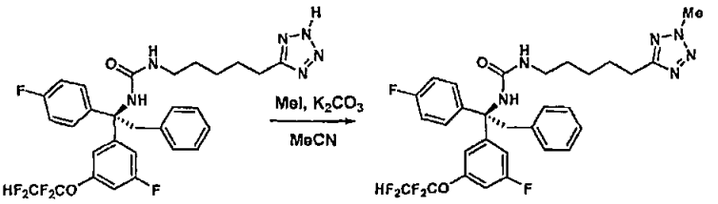
**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(5-(2-methyl-2H-tetrazol-5-yl)pentyl)urea**

**Procedure 55**



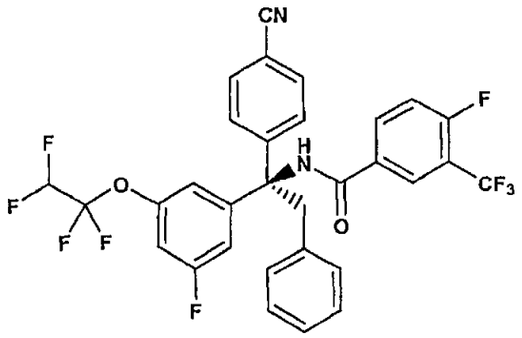

**[00296]** To a solution of (R)-1-(5-cyanopentyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea, prepared by the method described in Procedure 12 (45 mg, 0.080 mmol) in DME (161 μL) at rt was added $TMSN_3$ (0.013 mL, 0.16 mmol), followed by n-$Bu_2SnO_2$ (2 mg, 0.008 mmol). The reaction mixture was heated at 150 °C for 10 min under microwave irradiation. An additional amount of $TMSN_3$ (0.013 mL, 0.16 mmol) and n-$Bu_2SnO_2$ (2 mg, 0.008 mmol) was added, and the reaction mixture was heated at 150 °C for an additional 10 min under microwave irradiation. The reaction mixture was concentrated and the residue was dissolved in MeOH and purified by preparative HPLC (Phenoma Luna AXIA 10A, C18, eluting with MeCN / $H_2O$ containing 0.1% TFA, monitoring at 220 nm) to provide (R)-1-(5-(2H-tetrazol-5-yl)pentyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (23 mg, 47% yield) as a white solid. $^1H$ NMR (500 MHz, MeOH-$d_4$) δ 7.18-6.89 (m, 11 H), 6.71 (d, $J$ = 5

Hz, 2 H), 6.37-6.16 (m, 1 H), 3.93 (d, $J$ = 15 Hz, 1 H), 3.81 (d, $J$ = 15.0 Hz, 1 H), 3.08 (t, $J$ = 5 Hz, 2 H), 2.94 (t, $J$ = 5 Hz, 2 H), 1.83-1.76 (m, 2 H), 1.55-1.48 (m, 2 H), 1.41-1.35 (m, 2 H); LC/MS: RT = 3.736 min [M+H] 607.3 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm).



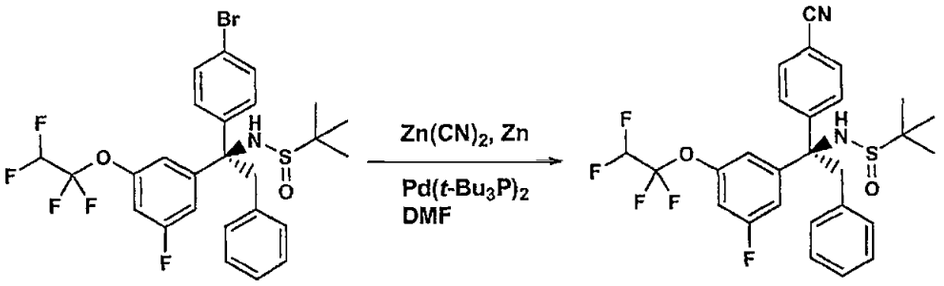

**[00297]** To a solution of (R)-1-(5-(2H-tetrazol-5-yl)pentyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (12 mg, 0.019 mmol) in MeCN (115 μL) at rt was added $K_2CO_3$ (3.2 mg, 0.023 mmol) followed by MeI (1.5 μL, 0.023 mmol). The reaction mixture was heated to 80 °C overnight. The reaction mixture was quenched by addition of $H_2O$ and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were concentrated and the residue was dissolved in MeOH and purified by preparative HPLC (Phenoma Luna AXIA 10A, C18, eluting with MeCN / $H_2O$ containing 0.1% TFA, monitoring at 220 nm) to provide (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(5-(2-methyl-2H-tetrazol-5-yl)pentyl)urea (Example 260, 2 mg, 18% yield) as white solid. $^1H$ NMR (500 MHz, $CDCl_3$) ppm 7.17-7.08 (m, 5 H), 6.99-6.85 (m, 5 H), 6.67 (d, $J$ = 5 Hz, 2 H), 5.98-5.75 (m, 1 H), 4.23 (s, 3 H), 3.82 (d, $J$ = 15 Hz, 1 H), 3.68 (d, $J$ = 15 Hz, 1 H), 3.10-3.07 (m, 2 H), 2.85-2.82 (m, 2 H), 1.77-1.71 (m, 2 H), 1.46-1.40 (m, 2 H), 1.32-1.26 (m, 2 H); LC/MS: RT = 3.218 min [M+H] 621.2 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm).

## EXAMPLE 261

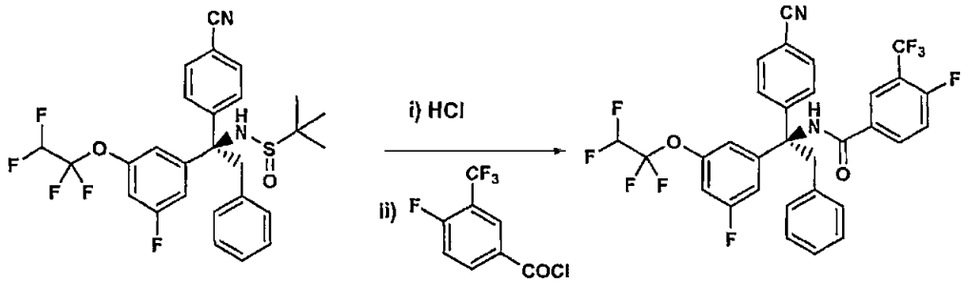


**(R)-N-(1-(4-cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

### Procedure 56

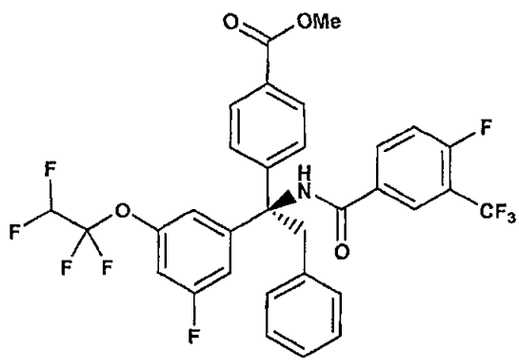



**[00298]** To a solution of (1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (2.44 g, 4.13 mmol), prepared as described in Procedure 3, 4, 5 and 6, in DMF (20 mL) were added zinc cyanide (970 mg, 8.27 mmol) and zinc dust (81 mg, 1.24 mmol). The reaction mixture was degassed with Ar and placed under nitrogen. Palladiumbistributylphosphine (41 mg, 0.20 mmol) was added and the reaction mixture was heated at 60 °C for 16 h. The reaction mixture was quenched with sat. sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were dried over $Mg_2SO_4$, filtered and concentrated to provide N-((R)-1-(4-cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a white solid (2.08 g, 93% yield). LC/MS: RT = 2.25 min [M+H] 537 (Chromolith Performance 18e 4.6 x 100 mm column, 10-90% $CH_3OH/H_2O$ with 0.1% TFA gradient over 2 min, 5 mL/min, monitoring at 220 nm).



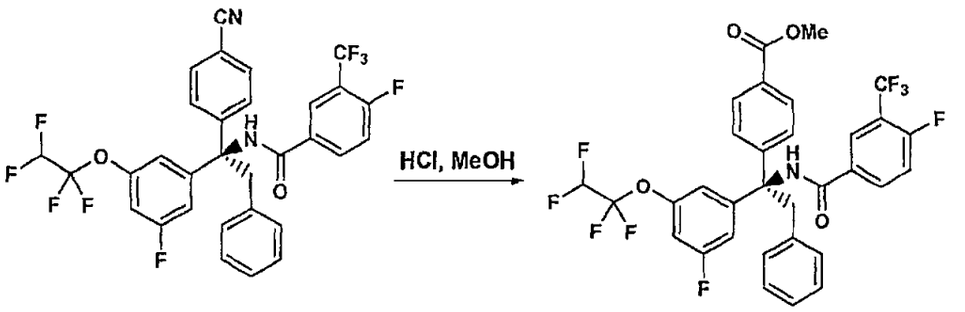

**[00299]** Following Procedure 6 and 7, (R)-N-(1-(4-cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 261) was prepared as a white powder (380 mg, 89% yield). LC/MS: RT = 2.33 min [M+H] 623 (Chromolith Performance 18e 4.6 x 100 mm column, 10-90% $CH_3OH/H_2O$ with 0.1% TFA gradient over 2 min, 5 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) ppm 7.91 (1 H, d, $J$=6.60 Hz), 7.81 - 7.86 (1 H, m), 7.67 (2 H, d, $J$=8.24 Hz), 7.38 (2 H, d, $J$=8.25 Hz), 7.24 ($CHCl_3$) 7.24 - 7.31 (2 H, m), 7.18 (2 H, t, $J$=7.42 Hz), 7.05 (1 H, m), 6.90 (2 H, m), 6.64 - 6.75 (3 H, m), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 3.90 (2 H, s).

**EXAMPLE 262**



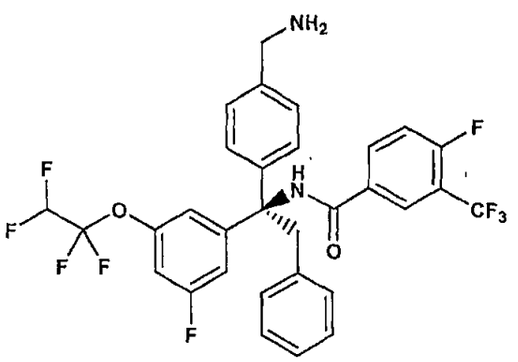

**(R)-methyl 4-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzoate**

**Procedure 57**



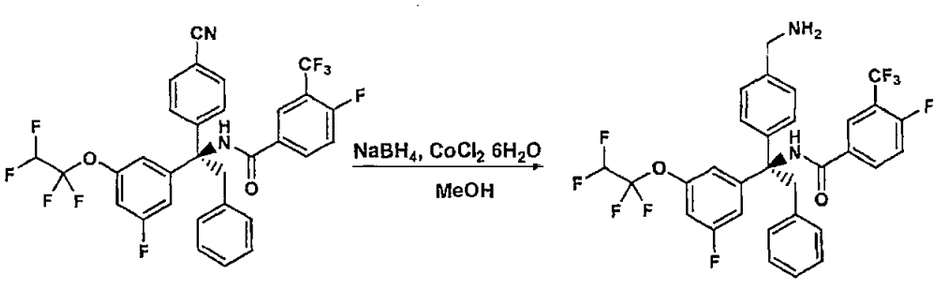

**[00300]** (R)-N-(1-(4-Cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 261, 118 mg, 0.19 mmol) was dissolved in methanol (10 mL). Hydrogen chloride gas was bubbled into the solution for 5 min and the reaction mixture was stirred at 55 °C for 22 h. Then hydrogen chloride gas was bubbled to the mixture again for 4 min. After stirring for additional 22 h, the reaction was quenched with sat. $NaHCO_3$ and the mixture was extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered and concentrated to yield a white solid. The resulting solid was purified by ISCO flash chromatography (12 g silica gel; 0-50% ethyl acetate/hexane gradient over 12 min., 30 mL/min) to provide (R)-methyl 4-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzoate (Example 262) as a white solid (92 mg, 74% yield). LC/MS: RT = 2.37 min [M+H] 656 (Chromolith Performance 18e 4.6 x 100 mm column, 10-90% $CH_3OH/H_2O$ with 0.1% TFA gradient over 2 min, 5 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) ppm 8.02 (2 H, d, $J$=8.25 Hz), 7.92 (1 H, d, $J$=6.60 Hz), 7.77 - 7.88 (2 H, m), 7.21 - 7.30 (3 H, m), 7.24 (s, $CHCl_3$), 7.15 (2 H, t, $J$=7.42 Hz), 6.89 - 7.00 (3 H, m), 6.64 - 6.72 (3 H, m), 5.87 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 4.03 (1 H, d, $J$=13.19 Hz), 3.93 (3 H, s), 3.86 (1 H, d, $J$=13.19 Hz).

## EXAMPLE 263



**(R)-N-(1-(4-(aminomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

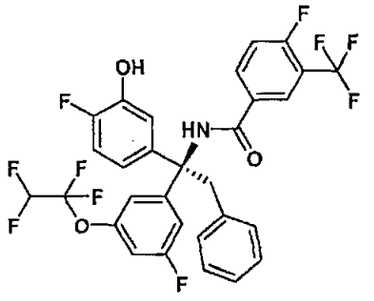
### Procedure 58




**[00301]** To a solution of (R)-N-(1-(4-Cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 261, 59 mg, 0.095 mmol) in methanol (2 mL) was added cobalt chloride hexahydrate (45 mg, 0.19 mmol), followed by sodium borohydride (36 mg, 0.95 mmol). The reaction mixture was stirred for 13 h, then quenched with HCl (1.0 M, 2 mL) and stirred for additional 1 h. The reaction mixture was diluted with sat. ammonium hydroxide then extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered and concentrated to yield a white solid. The resulting solid was purified by preparative HPLC (YMC ODS-A s-5 20 x 100 mm column; 50-90% MeOH/$H_2O$ with 0.1% TFA gradient over 10 min., 20 mL/min, monitoring at 220 nm) to provide (R)-N-(1-(4-(aminomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-(trifluoromethyl)benzamide (Example 263) as a white solid (39 mg, 56% yield). LC/MS: RT = 1.65 min [M+H]

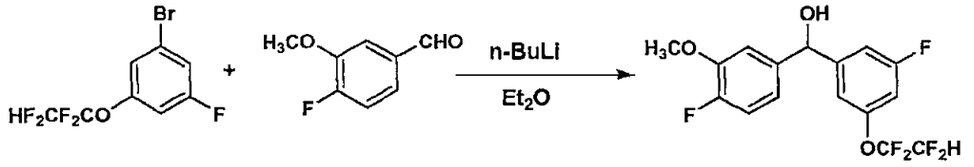
627 (Chromolith Performance 18e 4.6 x 100 mm column, 10-90% $CH_3OH/H_2O$ with 0.1% TFA gradient over 2 min, 5 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) ppm 8.06 (2 H, br s), 7.81 (1 H, d, *J*=6.05 Hz), 7.67 - 7.77 (1 H, m), 7.34 (2 H, d, *J*=7.70 Hz), 7.18 - 7.27 (3 H, m), 7.24 ($CHCl_3$, s), 7.13 (2 H, t, *J*=7.42 Hz), 6.90 (1 H, d, *J*=8.25 Hz), 6.72 - 6.81 (3 H, m), 6.66 (2 H, d, *J*=7.15 Hz), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 4.01 (2 H, br s), 3.77 - (2 H, dd, *J*=29.1 Hz, *J*=13.2 Hz).

**EXAMPLE 264**



**(R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

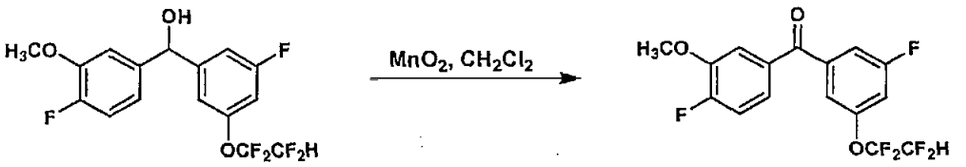
**Procedure 59a**



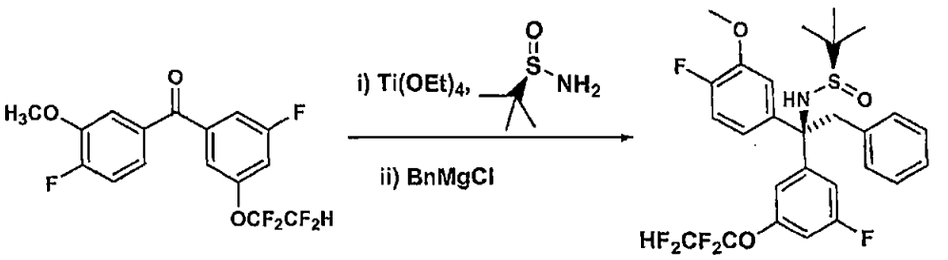

**[00302]** To a solution of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene, prepared as described in Procedure 3, (1.00 g, 3.44 mmol) in diethyl ether in (10 mL) at -72 °C was added 2.5 M n-BuLi (1.37 mL, 3.44 mmol) dropwise. Upon completion of addition, the reaction mixture was stirred for 15 minutes at -72 °C, then 4-fluoro-3-methoxybenzaldehyde (0.53 g, 3.44 mmol ) was added while the reaction mixture temperature was maintained below -52 °C. The reaction mixture was stirred for 3 h at -72 °C. The reaction mixture was quenched by the addition of 1N HCl and the aqueous portion was extracted with EtOAc (2 x). The combined organic layers were washed with sat. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was purified by ISCO using a gradient of 0-50% EtOAc/ hexane as eluent to yield (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol (0.83 g, 66% yield). HPLC: RT = 3.85 min (Phenomenex Luna C18 5µ column, eluting with 10-90% aqueous methanol containing 0.1% phosphoric acid over a 4 minute gradient, flow rate 4 mL/min, monitoring at 220 nm); $^1$H NMR ($CDCl_3$): 7.05 - 6.8 (m, 6 H), 5.87 (tt, J=2.8, 52.9Hz), 5.75 (s, 1 H), 3.85 (s, 3 H).

**Procedure 59b**

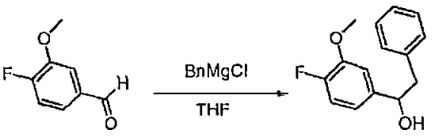



**[00303]** To a solution of (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol (0.58 g, 1.57 mmol) in $CH_2Cl_2$ (5 mL) was added activated manganese dioxide (0.80 g, 7.86 mmol). The reaction mixture was stirred overnight at rt. Additional manganese dioxide (0.80 g, 7.86 mmol) was added and the reaction stirred at rt for another overnight. The reaction mixture was diluted with $CH_2Cl_2$ and filtered through celite and the solid was washed with $CH_2Cl_2$. The filtrate was concentrated under reduced pressure to yield (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone (0.56 g, 98% yield). HPLC: RT = 4.048 minutes (Phenomenex Luna C18 5µ column, eluting with 10-90% aqueous methanol containing 0.1% phosphoric acid over a 4 minute gradient, flow rate 4 mL/min, monitoring at 220 nm); LCMS: [M+H] 365.2 (Phenomenex Luna C18 5µ column, eluting with 10-90% aqueous methanol containing 0.1% TFA over a 2 minute gradient, flow rate 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$): 7.5-7.1 (m, 6 H), 5.92 (tt, J=2.2, 53.6Hz, 1 H), 3.93 (s, 3 H).




**[00304]** (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide may also be prepared by the methods described in Procedure 59c, 59d, 59e and 59f.

**Procedure 59c**



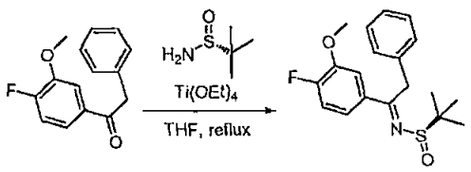

**[00305]** To a solution of 4-fluoro-3-methoxybenzaldehyde (25 g, 162 mmol) in THF (150 mL) was added a solution of benzyl magnesium chloride (2 M solution in THF, 122 mL, 243 mmol) in THF (50 mL). The reaction mixture was heated at 50 °C for 2 h. The reaction mixture was allowed to cool to rt and quenched by addition of sat. $NH_4Cl$. The reaction mixture was extracted with EtOAc (3 x) and the combined organic layers were washed with sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, eluting with 0-40% EtOAc/hexane) to yield 1-(4-fluoro-3-methoxyphenyl)-2-phenylethanol as a yellow oil (24 g, 60% yield). $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 7.27-7.32 (m, 2 H), 7.21-7.27 (m, 1 H), 7.16 (d, $J$ = 7 Hz, 2 H), 7.01 (dd, $J$ = 11, 8 Hz, 1 H), 6.92 (dd, $J$ = 8, 2 Hz, 1 H), 6.82 (ddd, $J$ = 8, 4, 1 Hz, 1 H), 4.80-4.88 (m, 1 H), 4.66 (d, $J$ = 6 Hz, 1 H), 3.84 (s, 3 H), 2.91-3.04 (m, 2 H).

**Procedure 59d**



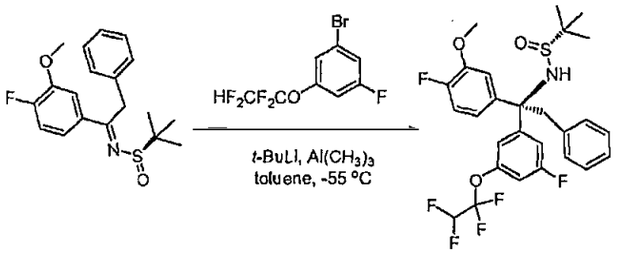
**[00306]** To a solution of 1-(4-fluoro-3-methoxyphenyl)-2-phenylethanol (23.7g, 40.6 mmol) in acetone (240 mL) was added Jones reagent (64 mL) at rt. The reaction mixture was stirred overnight, quenched by the addition of isopropanol and diluted with EtOAc. The organic portion was washed with 1 N HCl (2 x), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to yield the 1-(4-fluoro-3-methoxyphenyl)-2-phenylethanone (15 g, 66% yield). LCMS: RT = 3.250 min [M+H] 245.1 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (dd, $J$ = 8, 1 Hz, 1 H), 7.60-7.55 (m, 1 H), 7.35-7.29 (m, 2 H), 7.26-7.23 (m, 3 H), 7.10 (dd, $J$ = 10, 8 Hz, 1 H), 4.24 (s, 2 H), 3.89 (s, 3 H).

**Procedure 59e**



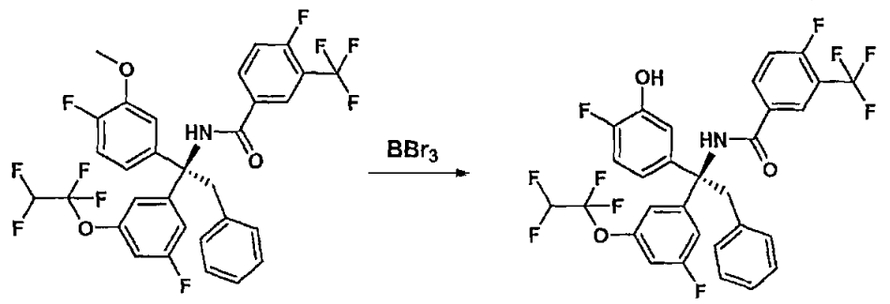

**[00307]** To a solution of 1-(4-fluoro-3-methoxyphenyl)-2-phenylethanone (13 g, 53 mmol) dissolved in THF (266 mL) was added (R)-2-methylpropane-2-sulfinamide (7.8 g, 64 mmol) at rt, followed by $Ti(OEt)_4$ (17 mL, 80 mmol). The reaction mixture was heated to reflux for 48 h, then allowed to cool to rt. The reaction mixture was concentrated under reduced pressure and the residue was diluted with $Et_2O$. $H_2O$ was added and the solid was filtered and washed with $Et_2O$. The filtrate was washed with $H_2O$, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, eluting with 0-100% EtOAc/hexane) to yield (R,E)-N-(1-(4-fluoro-3-methoxyphenyl)-2-phenylethylidene)-2-methylpropane-2-sulfinamide (12 g, 67% yield). LCMS: RT = 3.655 min [M+H] 348.2 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 7.60-7.53 (m, 1 H), 7.43-7.36 (m, 1 H), 7.29-7.15 (m, 5 H), 7.03 (dd, $J$ = 11, 8 Hz, 1 H), 4.75 (d, $J$ = 15Hz, 1 H), 4.54 (d, $J$ = 15Hz, 1 H), 3.84 (s, 3 H), 1.34 (s, 9 H).

**Procedure 59f**



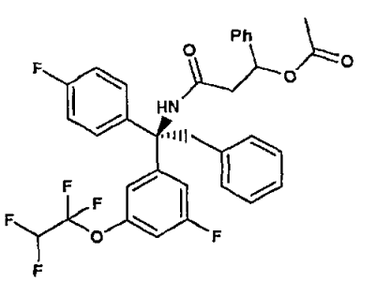

**[00308]** To a solution of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (357 mg, 1.23 mmol) in toluene (1.5 mL) at -60 °C was added n-BuLi (2.5 M in hexane, 352 mL, 0.88 mmol). The reaction mixture was stirred for 1.5 h at -20 °C to -55 °C. In a separate vial, to a -78 °C solution of (R,E)-N-(1-(4-fluoro-3-methoxyphenyl)-2-phenylethylidene)-2-methylpropane-2-sulfinamide (122 mg, 0.35 mmol) in toluene (1 mL) was added $Al(CH_3)_3$ (210 mL, 0.42 mmol). The resulting solution was stirred for 10-15 min, then added to the mixture of (3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)lithium. The combined reaction mixture was stirred at -55 °C overnight and then diluted with EtOAc . The organic portion was washed with $H_2O$ and the aqueous portion was extracted with EtOAc (3 x). The combined organic portions were concentrated under reduced pressure and the residue was purified by preparative HPLC (Phenomenex Luna AXIA 100A, C18, 5 μ; 10%-90% ACN/$H_2O$ containing 0.1% TFA, monitoring at 220 nm) to yield (R)-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (83 mg, 42% yield). LCMS: RT = 3.49 min [M+H] 560.1 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.21-7.12 (m, 3 H), 7.08 (dd, $J$ = 11, 8 Hz, 1 H), 7.00-6.94 (m, 1 H), 6.91-6.81 (m, 4 H), 6.72-6.62 (m, 2H), 5.99-5.70 (m, 1 H), 4.36 (s, 1 H), 3.96 (d, $J$ = 13 Hz, 1 H), 3.77 (s, 3 H), 3.55 (d, $J$ = 13 Hz, 1 H), 1.21 (s, 9 H).

**Procedure 59g**



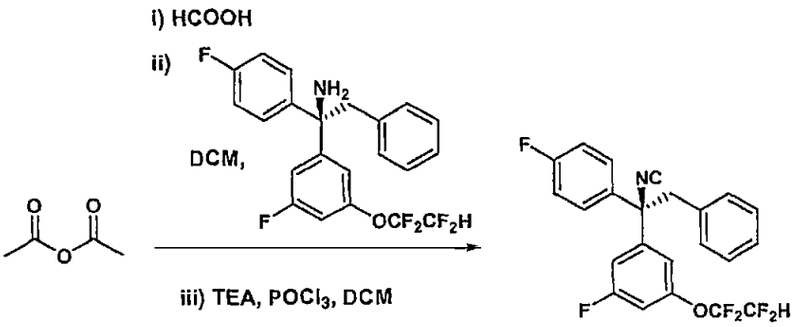

**[00309]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide, prepared as described in Procedure3, 59a-f, 6 and 7, (2.8 g, 4.43 mmol) in $CH_2Cl_2$ (15 mL) was added $BBr_3$ (12 mL, 12 mmol). The resulting mixture was stirred at room temperature for 2 h and quenched by addition of ice. The reaction mixture was diluted with EtOAc and washed with sat. $NaHCO_3$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated to afford (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264) as clear oil (2.9 g, 100 % yield). LCMS: RT = 4.176 min [M+H] 632.2 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 265**



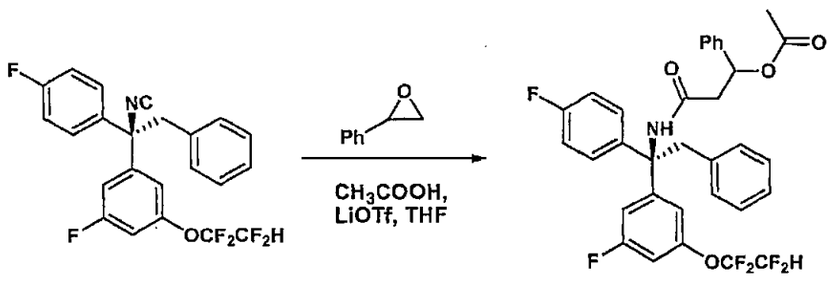

**3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-3-oxo-1-phenylpropyl acetate**

**Procedure 60**



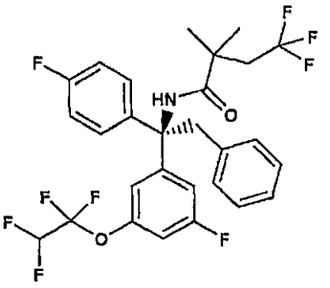

**[00310]** A solution of acetic anhydride (10 mL, 106 mmol) and formic acid (6 mL, 159 mmol) was heated at 60 °C for 3 h, then cooled to rt. An aliquot of the resulting solution (0.623 mL) was added to a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine prepared as described in Procedure 3, 4, 5 and 6 (83 mg, 0.2 mmol) in DCE (1 mL). The reaction mixture was stirred at rt for 1.5 h, then concentrated under reduced pressure to yield a clear oil. The resulting oil was dissolved in DCM and purified by ISCO chromatography (12 g) with 0-30% EtOAc in hexane to yield (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)formamide as white solid (72 mg, 81 % yield). LCMS: RT = 2.02 min [M-NHCOH] 409.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). At 0 °C to a solution of (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)formamide (72 mg, 0.16 mmol) in DCM (2 mL) was added triethylamine (0.06 mL, 0.43 mmol) and $POCl_3$ (0.016 mL, 0.18 mmol). The reaction mixture was stirred at rt overnight, then diluted with EtOAc (15 mL). The organic layer was washed with sat. $NaHCO_3$ and sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by ISCO chromatography (12 g) with 0-30% EtOAc in hexane to yield (R)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(1,1,2,2-tetrafluoroethoxy)benzene as a white solid (60 mg, 87 % yield). LCMS: RT = 2.10 min [M-NC] 409.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 3.56 - 3.65 (m, 2 H), 5.74 – 6.01 (m, 1 H), 6.84 (d, *J*=7.03 Hz, 2

H), 6.94 (d, *J*=7.03 Hz, 3 H), 7.04 - 7.10 (m, 2 H), 7.16 - 7.26 (m, 3 H), 7.32 (dd, *J*=9.01, 5.05 Hz, 2 H).



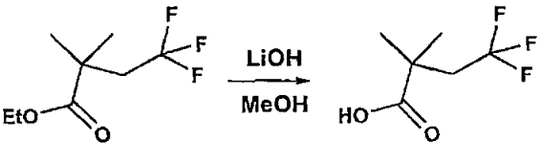

**[00311]** To a solution of 2-phenyloxirane (0.009 mL, 0.08 mmol) in THF (1.5 ml) was added LiOTf (12 mg, 0.08 mmol), (R)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(1,1,2,2-tetrafluoroethoxy)benzene (30 mg, 0.07 mmol) and acetic acid (0.004 mL, 0.08 mmol) in succession. The reaction mixture was heated to reflux for 3 h. The reaction was allowed to cool to rt and diluted with EtOAc (15 mL). The organic layer was washed with sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified by preparative HPLC YMC ODS S5 30 x 100 mm column 30-100% MeOH (90% in water, 0.1%TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm to yield 3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-3-oxo-1-phenylpropyl acetate (Example 265) as a white solid (26 mg, yield 62%, 1:1 RR: RS diastereomer mixture). LCMS: RT = 2.19 min [M+H] 616.3 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.27 min, Purity 100% (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); 1H NMR (400 MHz, $CDCl_3$) δ ppm 1.96 (d, *J*=4.95 Hz, 3 H), 3.01 (ddd, *J*=14.30, 6.87, 3.02 Hz, 1 H), 3.14 (td, *J*=8.94, 5.22 Hz, 1 H), 3.523 (d, *J*=13.2 Hz, 0.5 H), 3.62 (m, 0.5 H), 3.72 (m, 0.5 H), 3.82 (d, *J*=13.2 Hz, 0.5 H), 5.30 - 5.34 (m, 1 H), 5.74 - 5.97 (m, 1 H), 6.46 - 6.53 (m, 2 H), 6.60 (d, *J*=10.45 Hz, 1 H), 6.67 - 6.72 (m, 1 H), 6.80 - 7.31 (m, 13 H).

## EXAMPLE 266

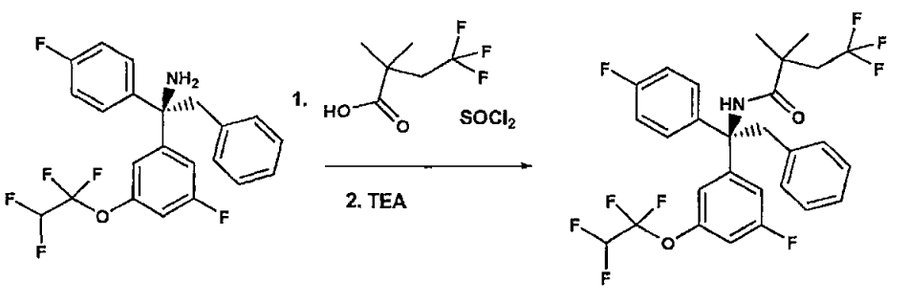


**(R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,2-dimethylbutanamide**

### Procedure 61



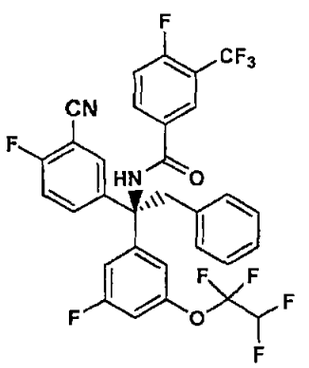

**[00312]** To a solution of ethyl 4,4,4-trifluoro-2,2-dimethylbutanoate (426 mg, 2.15 mmol) in MeOH (15 mL) was added a solution of LiOH in $H_2O$ (2 N, 5.35 mL, 10.75 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was concentrated and the resulting mixture was diluted with DCM and washed with 3 N HCl. The aqueous layer was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield 4,4,4-trifluoro-2,2-dimethylbutanoic acid as a colorless oil (370 mg, 100% yield). $^1H$ NMR (400 MHz, $CDCl_3$) ppm 1.35 (s, 6 H), 2.48 (ABqt, $J$=12 Hz, 2 H).




**[00313]** To a solution of 4,4,4-trifluoro-2,2-dimethylbutanoic acid (30 mg, 0.176 mmol) in DCE (1 mL) was added $SOCl_2$ (21 mg, 0.176 mmol) and the resulting

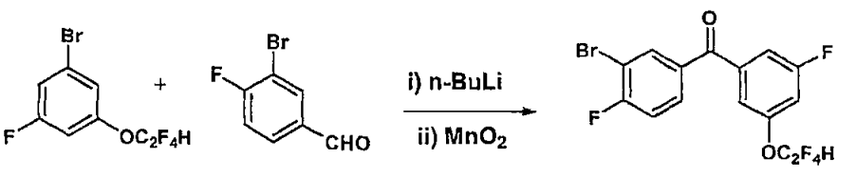
mixture was refluxed for 2 h. After cooling to room temperature, TEA was added (82 uL, 0.59 mmol), followed by the addition of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine, prepared as described in Procedure 3, 4, 5 and 6, (25 mg, 0.059 mmol). The reaction mixture was heated to reflux overnight, concentrated and the residue was purified by preparative HPLC (Axia column, 30 x 100 mm, 40 mL/min, 40-100% ACN/$H_2O$/0.1% TFA over 12 min) to give (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,2-dimethylbutanamide (Example 266) as a brownish oil (8 mg, 24% yield). LCMS: RT = 2.13 min [M+H] 578.3 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 1.28 (s, 6 H), 2.21 - 2.51 (m, 2 H), 3.77 (ABqt, *J*=13 Hz, 2 H), 5.83 (t, *J*=53 Hz, 1 H), 6.37 (s, 1 H), 6.65 - 6.74 (m, 2 H), 6.75 - 6.95 (m, 3 H), 6.94 - 7.09 (m, 4 H), 7.09 - 7.31 (m, 3 H).

**EXAMPLE 267**




**N-(1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2- phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

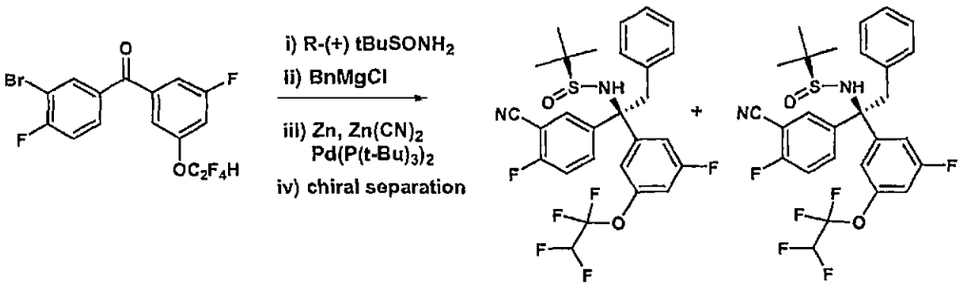
**Procedure 62**



**[00314]** To a solution of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (5.0 g, 17 mmol) in ether (40 mL) at -78 °C was added a solution of n-butyllithium (6.9 mL, 2.5 M,17 mmol). The reaction mixture was stirred for 15 minutes and was added a solution of 3-bromo-4-fluorobenzaldehyde (3.5 g, 17 mmol) in ether (10 mL). The reaction was stirred at -78 °C for 2 h, then quenched with sat. $NH_4Cl$ and warmed to room temperature. The ether layer was separated and dried over magnesium sulfate, filtered and concentrated to yield (3-bromo-4-fluorophenyl)(4-fluoro-2-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol as an amber oil (6.5 g, 92% yield). The product was used in the next step without further purification. To a solution of (3-bromo-4-fluorophenyl)(4-fluoro-2-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol (29.5 g, 71.3 mmol) in dichloromethane (600 mL) was added $MnO_2$ (30 g, 345 mmol). The reaction mixture was stirred for 6 h, then another 30 g of $MnO_2$ was added and the reaction continued to stir overnight. The $MnO_2$ addition was repeated twice and the reaction was stirred for a total of 48 h when the reaction was complete. The suspension was filtered through a pad of celite, the filtrate vas concentrated and the residue was purified by ISCO flash chromatography to yield (3-bromo-4-fluorophenyl)(4-fluoro-2-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone as a yellow oil (60% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (1 H, d, *J*=6.59 Hz), 7.76 (1 H, ddd, *J*=6.48, 4.50, 2.20 Hz), 7.38 - 7.44 (2 H, m), 7.21 - 7.29 (2 H, m), 6.09 - 5.83 (1 H, t).

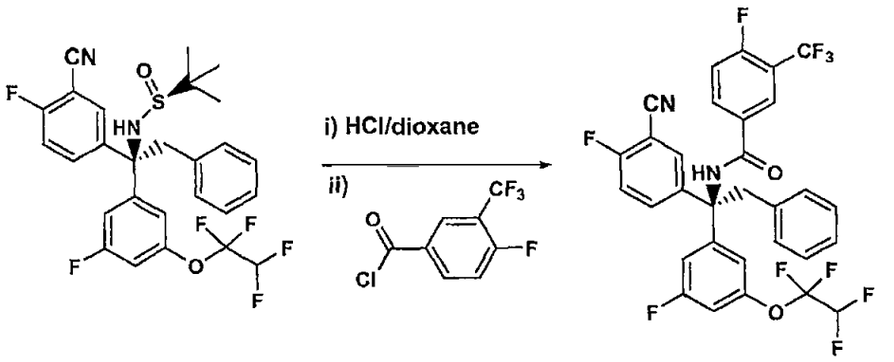
**[00315]** Alternatively, the following conditions may be used to oxidize 3-bromo-4-fluorophenyl)(4-fluoro-2-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol to (3-bromo-4-fluorophenyl)(4-fluoro-2-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone: To a solution of (3-bromo-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol (3.6 g, 8.67 mmol) in $CH_2Cl_2$ (53.0 ml) was added pyridinium dichromate (4.89 g, 13.01 mmol), and activated molecular sieves (8.67g, ~1g/mmole). The resulting slurry was stirred at room temperature for 2 h. Celite (5g) was added to the reaction mixture and the slurry stirred for 15 minutes then filtered. The filtrate was concentrated to *in vacuo*. The residue was dissolved in 20% EtOAc in Heptanes filtered through a 50ml Isolute SPE filtration column (part # 120-1028F) over $Na_2SO_4$ to give a clear pale yellow solution. The solvents were removed *in vacuo* to

a give a yellow liquid which was purified by ISCO silica gel chromatography (80g, 60 mL/min observation at 254 nm elution with heptane:EtOAc).



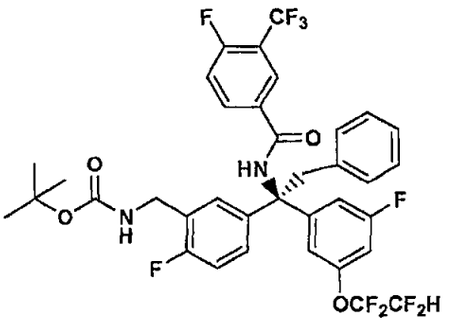

**[00316]** N-(1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2- phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide was prepared as described in Procedure 5 and 6. The diastereomer mixture of N-(1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide was separated by chiral preparative HPLC (chiralpak AD 20μ column, 5 × 50 cm, eluting with 60% IPA/Heptane with flow rate 50 mL/min). (R)-N-((S)-1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (0.224 g, 18% yield) was eluted at a retention time of 19 min. LCMS: RT = 2.23 min, Purity 71% [M+H] 555.3 (2 min Chromolith Performance RP 4.6 x 100 mm column, eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA with flow rate 5 mL/min, monitoring at 220 nm); Analytical Chiral HPLC: RT = 4.01 min (Chiralpak AD 10μ column 4.6 x 250 mm, isocratic elution with 50% IPA/Heptane with flow rate 1mL/min, monitoring at 254 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 1.23 (s, 9 H), 3.55 (d, *J*=12.3 Hz, 1 H), 3.97 (d, *J*=12.3 Hz, 1 H), 5.89 (t, J=53.17Hz, 1H) 6.85 (d, *J*=6.6 Hz, 2 H), 6.94 (s, 1 H), 7.00 (d, *J*=8.3 Hz, 1 H), 7.12 - 7.22 (m, 4 H), 7.24 - 7.29 (m, 2 H), 7.37 (d, *J*=4.8 Hz, 1 H). (R)-N-((R)-1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (0.266 g, 22% yield) was eluted at a retention time of 41 min. LCMS: RT = 2.23 min, purity 84% [M+H] 555 .3 (2 min Chromolith Performance RP 4.6 x 100 mm column, eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA with flow rate 5 mL/min, monitoring at 220 nm); Analytical Chiral HPLC: RT = 10.09 min (Chiralpak AD 10μ column 4.6 x 250 mm,

isocratic elution with 50% IPA/Heptane with flow rate 1mL/min, monitoring at 254 nm); $^1$H NMR (400 MHz, $CDCl_3$) ppm 1.18 - 1.25 (m, 9 H), 3.59 (d, *J*=12.3 Hz, 1 H), 3.99 (d, *J*=12.3 Hz, 1 H), 4.30 (s, 1 H), 5.87 (t, 1H) 6.64 - 6.71 (m, 2 H), 6.90 (d, *J*=7.0 Hz, 3 H), 7.15 - 7.22 (m, 3 H), 7.23 - 7.29 (m, 2 H), 7.64 - 7.71 (m, 2 H).



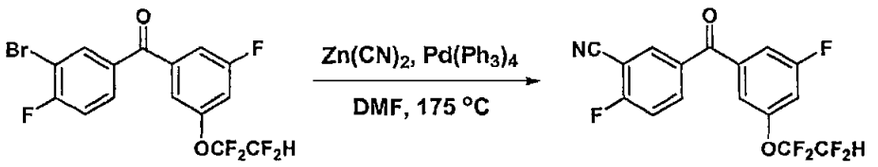

**[00317]** (R)-N-(1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 267) was prepared as described in Procedure 6 and 7. LCMS: RT = 2.342 min [M+H] 641.3 (2 min Chromolith Performance RP 4.6 x 100 mm column eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA with flow rate 5 mL/min. monitoring at 220 nm); HPLC: RT = 4.358 min, Purity 95% (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA with flow rate 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 3.76 - 3.81 (m, 2 H), 5.89 (t, *J*=53.1Hz, 1 H), 6.68 - 6.73 (m, 3 H), 6.81 - 6.85 (m, 2 H), 6.99 (d, *J*=8.3 Hz, 1 H), 7.19 - 7.30 (m, 6 H), 7.54 - 7.58 (m, 2 H), 7.82 - 7.86 (m, 1 H), 7.92 (d, *J*=6.6 Hz, 1 H).

## EXAMPLE 268

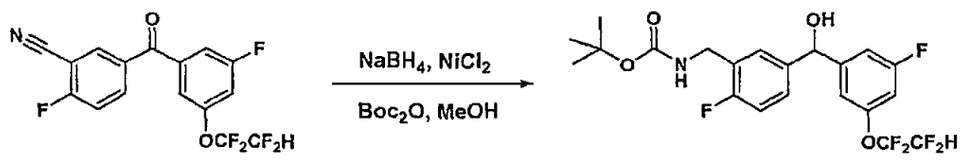


**(R)-tert-butyl 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzylcarbamate**

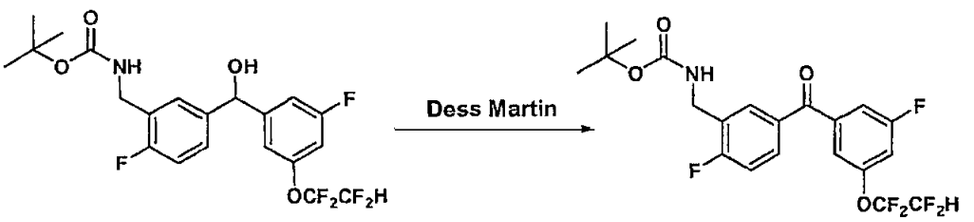
### Procedure 63



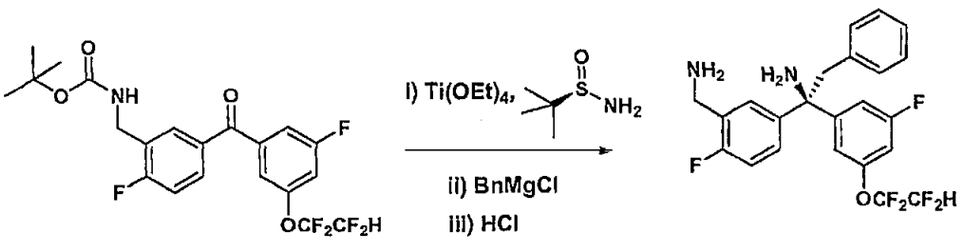
**[00318]** A mixture of (3-bromo-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone, prepared as described in Procedure 3 and 62, (2.0 g, 4.84 mmol), zinc cyanide (568 mg, 4.84 mmol) and tetrakis(triphenyphoshine)palladium (559 mg, 0.48 mmol) in DMF was heated at 175 °C under microwave irradiation for 10 minutes. The reaction mixture was allowed to cool to room temperature, poured into $H_2O$ and the aqueous layer was extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by ISCO chromatography (12 g column, 0-20% EtOAc/hexane) to yield 2-fluoro-5-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzoyl)benzonitrile as a colorless oil (1.5 g, 86% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (m, 2 H), 7.41 (m, 3 H), 7.27 (m, 1 H), 5.97 (m, 1 H).



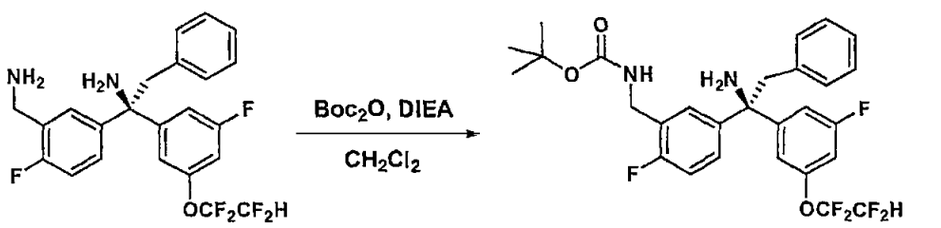
**[00319]** To a solution of 2-fluoro-5-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzoyl)benzonitrile (1.30 g, 3.62 mmol), $BOC_2O$ (1.68 mL, 7.24 mmol) and Nickel (II) chloride (0.47 g, 3.62 mmol) in MeOH at 0 °C was added sodium borohydride (0.96 g, 25.3 mmol). The reaction mixture was stirred at 0 °C for 30 minutes and then at room temperature for 6 h. The reaction mixture was filtered through celite and the filtrate was concentrated. The residue was diluted with EtOAc and the solution was washed with sat. $NaHCO_3$. The organic layer was dried over $Na_2SO_4$, filtered and concentrated to yield tert-butyl 2-fluoro-5-((3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(hydroxy)methyl)benzylcarbamate as a clear, colorless oil (1.43 g, 85% yield). This product was used in the next step without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.32 (m, 1 H), 7.22 (m, 1 H), 7.03 (m, 3 H), ), 6.87 (d, *J*=8.84 Hz, 1 H), 5.90 (m, 2 H), 4.98 (br. s., 1 H), 4.31 (d, *J*=5.05 Hz, 2 H).



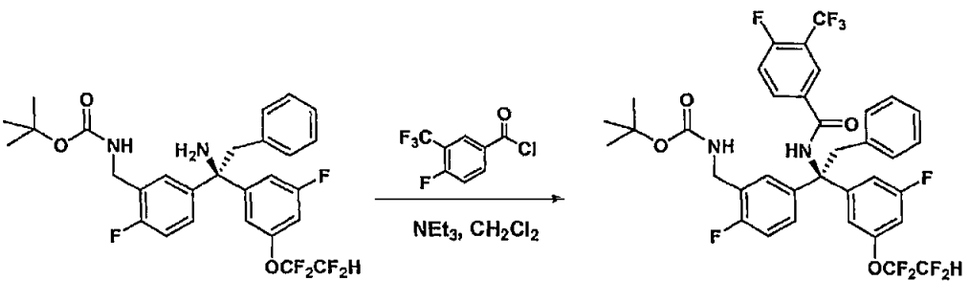

**[00320]** To a solution of tert-butyl 2-fluoro-5-(hydroxy(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethyl)phenyl)methyl)benzylcarbamate (1.43 g, 2.77 mmol) in $CH_2Cl_2$ (25 mL) was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (1.77 g, 4.16 mmol) at rt. Water (0.2 mL) in $CH_2Cl_2$ (1 mL) was then added to the reaction mixture and the resulting solution was stirred at rt for 3 h, then the solid was filtered and the filtrate was concentrated. The residue was purified by ISCO chromatography (12 g column, 0-30% EtOAc/hexane) to yield tert-butyl 2-fluoro-5-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzoyl) as a clear, colorless oil (915 mg, 64% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (d, *J*=7.07 Hz, 1 H), 7.73 (m, 1 H), 7.40 (m, 2 H), 7.18 (m, 2 H), 7.00 (m, 1 H), 5.96 (m, 1 H), 1.41 (m, 9 H).




**[00321]** Following Procedure 5 and 6, tert-butyl 5-((1R)-1-(1,1-dimethylethylsulfinamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-fluorobenzylcarbamate was prepared and isolated by ISCO chromatography (40 g column, eluting with 0-40% EtOAc/hexane). Following Procedure 6, (R)-1-(3-(aminomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)-phenyl)-2-phenylethanamine was prepared as a colorless oil (214 mg, 40% yield). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 (d, *J*=5.50 Hz, 1 H), 7.19 (m, 4 H), 6.98 (br. s., 3 H), 6.84 (d, *J*=7.70 Hz, 1 H), 6.72 (d, *J*=6.60 Hz, 2 H), 5.86 (t, *J*=53.06 Hz, 1 H), 3.85 (br. s., 2 H), 3.50 (m, 2 H).

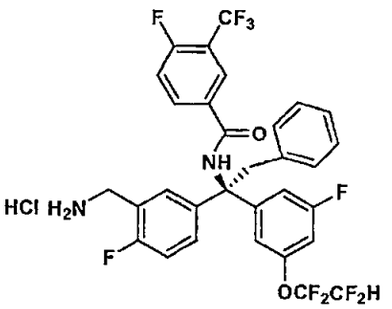



**[00322]** To a solution of (R)-1-(3-(aminomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine (229 mg, 0.50 mmol) at 0 °C in $CH_2Cl_2$ (5 mL) was added DIEA (0.11 mL, 0.61 mmol) and $(Boc)_2O$ (0.12 mL, 0.50 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and was then poured into sat. $NH_4Cl$ and the aqueous layer was extracted with EtOAc. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. The resulting residue was purified by ISCO column chromatography (12 g, 0-30% EtOAc/hexane) to yield (R)-tert-butyl 5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-fluorobenzylcarbamate as a white foam (202 mg, 72% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 3.49 (s, 2 H), 7.34 (m, 1 H), 7.17 (m, 4 H), 6.97 (m, 3 H), 6.83 (d, *J*=8.84 Hz, 1 H), 6.73 (d, *J*=6.32 Hz, 2 H), 5.86 (m, 1 H), 4.86 (br. s., 1 H), 4.31 (d, *J*=4.55 Hz, 2 H), 3.49 (s, 2 H), 1.42 (s, 9 H).



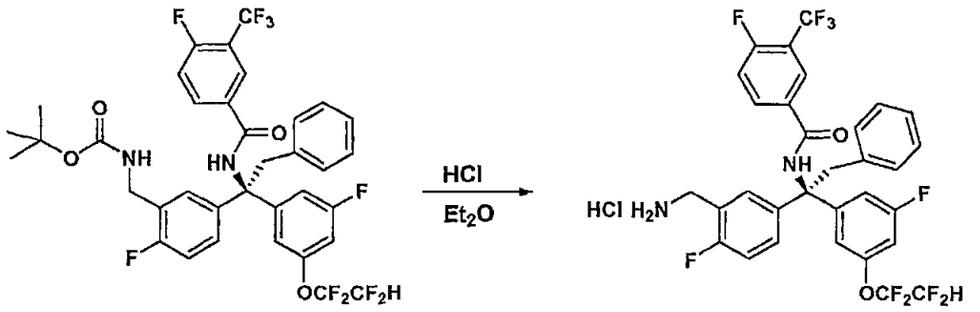

**[00323]** (R)-tert-Butyl 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzylcarbamate (Example 268) was prepared as a colorless oil (220 mg, 91% yield) using the method described in Procedure 7. LCMS: RT = 3.47 min [M+H-17] 538 (Phemonenex Luna C18, 50 x 4.6 mm, 4 min gradient, eluting with 105 -90% MeOH/$H_2O$ containing 0.1%TFA, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (d, *J*=5.31 Hz, 1 H), 7.84 (br. s., 1 H), 7.24 (m, 2 H), 7.15 (m, 3 H), 6.96 (m, 5 H), 6.71 (m, 3 H), 5.86 (m, 1 H), 4.84 (br. s., 1 H), 4.27 (t, *J*=6.19 Hz, 2 H), 4.02 (m, 1 H), 3.79 (d, *J*=13.14 Hz, 1 H), 1.37 (s, 9 H).

## EXAMPLE 269



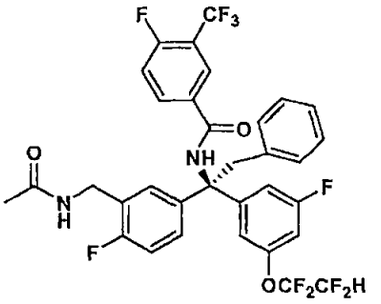

**(R)-N-(1-(3-(aminomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide hydrochloride**

**Procedure 64**



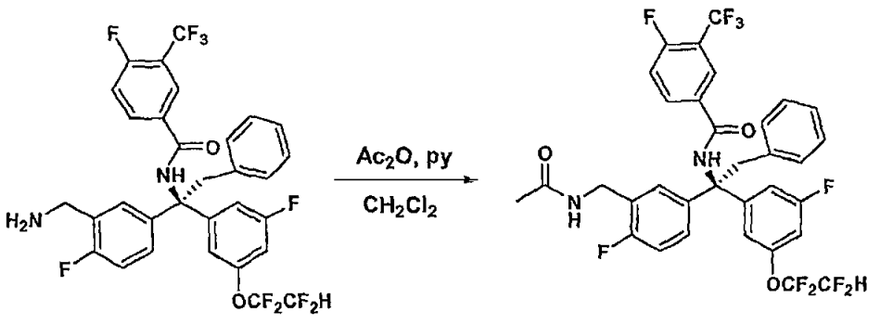

**[00324]** To a solution of (R)-tert-butyl 5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-fluorobenzylcarbamate (222 mg, 0.30 mmol) in DCM (5 ml) at rt was added 2 M HCl in diethyl ether (1.49 mL, 1.49 mmol). The reaction mixture was stirred for 2 h, then concentrated under reduced pressure to yield (R)-N-(1-(3-(aminomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide hydrochloride (Example 269) as a white foam (216 mg, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.95 (m, 1 H), 7.84 (m, 1 H), 7.19 (m, 4 H), 6.91 (m, 3 H), 6.70 (d, *J*=7.07 Hz, 2 H), 5.88 (m, 1 H), 4.24 (t, *J*=5.31 Hz, 1 H), 4.06 (m, 1 H), 3.79 (m, 2 H).

**EXAMPLE 270**



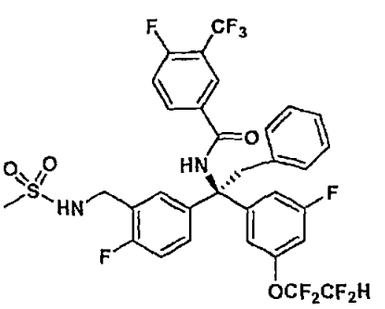

**(R)-N-(1-(3-(acetamidomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

**Procedure 65**



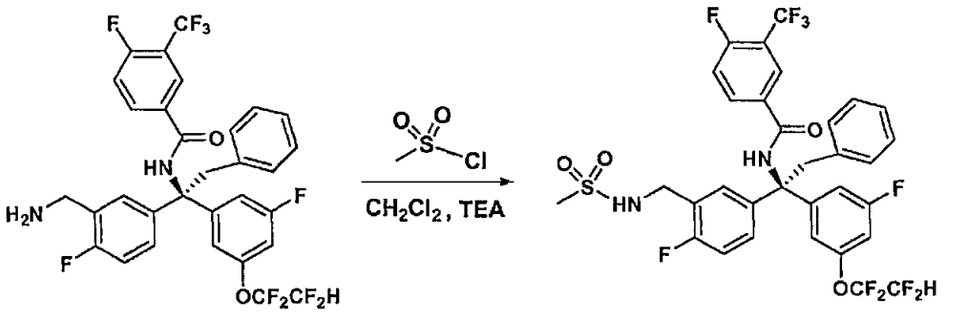

**[00325]** To a solution of (R)-N-(1-(3-(aminomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide hydrochloride (Example 269, 30 mg, 0.04 mmol) in DCM (2 mL) at rt was added pyridine (7.8 μL, 0.1 mmol) followed by acetic anhydride (4.6 μL, 0.05 mmol). The reaction mixture was stirred at rt for 1 h, then poured into 1N HCl and the aqueous layer was extracted with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The resulting residue was purified by ISCO column chromatography (4 g, 0-50% EtOAc/hexane) to yield (R)-N-(1-(3-(acetamidomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 270) as a white foam (21 mg, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (dd, *J*=6.57, 2.02 Hz, 1 H), 7.86 (dt, *J*=8.53, 2.18 Hz, 1 H), 7.25 (m, 2 H), 7.13 (m, 3 H), 6.99 (m, 5 H), 6.81 (s, 1 H), 6.69 (m, 2 H), 5.87 (m, 2 H), 4.38 (m, 2 H), 4.04 (d, *J*=13.14 Hz, 1 H), 3.75 (d, *J*=13.14 Hz, 1 H), 1.92 (s, 3 H).

**EXAMPLE 271**



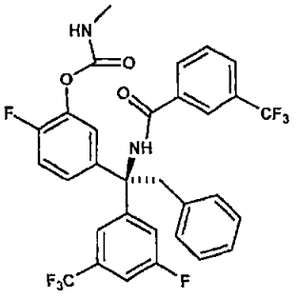
**(R)-4-fluoro-N-(1-(4-fluoro-3-(methylsulfonamidomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

**Procedure 66**



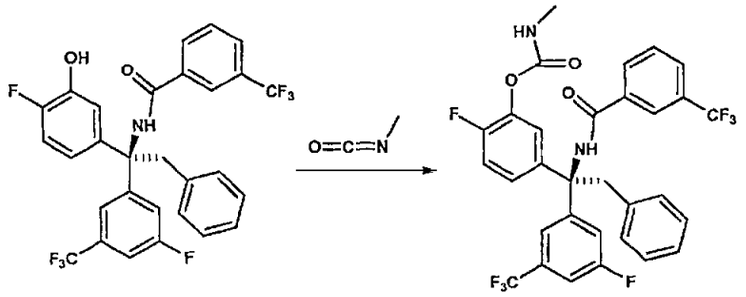

**[00326]** To a solution of (R)-N-(1-(3-(aminomethyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide hydrochloride (Example 269, 30 mg, 0.04 mmol) in DCM (2 mL) at rt was added TEA (6.8 μL, 0.05 mmol) followed by methanesulfonyl chloride (3.4 μL, 0.04 mmol). The reaction mixture was stirred at rt for 1 h and then poured into 1 N HCl. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by ISCO column chromatography (4 g, 0-40% EtOAc/hexane) to yield (R)-4-fluoro-N-(1-(4-fluoro-3-(methylsulfonamidomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 271) as a clear, colorless film (12 mg, 41%). $^1$H NMR (400 MHz, $CDCl_3$)7.95 (dd, *J*=6.57, 2.02 Hz, 1 H), 7.86 (m, 1 H), 7.22 (m, 7 H), 7.07 (t, *J*=8.97 Hz, 1 H), 6.93 (m, 3 H), 6.71 (m, 3 H), 5.88 (m, 1 H), 4.55 (t, *J*=6.32 Hz, 1 H), 4.30 (t, *J*=5.81 Hz, 2 H), 3.97 (m, 1 H), 3.83 (m, 1 H), 2.81 (s, 3 H).

**EXAMPLE 272**



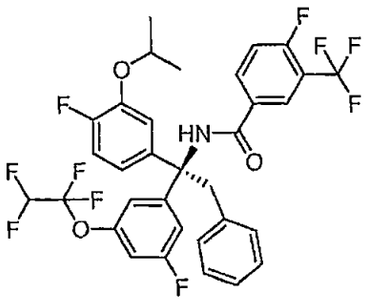
**(*R*)-2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)benzamido)ethyl)phenyl methylcarbamate**

**Procedure 67**



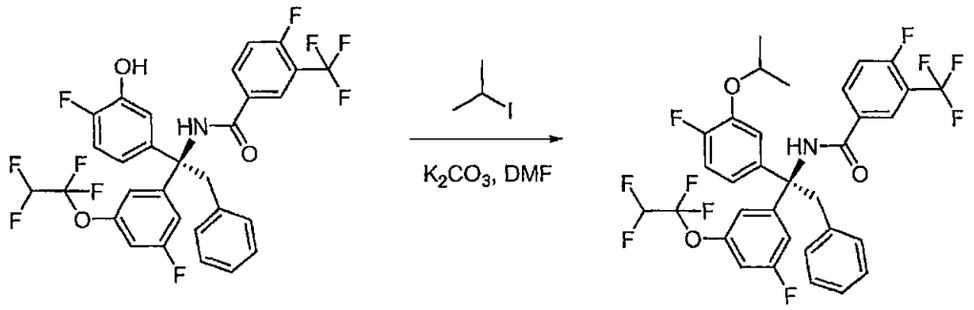
**[00327]** A solution of (R)-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide, prepared as described in Example 264, (15 mg, 0.027 mmol), methylisocyanate (0.01 mL), and $Et_3N$ (0.02 mL) in $CH_2Cl_2$ (0.3 mL) was heated at 80 °C under microwave irradiation for 10 min. After cooling, the reaction mixture was diluted with EtOAc and the organic layer was washed with $H_2O$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by ISCO flash chromatography (silica gel, hexanes/EtOAc) to yield (*R*)-2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)-benzamido)-ethyl)phenyl methylcarbamate (Example 272, 11 mg, yield: 61%). LCMS: RT = 2.13 min [M+H] 623.3 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**EXAMPLE 273**



**(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

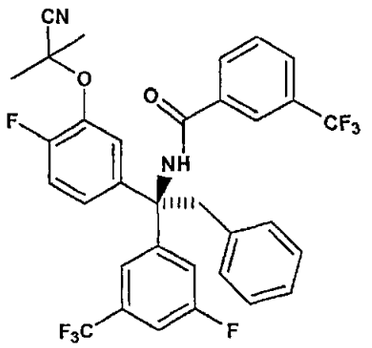
**Procedure 68**




**[00328]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264, 2.70 g, 4.27 mmol) in DMF (6 mL) was added $K_2CO_3$ (1.47 g, 10.69 mmol), followed by isopropyl iodide (0.64 mL, 6.40 mmol). The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered and the solid was washed with EtOAc. The filtrate was washed with $H_2O$, sat. NaCl, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by ISCO silica gel column using 0 to 50% EtOAc in hexane as eluting solvents to yield (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 273) as white powder (2.4 g, 83% yield). LCMS: RT = 4.05 min [M+H] 674.1 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CD_3OD$) δ ppm 7.95 - 8.00 (2 H, m), 7.42 - 7.47 (1 H, m), 7.19

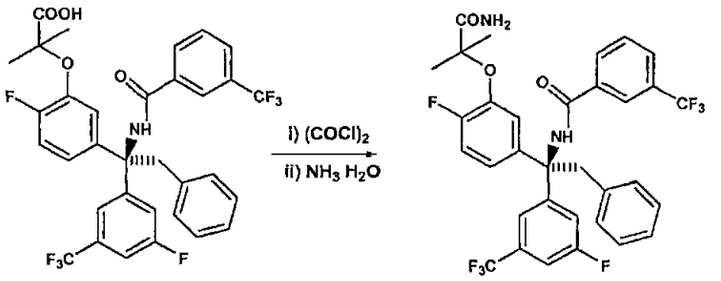
(1 H, t, *J*=7.47 Hz), 7.12 (3 H, t, *J*=7.25 Hz), 6.99 - 7.07 (3 H, m), 6.71 - 6.81 (4 H, m), 6.14 - 6.41 (1 H, m), 4.26 - 4.32 (1 H, m, *J*=6.15, 6.15, 6.15, 6.15 Hz), 4.12 (1 H, d, *J*=13.18 Hz), 3.85 (1 H, d, *J*=12.74 Hz), 1.23 (3 H, d, *J*=6.15 Hz), 1.17 (3 H, d, *J*=6.15 Hz).

**EXAMPLE 274**



**(*R*)-N-(1-(3-(1-amino-2-methyl-1-oxopropan-2-yloxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

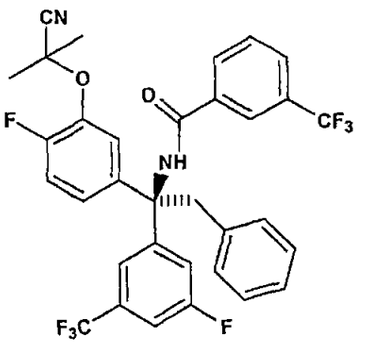
**Procedure 69**




**[00329]** At 0 °C to a solution of (R)-2-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)benzamido)ethyl)phenoxy)-2-methylpropanoic acid, prepared as described in Procedure 68 and 23, (60 mg, 0.092 mmol, yield 91%) in $CH_2Cl_2$ was added DMF (1 drop), followed by the addition of $(COCl)_2$ (0.02 mL). The reaction mixture was stirred at 0 °C for 30 min, then concentrated and dried *in vacuo*. The resulting residue was dissolved in THF (1 mL) and cooled to 0 °C followed by the addition of concentrated $NH_4OH$ (3 mL). The resulting mixture was stirred at rt for 1 h, then concentrated under reduced pressure. The residue was diluted with $CH_2Cl_2$ and the organic layer was washed with $H_2O$,

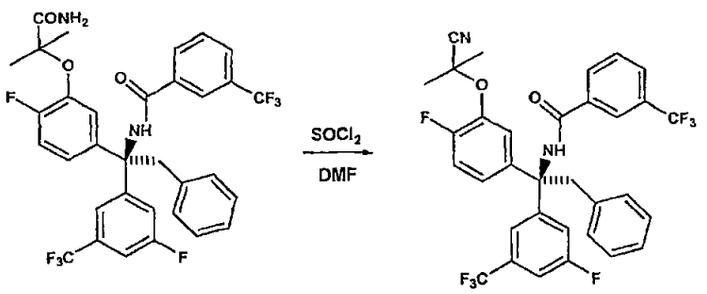
saturated NaCl, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give pure (*R*)-N-(1-(3-(1-amino-2-methyl-1-oxopropan-2-yloxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 274, 40 mg, yield: 67%). LCMS: RT = 2.15 min [M+H] 651.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**EXAMPLE 275**



**(*R*)-N-(1-(3-(2-cyanopropan-2-yloxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

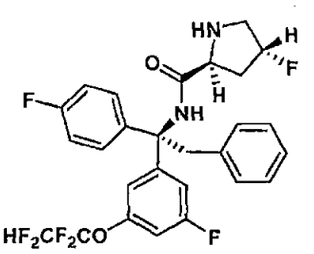
**Procedure 70**




**[00330]** To a solution of (R)-N-(1-(3-(1-amino-2-methyl-1-oxopropan-2-yloxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 274, 30 mg, 0.046 mmol) in DMF (1 mL) at room temperature was added thionyl chloride (3 drops). The reaction mixture was stirred for 40 min and diluted with $H_2O$ and EtOAc. The organic layer was washed

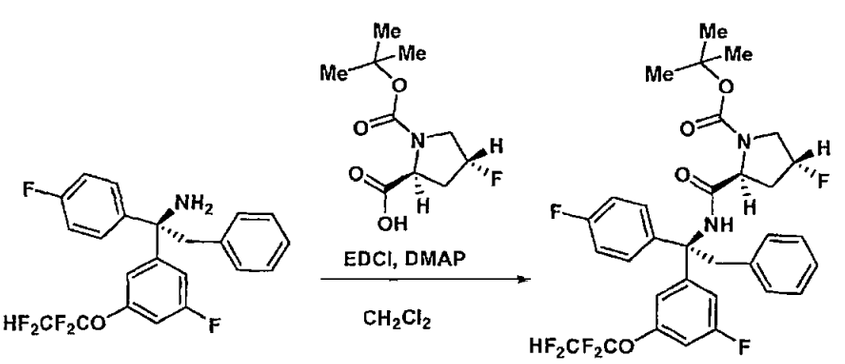
with $H_2O$, saturated $NaHCO_3$, $H_2O$ and saturated NaCl, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, hexanes/EtOAc) to give pure (*R*)-N-(1-(3-(2-cyanopropan-2-yloxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 275, 16 mg, yield: 55%). LCMS: RT = 2.21 min [M+H] 633.3 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**EXAMPLE 276**



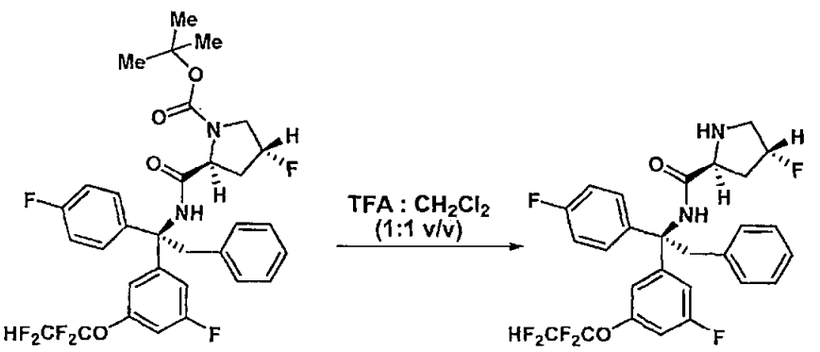
**(2S,4R)-4-fluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)-phenyl)-1-(4-fluorophenyl)-2-phenylethyl)pyrrolidine-2-carboxamide**

**Procedure 71**




**[00331]** To a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (42 mg, 0.1 mmol), prepared as described in Procedure 3, 4, 5 and 6, and (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (23 mg, 0.1 mmol) in $CH_2Cl_2$ (1 mL) was added EDCI (25 mg, 0.1 mmol) and DMAP (16 mg, 0.1 mmol). The reaction mixture was stirred overnight

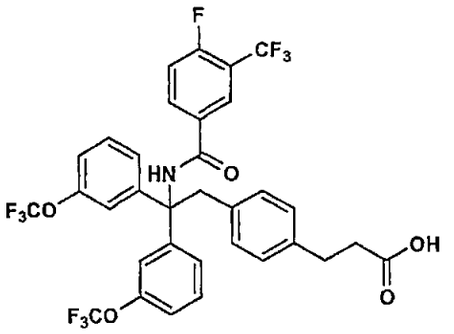
and concentrated to dryness under a stream of argon. The resulting residue was dissolved in MeOH and purified by preparative HPLC (Phenoma Luna AXIA 10A, C18, eluting with 10-90% MeCN / $H_2O$ containing 0.1% TFA, monitoring at 220 nm) to provide (2S,4R)-tert-butyl 4-fluoro-2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylcarbamoyl)pyrrolidine-1-carboxylate (40 mg, 64% yield) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 8.30 (s, 1H), 7.13-7.03 (m, 5H), 6.95-6.90 (m, 2H), 6.80-6.78 (m, 2H), 6.70 (bs, 1H), 6.51-6.47 (m, 2H), 5.88-5.67 (m, 1H, -$CF_2H$), 5.10 (app d, $J$ = 50 Hz, 1H, -CFH), 4.48-4.45 (m, 1H), 3.89-3.78 (m, 2H), 3.70 (d, J = 10 Hz, 1H0, 3.29-3.18 (m, 1H), 2.79-2.55 (m, 2H), 2.25-2.11 (m, 1H), 1.32 (s, 9H); LC/MS: RT = 3.746 min [M+H] 641.2 Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm.




**[00332]** (2S,4R)-tert-butyl 4-fluoro-2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylcarbamoyl)pyrrolidine-1-carboxylate (18 mg, 0.03 mmol) was dissolved in a solution of $CH_2Cl_2$ (1 mL)/ TFA (1 mL) at rt. The reaction mixture was stirred overnight and concentrated to dryness under a stream of argon. The resulting residue was dissolved in MeOH and purified by preparative HPLC (Phenoma Luna AXIA 10A, C18, eluting with 10% - 90% MeCN / $H_2O$ containing 0.1% TFA, monitoring at 220 nm) to provide (2S,4R)-4-fluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)-phenyl)-1-(4-fluorophenyl)-2-phenylethyl)pyrrolidine-2-carboxamide (Example 276) as a white solid (13 mg, 83% yield). $^1$H NMR (500 MHz, MeOH-$d_4$) δ ppm 7.22-7.13 (m, 7H), 7.07-6.96 (m,

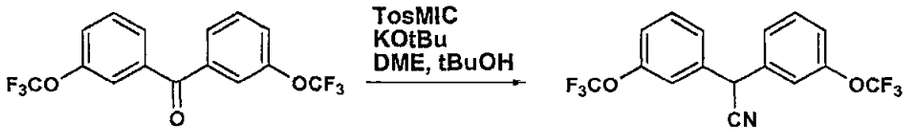
7H), 6.68 (d, J = 5 Hz, 2H), 6.40-6.18 (m, 1H, -$CF_2H$), 5.43 (app d, $J$ = 50 Hz, 1H, -CFH), 4.55-4.51 (m, 1H), 4.01 (d, $J$ = 10 Hz, 1H), 3.92 (d, $J$ = 15 Hz, 1H), 3.65-3.49 (m, 2H), 2.72-2.64 (m, 1H), 2.10-1.96 (m, 1H); LC/MS: RT = 3.310 min [M+H] 541.2 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 277**




**3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy)phenyl)ethyl)phenyl)propanoic acid**

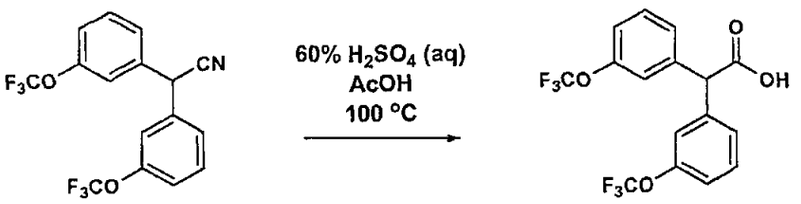
**Procedure 72**




**[00333]** At 0 °C to a solution of bis(3-(trifluoromethoxy)phenyl)methanone (3 g, 8.6 mmol), prepared as described in Procedure 11, in DME (60 mL) was added 1-(isocyanomethylsulfonyl)-4-methylbenzene (3.3 g, 17.1 mmol) and tBuOK (25.7 mL, 1.0 M solution in tBuOH, 25.7 mmol). The reaction mixture was allowed to warm to rt and stirred for 18 h. $H_2O$ (100 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were washed with sat. NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by ISCO chromatography (150 g) using hexane/EtOAc (0-5% over 30 min, 5-20% over 20 min) to give 2,2-bis(3-(trifluoromethoxy)phenyl)acetonitrile as a yellow oil at a retention time of 46 min

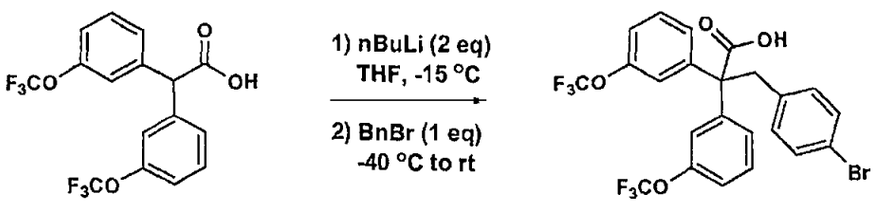
(1.4 g, 45% yield). HPLC: RT = 4.13 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). NMR: 400 MHz $^1H$ ($CDCl_3$) 7.45 ppm, 2 H, t, *J*=8.13 Hz; 7.30 ppm, 2 H, d, *J*=7.91 Hz; 7.23 ppm, 2 H, d, *J*=9.23 Hz; 7.17 ppm, 2 H, s; 5.17 ppm, 1 H, s.

**Procedure 73**



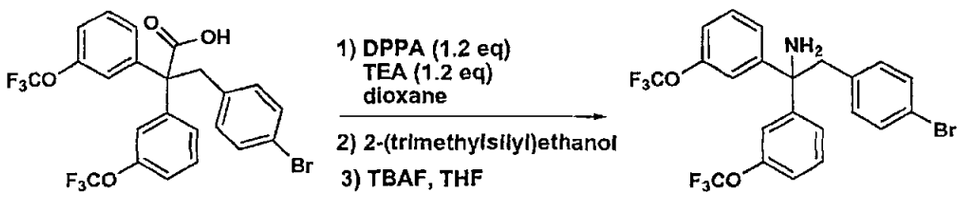

**[00334]** To a solution of 2,2-bis(3-(trifluoromethoxy)phenyl)acetonitrile (1.0 g, 2.8 mmol) in AcOH (15 mL) was added 60% $H_2SO_4$ (aq) (10 mL) and the reaction mixture was heated at 100 °C for 10 h. The reaction mixture was allowed to cool to rt and extracted with toluene (2 x 25 mL). The combined organic portions were washed with $H_2O$ (25 mL) and sat. NaCl (25 mL), then extracted with 0.5 N NaOH (50 mL and 10 mL). The combined basic extracts were made acidic using concentrated HCl then extracted with toluene (2 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2,2-bis(3-(trifluoromethoxy)phenyl)acetic acid (700 mg, 67% yield) as a pale tan oil. LCMS: RT = 1.99 min [M+H] 381.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) δ ppm 5.05 (s, 1 H), 7.14 - 7.19 (m, 4 H), 7.25 (d, *J*=7.47 Hz, 2 H), 7.37 (t, *J*=7.69 Hz, 2 H).

**Procedure 74**



[00335] To a solution of 2,2-bis(3-(trifluoromethoxy)phenyl)acetic acid (198 mg, 0.52 mmol) in THF (3.5 mL) at - 15 °C was added dropwise a 1.6 M solution of nBuLi in hexanes (0.65 mL, 1.04 mmol). The reaction mixture was stirred for 45 min. The solution was cooled to - 40 °C and a solution of benzylbromide (130 mg, 0.52 mmol) in THF (0.6 mL) was added dropwise. The ice-bath was removed and the reaction mixture was allowed to warm up to rt. The reaction was quenched by addition of sat. $NH_4Cl$ (5 mL) and extracted with $Et_2O$ (3 x 5 mL). The combined organic portions were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography, eluting with 30% EtOAc/hexane containing 1% AcOH to give 3-(4-bromophenyl)-2,2-bis(3-(trifluoromethoxy)phenyl)propanoic acid (232 mg, 81% yield) as a clear colorless oil. LCMS: RT = 1.93 min [M+H] 549.0 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) δ ppm 3.62 (s, 2 H), 6.53 (d, *J*=8.35 Hz, 2 H), 7.04 (s, 2 H), 7.10 (d, *J*=7.91 Hz, 2 H), 7.13 – 7.19 (m, 4 H), 7.30 (t, *J*=8.13 Hz, 2 H).

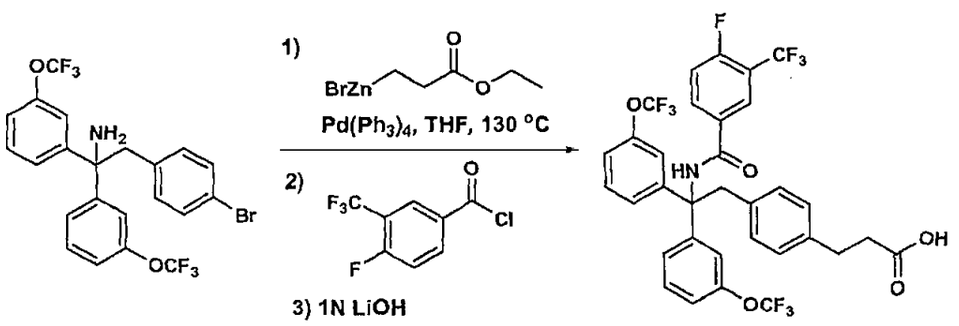
**Procedure 75**




[00336] To a solution of 3-(4-bromophenyl)-2,2-bis(3-(trifluoromethoxy)phenyl)propanoic acid (224 mg, 0.41 mmol) in dioxane (5 mL) was added 4 Å molecular sieves (appx 100 mg), triethylamine (0.068 mL, 0.49 mmol) and diphenylphosphoryl azide (0.11 mL, 0.49 mmol) and the reaction mixture was stirred for 45 minutes. 2-(Trimethylsilyl)ethanol (0.176 mL, 1.23 mmol) was added and the reaction mixture was heated at reflux for 1 h. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure. The residue was diluted with $Et_2O$ (10 mL) and washed with sat. $NH_4Cl$ (5 mL), sat. $NaHCO_3$ (5 mL) and sat. NaCl (5 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was diluted with THF (5 mL) and cooled in an ice-

bath, then a 1M solution of tetrabutylammonium fluoride in THF (0.80 mL, 0.80 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL) and washed with $H_2O$ (5 mL) and sat. NaCl (5 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified on ISCO silica chromatography with elution at 0 to 50% EtOAc/hexane to give 2-(4-bromophenyl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine (78 mg, 37% yield) as a clear colorless oil. LCMS: RT = 1.87 min [M-$NH_2$] 505.0 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) δ ppm 1.68 (bs, 2 H), 3.46 (s, 2 H), 6.57 (d, *J*=8.35 Hz, 2 H), 7.10 (d, *J*=8.35 Hz, 2 H), 7.18 (s, 2 H), 7.21 - 7.26 (m, 4 H), 7.32 (t, *J*=8.13 Hz, 2 H).

**Procedure 76**

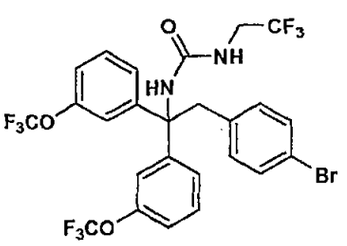



**[00337]** To a solution of 2-(4-bromophenyl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine (26 mg, 0.050 mmol) in THF (0.5 mL) was added a 0.5 M solution of 3-ethoxy-3-oxopropylzinc bromide in THF (0.18 mL, 0.090 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (3 mg, 5 mol%). The reaction mixture was heated at 130 °C under microwave irradiation for 0.5 h. The reaction mixture was filtered through silica gel and eluted with THF. The solvents were removed under reduced pressure and the residue was dissolved into $CH_2Cl_2$ (0.5 mL) then triethylamine (0.020 mL, 0.15 mmol) was added followed by 4-fluoro-3-(trifluoromethyl)benzoylchloride (0.020 mL, 0.13 mmol). The reaction mixture was stirred at rt for 3 h then diluted with $Et_2O$ (10 mL) and the organic layer was washed with sat. $NH_4Cl$ (2 mL), sat. $NaHCO_3$ (2 mL) and sat. NaCl (2 mL). The organic

layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by prep TLC plate, eluting with 20% EtOAc/hexane to give ethyl 3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy)phenyl)ethyl)phenyl)propanoate (11 mg, 31% yield) as a clear, colorless oil. LCMS: RT = 2.26 min [M+H] 731.93 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

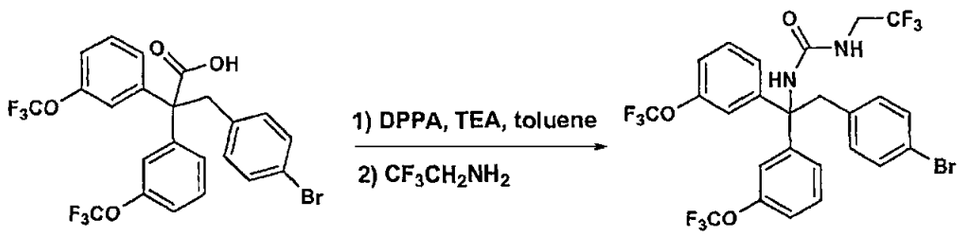
**[00338]** To a solution of ethyl 3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy)phenyl)ethyl)phenyl)propanoate (11 mg, 0.015 mmol) in THF (0.75 mL) was added 1 N LiOH (0.15 mL) and methanol (0.30 mL). The reaction mixture was heated at 50 °C for 0.5 h. The solvents were removed under a stream of nitrogen then 1 N HCl (2 mL) was added to the residue and the mixture was extracted with $CH_2Cl_2$ (2 x 5 mL). The combined organics were dried over $Na_2SO_4$, filtered and the volatiles removed. The resulting residue was purified on ISCO silica gel eluting with 0 to 10% MeOH/$CH_2Cl_2$ to give 3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy)phenyl)ethyl)phenyl)propanoic acid (Example 277) as a clear, colorless oil (9 mg, 85% yield). LCMS: RT = 2.18 min [M+H] 704.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) δ ppm 2.55 (t, *J*=7.69 Hz, 2 H), 2.82 (t, *J*=7.69 Hz, 2 H), 3.83 (s, 2 H), 6.54 (d, *J*=8.35 Hz, 2 H), 6.60 (s, 1 H), 6.93 (d, *J*=7.91 Hz, 2 H), 6.97 (s, 2 H), 7.08 – 7.14 (m, 4 H), 7.17 - 7.23 (m, 1 H), 7.28 - 7.33 (m, 2 H), 7.73 - 7.77 (m, 1 H), 7.83 - 7.86 (m, 1 H).

**EXAMPLE 278**



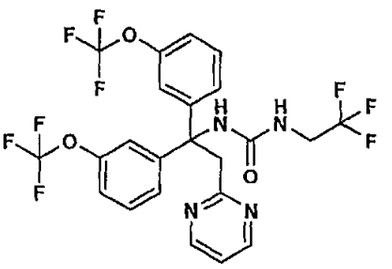
**1-(2-(4-bromophenyl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea**

**Procedure 77**



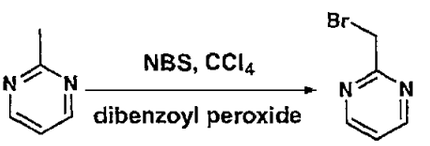

**[00339]** To a solution of 3-(4-bromophenyl)-2,2-bis(3-(trifluoromethoxy)phenyl)propanoic acid (260 mg, 0.47 mmol) in toluene (10 mL) was added diphenylphosphoryl azide (0.409 mL, 1.9 mmol) followed by triethylamine (0.264 mL, 1.9 mmol). The reaction mixture was heated at reflux for 1 h, then trifluoroethylamine was added and the reaction mixture was heated at reflux for another 1 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (30 mL) and washed successively with sat. $NH_4Cl$ (10 mL), sat. $NaHCO_3$ (10 mL) and sat. NaCl (20 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified on a ISCO silica gel column (12 g) with elution at 0 to 20% EtOAc/hexane over 20 min, then further purified by preparative HPLC YMC ODS S5 30 x 100 mm column 40-100% MeOH/$H_2O$ (90% in water, 0.1% TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm to yield 1-(2-(4-bromophenyl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea (Example 278) as a white solid (200 mg, yield 65%). LCMS: RT = 2.24 min [M+H] 645.0 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.476 min, Purity 100% (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 3.68 - 3.77 (m, 2 H), 3.81 (s, 2 H), 4.80 (t, *J*=6.15 Hz, 1 H), 5.15 (s, 1 H), 6.52 (d, *J*=7.91 Hz, 2 H), 6.97 (s, 2 H), 7.09 - 7.17 (m, 4 H), 7.23 - 7.27 (m, 3 H), 7.34 (t, *J*=7.91 Hz, 2 H).

## EXAMPLE 279

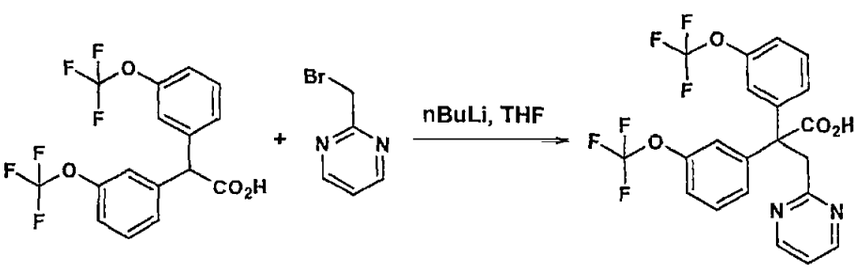


**1-(2-(pyrimidin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea**

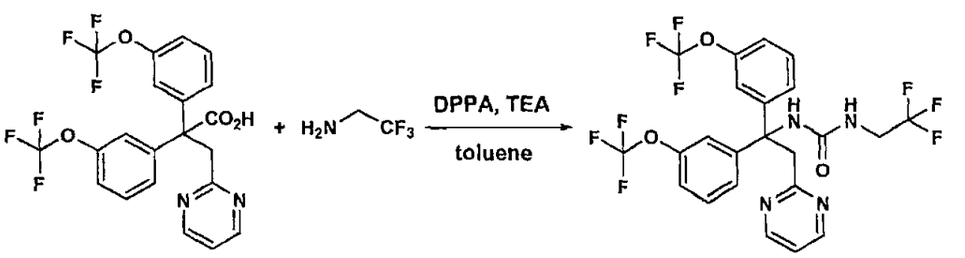
### Procedure 78




**[00340]** To a solution of 2-methylpyrimidine (2.0 g, 21.3 mmol) in $CCl_4$ (80 mL) was added benzoyl peroxide (80 mg, 0.33 mmol). The reaction mixture was heated to reflux, then NBS (4.5 g, 25.56 mmol) was added in portions over 3.5 h. Reflux was maintained for 18 h and the reaction mixture was allowed to cool to rt, filtered through a celite pad and the celite was rinsed with ether (200 mL). The organic layer was concentrated and the residue was purified by ISCO chromatography (120 g column) using hexane/EtOAc (0-80% over 30 min) to give 2-(bromomethyl)pyrimidine as a yellow oil at a retention time of 18 min (412 mg, 11% yield). NMR: 400 MHz $^1H$ ($CDCl_3$) 8.76 ppm, 2 H, d, $J$=5.27 Hz; 7.23 ppm, 1 H, m; 4.62 ppm, 2 H, d, $J$=2.20 Hz.



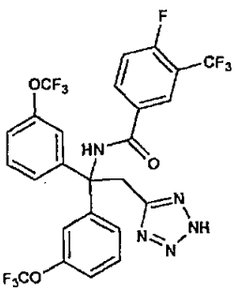
[00341] At -15 °C to a solution of 2,2-bis(3-(trifluoromethoxy)phenyl)acetic acid prepared as described in Procedure 73 (607 mg, 1.6 mmol) in THF (6 mL) was added nBuLi (1.6 mL, 2M in hexane, 3.2 mmol). The mixture was stirred at -15 °C for 45 min. 2-(Bromomethyl)pyrimidine (412 mg, crude) in THF (1 mL) was added and the reaction mixture was allowed to warm to rt and stirred for 18 h, then quenched with saturated $NH_4Cl$. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated to give 3-(pyrimidin-2-yl)-2,2-bis(3-(trifluoromethoxy)phenyl)propanoic acid as a yellow solid (437 mg, 58% crude). This crude solid was carried onto the next step without further purification.




[00342] To a mixture of 3-(pyrimidin-2-yl)-2,2-bis(3-(trifluoromethoxy)phenyl)propanoic acid (20 mg, 0.042 mmol) and diphenyl phosphoryl azide (70 mg, 0.254 mmol) in toluene (1.5 mL) was added TEA (88 μL, 0.63 mmol) dropwise and the reaction mixture was heated at 110 °C for 20 min. 2,2,2-Trifluoroethanamine (7 μL, 0.084 mmol) was added and the reaction mixture was stirred at 110 °C for 1 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (25 mL). The organic layer was washed with $H_2O$ (25 mL), 1 N HCl (25 mL) and saturated $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Shimadzu-YMC-Sunfire 5μ column, 30 × 100 mm eluting with 40-100% MeOH (90% in $H_2O$, 0.1%TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm). The product that eluted at retention time of 9.42 min was isolated as a clear oil, and further purified by Prep TLC (Uniplate, Silica Gel GF, 20 x 20 cm, 1000 Microns) using Hexane/EtOAc (1/2) to yield 1-(2-(pyrimidin-2-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea (Example 279) as a

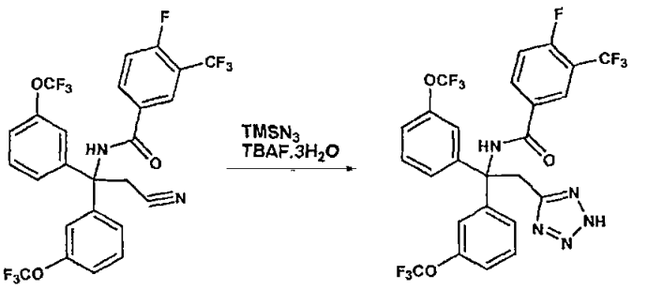
white solid (4 mg, 16% yield). LCMS: RT = 1.867 min [M+H] 568.87 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.973 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 8.52 ppm, 2 H, d, *J*=4.83 Hz; 7.98 ppm, 1 H, s; 7.33 ppm, 5 H, m; 7.23 ppm, 2 H, s; 7.08 ppm, 3 H, t, *J*=5.05 Hz; 4.61 ppm, 1 H, t, *J*=6.37 Hz; 3.85 ppm, 2 H, s; 3.77 ppm, 2 H, ddd, *J*=15.71, 9.12, 9.01 Hz.

**EXAMPLE 280**



**N-(2-(2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

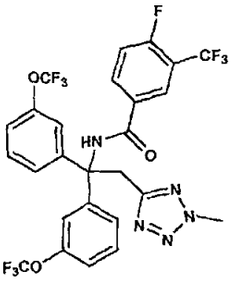
**Procedure 79**




**[00343]** N-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide was prepared as described in Procedure 11, 18, 6 and 7. LCMS: RT = 4.04 min [M+H] 581.16 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). A mixture of N-(2-cyano-1,1-bis(3-

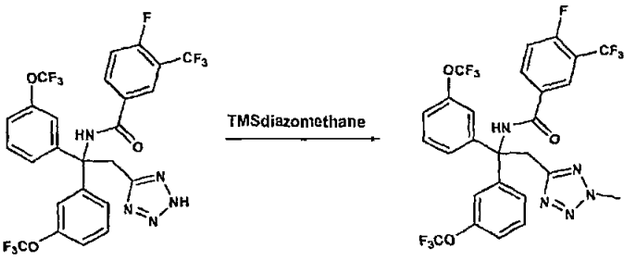
(trifluoromethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (70 mg, 0.12 mmol), $TMSN_3$ (0.025 ml. 1.6 eq) and $TBAF{\cdot}3H_2O$ (19 mg, 0.5 eq) was heated in a sealed tube at 110 °C for 24 h. After allowing to cool to rt, the residue was dissolved in $CH_2Cl_2$, and purified by ISCO flash chromatography (silica gel, $CH_2Cl_2$/MeOH) to give N-(2-(2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 280, 54 mg, yield: 72%). LCMS: RT = 3.91 min [M+H] 624.06, [M+Na] 647.06 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 281**



**4-fluoro-N-(2-(2-methyl-2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(trifluoromethyl)benzamide**

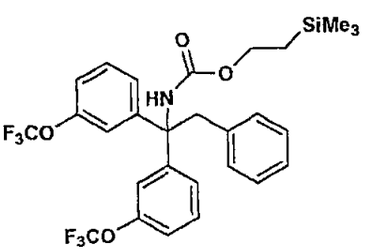
**Procedure 80**




**[00344]** To a solution of N-(2-(2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (18 mg, 0.029 mmol) in THF (0.4 mL) and MeOH (0.1 mL) at rt was added (diazomethyl)trimethylsilane (0.02 mL, 2.0 M solution). The resulting solution was stirred at rt for 20 min. The solvents were evaporated and resulting residue was

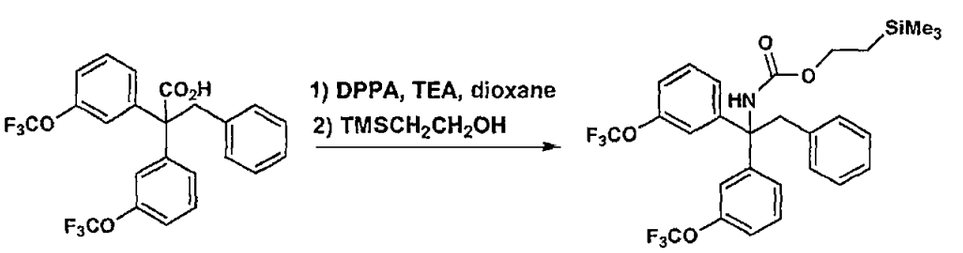
purified by ISCO flash chromatography (silica gel, hexane/ EtOAc) to give 4-fluoro-N-(2-(2-methyl-2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(trifluoromethyl)benzamide (Example 281, 11 mg, yield: 60%). LCMS: RT = 4.06 min [M+H] 638.23, [M+Na] 661.26 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 282**




**2-(trimethylsilyl)ethyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethylcarbamate**

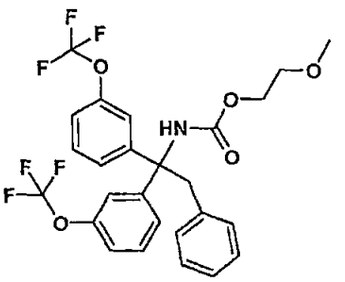
**Procedure 81**




**[00345]** To a solution of 3-phenyl-2,2-bis(3-(trifluoromethoxy)phenyl)propanoic acid (0.055 g, 0.117 mmol ) in 1,4-dioxane (2 mL) was added triethylamine (0.014 g, 20 μL, 0.14 mmol ), 4Å molecular sieves (0.05 g), diphenylphosphoryl azide (0.040 g, 31 μL, 0.14 mmol) and trimethylsilylethanol (0.042 g, 50 μL, 0.35 mmol ). The reaction mixture was stirred for 1 h at rt, then heated at 75 °C for 1.5 h. The cooled reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated under reduced pressure and purified by ISCO silica gel chromatography using a gradient of 0-20% EtOAc/hexane as eluent to yield 2-(trimethylsilyl)ethyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethylcarbamate (Example 282) as a

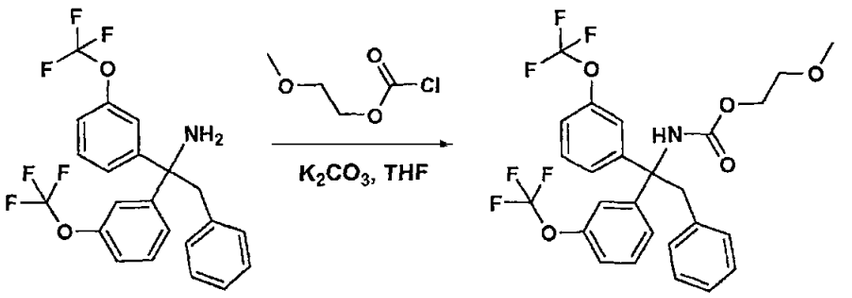
colorless band (0.037 g, 54% yield). HPLC: RT = 4.828 min (Phenomenex Luna C18 5μ column 4.6 x 50 mm, eluting with 10-90% MeOH/$H_2O$ containing 0.1% PPA over a 4 minute gradient, monitoring at 220nm). No molecular ion was obtained. $^1H$ NMR (400 MHz, $CDCl_3$): 7.32 ( t, J=8.1 Hz, 2H), 7.18-7.11 (m, 7H), 6.99 ( s, 2H), 6.65 (d, J=7.1 Hz, 2H), 5.35 ( s, 1H ), 4.08 ( t, J=8.8Hz, 2H), 3.78 ( s, 2H ), 0.88 ( br, 2H ), 0.00 ( s, 9H ).

**EXAMPLE 283**



**2-methoxyethyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethylcarbamate**

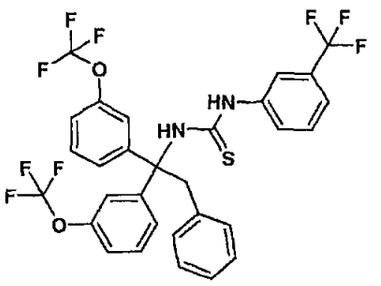
**Procedure 82**




**[00346]** To a solution of 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethanamine (20 mg, 0.045 mmol) in THF (6 mL) was added 1M $K_2CO_3$ (20 mg in 0.1 mL), followed by 2-methoxyethyl carbonochloridate (0.106 mL, 0.91 mmol). The resulting mixture was stirred at rt for 16 h. The crude product was purified by prep HPLC (phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford 2-methoxyethyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethylcarbamate (Example 283) as white lyophillate (12 mg, 51% yield). LCMS: RT = 4.19 min

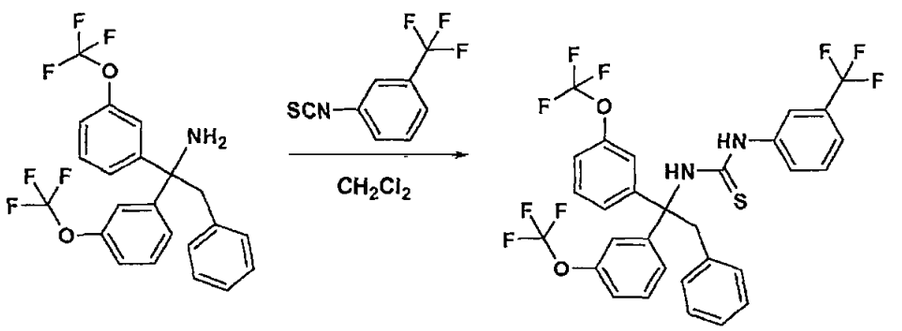
[M+H] 544.2 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

**EXAMPLE 284**



**1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(3-(trifluoromethyl) phenyl)thiourea**

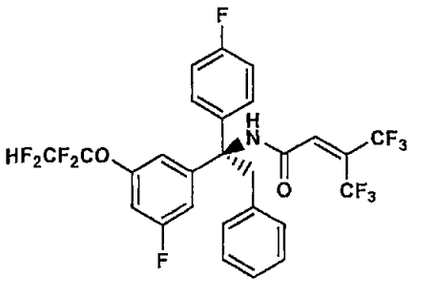
**Procedure 83**




**[00347]** To a solution of bis(3-(trifluoromethoxy)phenyl)methanamine (20 mg, 0.057 mmol) in $CH_2Cl_2$ (0.1 mL) was added 1-isothiocyanato-3-(trifluoromethyl)benzene (35 mg, 0.17 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated and the residue was purified by prep HPLC (phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(3-(trifluoromethyl) phenyl)thiourea (Example 284) as white lyophillate (30 mg, 81%). LCMS: RT = 4.51min [M+H] 645.14 (Phenomenex Luna C18 column, 4.6 × 50 mm

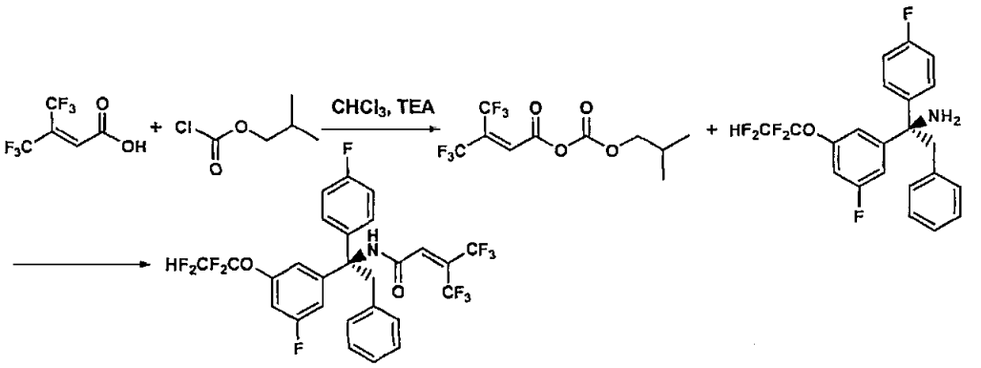
eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 285**



**(R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)but-2-enamide**

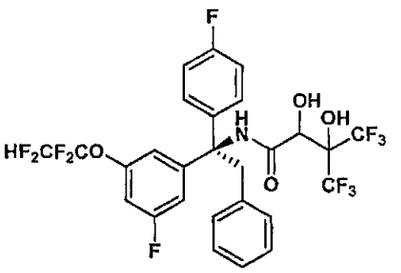
**Procedure 84**



**[00348]** At 0 °C under argon to a solution of 4,4,4-trifluoro-3-(trifluoromethyl)crotonic acid (29 mg, 0.14 mmol) and TEA (25 μL, 0.18 mmol) in $CHCl_3$ (0.5 mL) was added isobutyl chloroformate (18 μL, 0.14 mmol). The reaction mixture was stirred at 0 °C for 10 min. A solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine, prepared as described in Procedure 3, 4, 5 and 6, (50 mg, 0.12 mmol) in $CHCl_3$ (0.5 mL) was added and the reaction was stirred at rt for 18 h. The reaction mixture was concentrated and purified by preparative HPLC Shimadzu-YMC Sunfire 5μ column, 30 × 100 mm eluting with 40-100% MeOH (90% in $H_2O$, 0.1% TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm. (R)-4,4,4-trifluoro-N-

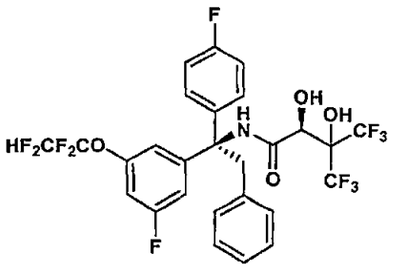
(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)but-2-enamide (Example 285) was eluted at a retention time of 11.11 min and was isolated as a clear oil (63 mg, yield 73%). LCMS: RT = 2.19 min [M+H] 616.1 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.31 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.36 ppm, 2 H, s; 7.21 ppm, 3 H, m; 7.09 ppm, 2 H, m; 7.01 ppm, 2 H, t, *J*=8.57 Hz; 6.91 ppm, 3 H, m; 6.64 ppm, 2 H, d, *J*=7.03 Hz; 6.43 ppm, 1 H, s; 3.94 ppm, 1 H, d, *J*=13.18 Hz; 3.78 ppm, 1 H, d, *J*=13.18 Hz; 2.13 ppm, 2 H, s.

**EXAMPLE 286**



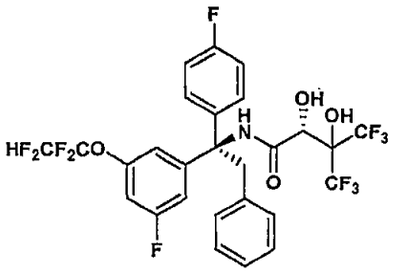

**(4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide**

**EXAMPLE 287A**



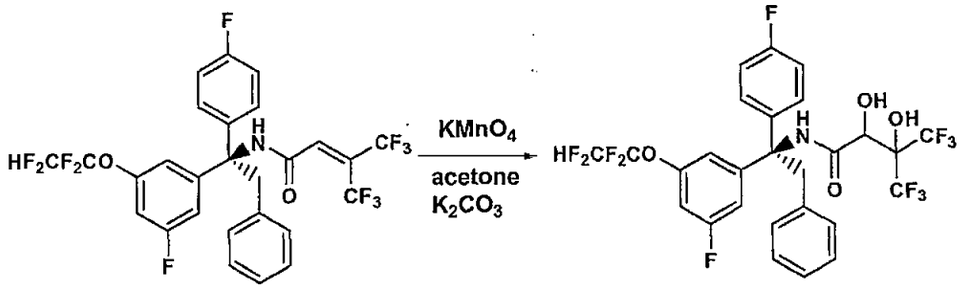

**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide**

## EXAMPLE 287B



**(R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide**

### Procedure 85




**[00349]** At -78 °C to a mixture of (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)but-2-enamide (Example 285, 36 mg, 0.06 mmol) and $K_2CO_3$ (28 mg, 0.2 mmol) in acetone (0.5 mL) was added $KMnO_4$ (9 mg, 0.06 mmol). The resulted purple reaction mixture was stirred at -78 °C for 1 h, then at 0 °C for 30 min. The reaction mixture was diluted with EtOAc (25 mL) and the organic layer was washed by 1 N HCl (2 × 25 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by preparative HPLC Shimadzu-YMC Sunfire 5μ column, 30 × 100 mm eluting with 60-100% MeOH (90% in $H_2O$, 0.1% TFA) gradient over 14 min with flow rate 40 mL/min and UV detection at 220 nm. 4,4,4-Trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 286) was eluted at a retention time of 12.86 min and was isolated as a clear oil (15 mg, yield 39%). LCMS: RT = 2.12 min [M+H] 650.92 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at

220 nm); HPLC: RT = 4.36 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400 MHz $^1H$ ($CDCl_3$) 7.92 ppm, 1 H, d, *J*=6.15 Hz; 7.19 ppm, 5 H, m; 7.06 ppm, 1 H, t, *J*=8.57 Hz; 6.97 ppm, 5 H, m; 6.71 ppm, 1 H, m; 6.62 ppm, 2 H, t, *J*=6.37 Hz; 5.88 ppm, 1H, m; 4.51 ppm, 1 H, s; 4.11 ppm, 1 H, m; 3.56 ppm, 1 H, m; 3.25 ppm, 1H, m.

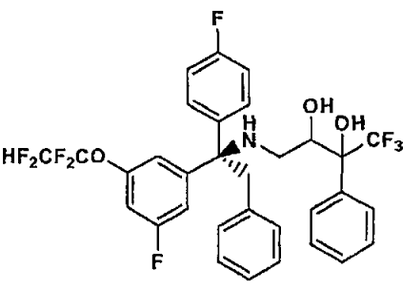
**[00350]** The diastereomer mixture of 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 286, 189 mg, 0.3 mmol) was separated by chiral preparative HPLC chiralpak AD 20μ column, 5 × 50 cm, eluting with 5% IPA/Heptane with flow rate 50 mL/min. (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287A) was eluted at a retention time of 52 min and (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287B) was eluted at a retention time of 70 min. The stereochemistry of (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287A) and (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287B) was assigned arbitrarily.

**[00351]** (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287A) was further purified by ISCO chromatography (40 g column, flow rate 20 mL/min) using hexanes/EtOAc (0-30% over 30 min) to give (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287A) as a white solid at a retention time of 28 min (95 mg, 50% yield). LCMS: RT = 2.12 min [M+H] 650.00 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.241 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90%

MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400 MHz $^1H$ ($CDCl_3$) 7.95ppm, 1 H, s; 7.22 ppm, 2 H, m; 7.16 ppm, 2 H, t, *J*=7.25 Hz; 6.99 ppm, 8 H, m; 6.62 ppm, 2 H, d, *J*=7.47 Hz; 5.89 ppm, 1H, t, *J*=52.95 Hz; 4.52 ppm, 1 H, d, *J*=6.15 Hz; 4.08 ppm, 1 H, d, *J*=3.95 Hz; 3.53 ppm, 2 H, d, *J*=13.18 Hz.

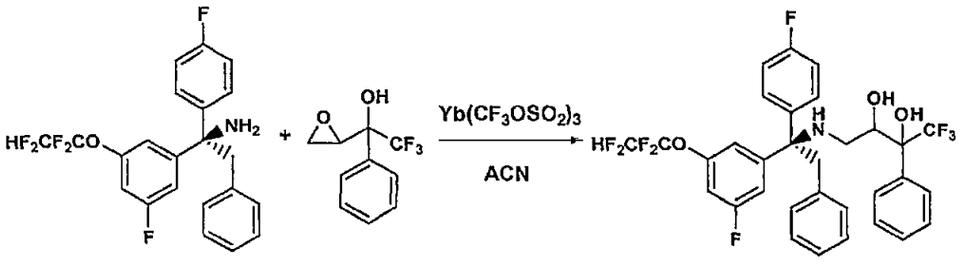
**[00352]** (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287B) was further purified by ISCO chromatography (40 g column, flow rate 20 mL/min) using hexanes/EtOAc (0-30% over 30 min) to give (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 287B) as a clear oil at a retention time of 28 min (57 mg, 30% yield). LCMS: RT = 2.12 min [M+H] 650.00 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.285 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 1H NMR (400 MHz, Solvent) δ ppm 7.95 ppm, 1 H, s; 7.20 ppm, 6 H, m; 7.05 ppm, 2 H, t, *J*=8.57 Hz; 6.93 ppm, 1 H, d, *J*=8.79 Hz; 6.71 ppm, 2 H, m; 6.63 ppm, 2 H, d, *J*=7.03 Hz; 5.85 ppm, 1 H, tt, *J*=52.95, 2.64 Hz; 4.49 ppm, 1 H, d, *J*=6.15 Hz; 4.02 ppm, 1 H, d, *J*=13.62 Hz; 3.79 ppm, 1 H, d, *J*=6.15 Hz; 3.59 ppm, 1 H, d, *J*=13.18 Hz.

**EXAMPLE 288**



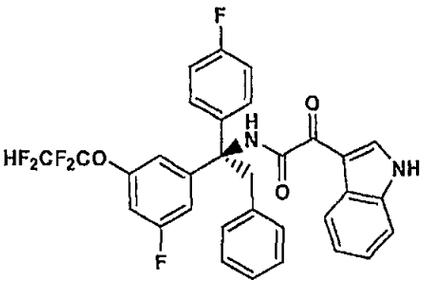

**1,1,1-trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-2-phenylbutane-2,3-diol**

**Procedure 87**



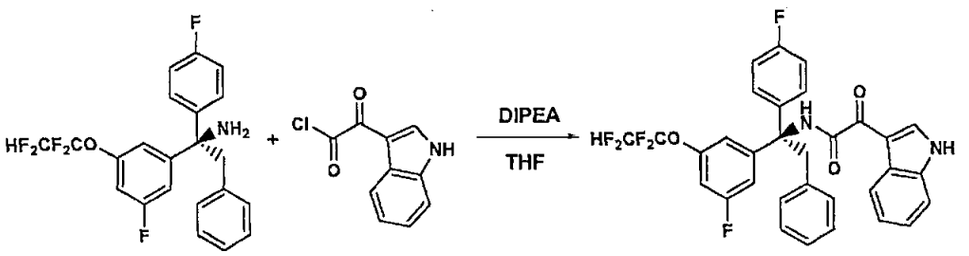

**[00353]** A mixture of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine, prepared as described in Procedure 3, 4, 5 and 6, (20 mg, 0.047 mmol), 2,2,2-trifluoro-1-(oxiran-2-yl)-1-phenylethanol (63 mg, 0.28 mmol), and $Yb(CF_3OSO_2)_3$ (10 mg) in dichloroethane (0.5 mL) were heated at 45 °C for 72 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC Shimadzu-YMC Sunfire 5μ column, 30 × 100 mm eluting with 40-100% MeOH (90% in $H_2O$, 0.1% TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm. 1,1,1-Trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-2-phenylbutane-2,3-diol (Example 288) was eluted at a retention time of 9.11 min and was isolated as a clear oil (11 mg, yield 37%). LCMS: RT = 1.85 min [M+H] 643.95 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.20 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.34 ppm, 5 H, m; 7.17 ppm, 1 H, t, *J*=7.47 Hz; 7.07 ppm, 4 H, m; 6.95 ppm, 2 H, m; 6.84 ppm, 1 H, m; 6.73 ppm, 2 H, m; 6.44 ppm, 2 H, d, *J*=7.47 Hz; 5.86 ppm, 1H, m; 4.02 ppm, 2 H, dd, *J*=6.59, 3.95 Hz; 3.33 ppm, 2 H, m; 2.32 ppm, 1 H, dt, *J*=12.74, 4.61 Hz; 2.18 ppm, 1 H, ddd, *J*=14.72, 12.52, 7.03 Hz.

## EXAMPLE 289



**(R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-(1H-indol-3-yl)-2-oxoacetamide**

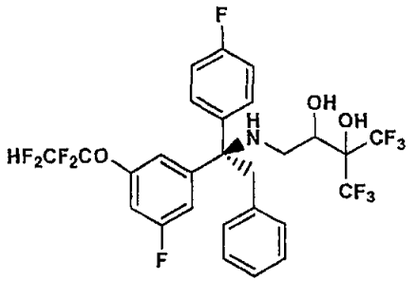
**Procedure 88**




**[00354]** At 0 °C, to a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine, prepared as described in Procedure 3, 4, 5 and 6, (20 mg, 0.045 mmol) and 2-(1H-indol-3-yl)-2-oxoacetyl chloride (10 mg, 0.05 mmol) in THF (0.5 mL) was added dropwise diisopropylethylamine (10 μL, 0.06 mmol). The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC Shimadzu-YMC Sunfire 5μ column, 30 × 100 mm eluting with 40-100% MeOH (90% in $H_2O$, 0.1% TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm. (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-(1H-indol-3-yl)-2-oxoacetamide (Example 289) was eluted at a retention time of 11.65 min and was isolated as a clear oil (13 mg, yield 48%). LCMS: RT = 2.20 min [M+H] 596.96 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.45 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-

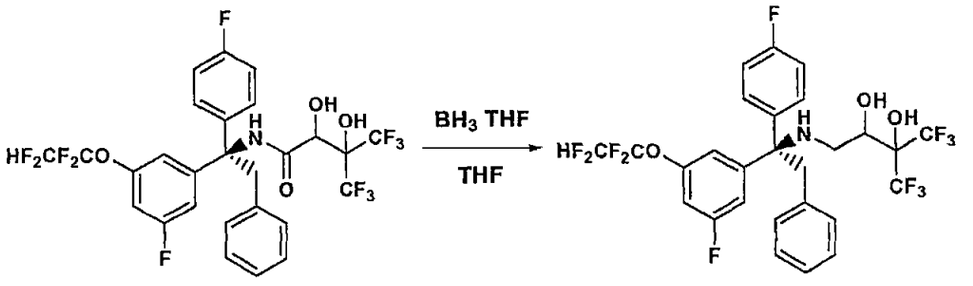
90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). NMR: 400 MHz $^1H$ ($CDCl_3$) 8.98 ppm, 1 H, d, *J*=3.52 Hz; 8.83 ppm, 1 H, s; 8.43 ppm, 1 H, s; 8.40 ppm, 1 H, d, *J*=7.03 Hz; 7.42 ppm, 1 H, m; 7.34 ppm, 2 H, m; 7.14 ppm, 5 H, m; 7.01 ppm, 2 H, t, *J*=8.57 Hz; 6.93 ppm, 3 H, m; 6.68 ppm, 2 H, d, *J*=7.03 Hz; 5.86 ppm, 1 H, tt, *J*=53.06, 2.86, 2.64 Hz; 3.96 ppm, 1 H, d, *J*=12.74 Hz; 3.82 ppm, 1 H, m.

**EXAMPLE 290**




**1,1,1-trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-2-(trifluoromethyl)butane-2,3-diol**

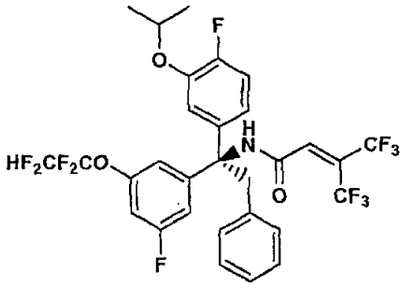
**Procedure 89**




**[00355]** A mixture of 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl)butanamide (Example 286, 20 mg, 0.031 mmol) and $BH_3$/THF (248 μL, 1.0 M solution in THF, 0.248 mmol) in THF (0.5 mL) was heated at 100 °C under microwave irradiation for 30 min. The reaction mixture was concentrated, diluted with EtOAc (25 mL) and the organic layer was washed with saturated $Na_2CO_3$ (25 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by preparative HPLC Shimadzu-YMC Sunfire 5μ column, 30 × 100 mm eluting with

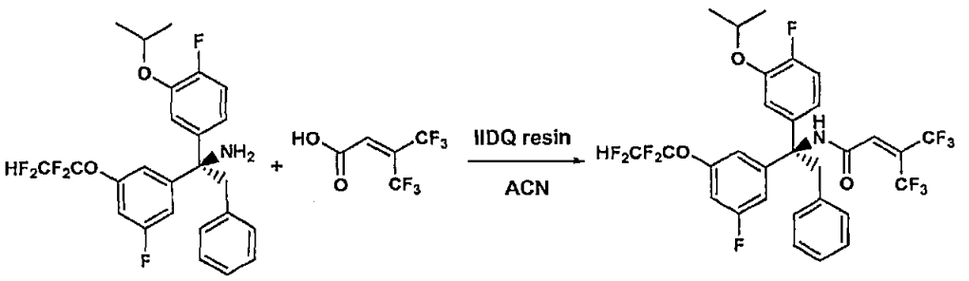
40-100% MeOH (90% in $H_2O$, 0.1%TFA) gradient over 12 min with flow rate 40 mL/min and UV detection at 220 nm. 1,1,1-Trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-2-(trifluoromethyl)butane-2,3-diol (Example 290) was eluted at a retention time of 11.09 min and isolated as a clear oil (12 mg, yield 62%). LCMS: RT = 1.95 min [M+H] 636.38 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.01 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1$H ($CDCl_3$) 7.21 ppm, 4 H, dd, *J*=8.57, 5.49 Hz; 7.15 ppm, 2 H, t, *J*=7.25 Hz; 7.06 ppm, 2 H, t, *J*=8.57 Hz; 6.90 ppm, 1 H, d, *J*=8.35 Hz; 6.80 ppm, 1 H, dd, *J*=9.67, 2.20 Hz; 6.77 ppm, 1 H, s; 6.60 ppm, 2 H, d, *J*=6.59 Hz; 5.87 ppm, 1 H, tt, *J*=52.95, 2.86 Hz; 3.84 ppm, 1 H, t, *J*=5.71 Hz; 3.59 ppm, 1 H, m; 3.46 ppm, 1 H, m; 3.07 ppm, 1 H, dd, *J*=12.74, 6.15 Hz; 2.86 ppm, 1 H, dd, *J*=12.96, 5.49 Hz.

**EXAMPLE 291**



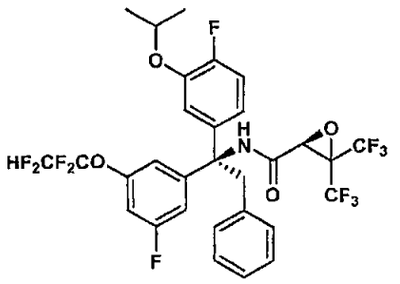

**(R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)but-2-enamide**

**Procedure 90**



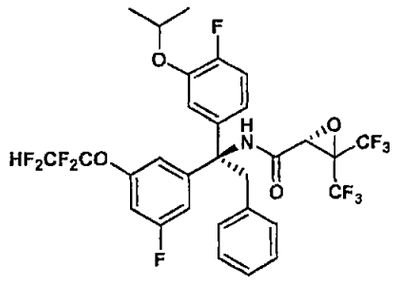

**[00356]** A round bottom flask was charged with IIDQ polystyrene resin (493 mg, 1.5 mmol/g, 0.74 mmol) and acetonitrile (5 mL) and sealed with a rubber septum. The suspension was vacuumed and reflushed with argon three times. To the resulting slurry was added a solution of (R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine, prepared as described in Procedures 109, 110, 111, 112, 113, 114, (180 mg, 0.37 mmol) and 4,4,4-trifluoro-3-(trifluoromethyl)crotonic acid (93 mg, 0.45 mmol) in acetonitrile (5 mL) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure and purified by ISCO chromatography (40 g column) using hexane/EtOAc (0-15% over 30 min) to give (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)but-2-enamide (Example 291) as a white solid at a retention time of 20 min (199 mg, 74% yield). LCMS: RT = 2.18 min [M+H] 674.33 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.25 min, Purity 98% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.19 ppm, 3 H, m; 7.02 ppm, 1 H, dd, *J*=10.55, 8.79 Hz; 6.95 ppm, 3 H, m; 6.85 ppm, 1 H, s; 6.67 ppm, 3 H, d, *J*=7.03 Hz; 6.62 ppm, 1 H, m; 6.13 ppm, 1 H, s; 5.88 ppm, 1 H, tt, *J*=53.00, 2.86, 2.75 Hz; 4.36 ppm, 1 H, ddd, *J*=11.97, 6.15, 6.04 Hz; 3.99 ppm, 1 H, d, *J*=13.18 Hz; 3.71 ppm, 1 H, d, *J*=13.18 Hz; 1.26 ppm, 6 H, m.

**EXAMPLE 292A**



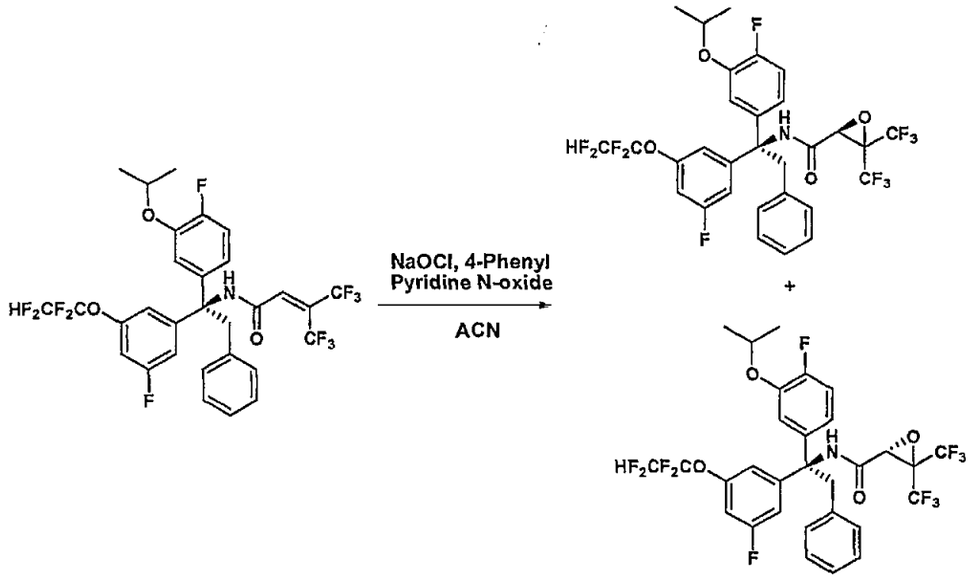
**(S)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide**

**EXAMPLE 292B**



**(R)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide**

**Procedure 91**




**[00357]** At 0 °C to a solution of (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)but-2-enamide (Example 291, 130 mg, 0.19 mmol) and 4-phenyl pyridine N-oxide (26 mg, 0.15 mmol) in acetonitrile (5 mL) was added NaOCl solution (206 µL, chlorine wt% 10-3%, 0.58 mmol). The reaction mixture was stirred at 0 °C for 10 min, then at rt for 1 h. The solvents were removed under reduced pressure and the residue was diluted with EtOAc (30 mL), washed with saturated $Na_2SO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was right away purified by ISCO chromatography (40 g column, flow rate 25 mL/min) using hexanes/EtOAc (0-10% over 30 min) to give N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide as a diastereomer mixture at a retention time of 26 min (97 mg, 74% yield). The diastereomer mixture was separated by Chiral preparative HPLC chiralpak AD 20µ column, 5 × 50 cm, eluting with 5% IPA/Heptane with flow rate 50 mL/min.

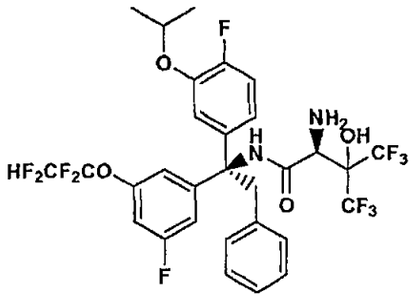
**[00358]** (S)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (Example 292A) was eluted at a retention time of 30 min and isolated as a clear oil (50 mg, yield 51%). LCMS: RT = 2.25 min [M+H] 690.30 (Phenomenex

Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.225 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.20 ppm, 3 H, ddd, *J*=14.72, 7.25, 7.03 Hz; 6.98 ppm, 3 H, m; 6.90 ppm, 1 H, s; 6.60 ppm, 5 H, m; 5.87 ppm, 1H, t; 4.31 ppm, 1 H, ddd, *J*=12.19, 6.04, 5.93 Hz; 4.10 ppm, 1 H, d, *J*=13.18 Hz; 3.95 ppm, 1 H, s; 3.51 ppm, 1 H, d, *J*=13.18 Hz; 1.28 ppm, 3 H, d, *J*=5.71 Hz; 1.21p pm, 3 H, d, *J*=5.71 Hz.

**[00359]** (R)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (Example 292B) was eluted at a retention time of 40 min and isolated as a clear oil (38 mg, yield 39%). LCMS: RT = 2.27 min [M+H] 690.30 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.20 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.20 ppm, 3 H, m; 7.05 ppm, 1 H, m; 6.95 ppm, 1 H, d, *J*=7.91 Hz; 6.85 ppm, 2 H, m; 6.72 ppm, 2 H, m; 6.64 ppm, 2 H, d, *J*=7.47 Hz; 6.59 ppm, 1 H, s; 5.87 ppm, 1H, m; 4.36 ppm, 1 H, m; 3.92 ppm, 1 H, m; 3.88 ppm, 1 H, m; 3.70 ppm, 1 H, m; 1.26 ppm, 6 H,9 m.

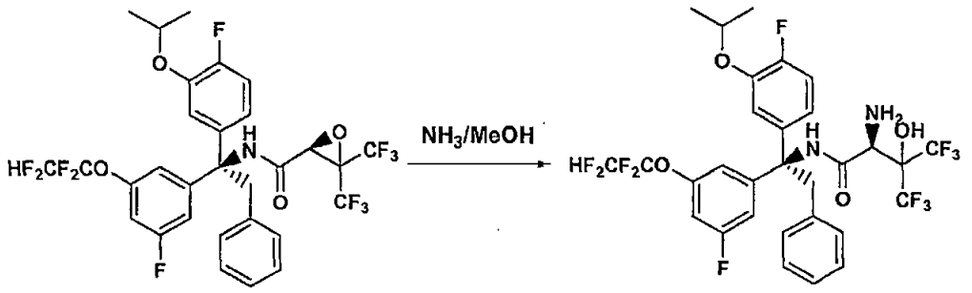
**[00360]** The relative stereochemistry of (S)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (Example 292A) and (R)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (Example 292B) was assigned arbitrarily.

## EXAMPLE 293



**(S)-2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl)butanamide**

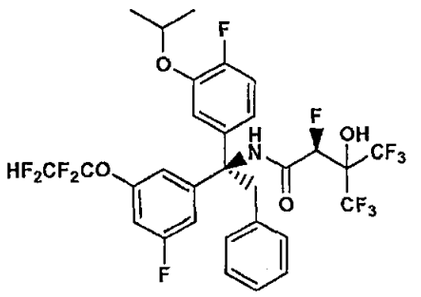
### Procedure 92



**[00361]** A solution of $NH_3$ in MeOH (7 M, 1.0 mL) was added to (S)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (Example 292A, 28 mg, 0.04 mmol) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated and purified by preparative HPLC (Shimadzu-Phenomenex Luna AXIA 5 μ column, 21.2 × 100 mm eluting with 30-100% ACN (90% in $H_2O$, 0.1%TFA) gradient over 14 min with flow rate 20 mL/min and UV detection at 220 nm). (S)-2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl)butanamide (Example 293) was eluted at a retention time of 12.83 min and isolated as a clear oil (20 mg, yield 70%). LCMS: RT = 2.11 min [M+H] 707.41 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm);

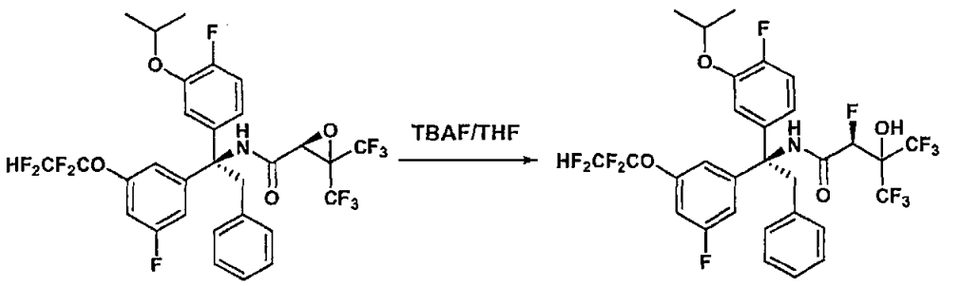
HPLC: RT = 3.99 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400 MHz $^1H$ ($CDCl_3$) 9.00 ppm, 1 H, s; 7.19 ppm, 3 H, m; 7.04 ppm, 1 H, m; 6.93 ppm, 1 H, d, *J*=8.79 Hz; 6.76 ppm, 4 H, m; 6.64 ppm, 2 H, d, *J*=7.03 Hz; 5.8 ppm, 1H, m; 4.38 ppm, 1 H, dq, *J*=6.15, 6.01 Hz; 3.87 ppm, 1 H, m; 3.70 ppm, 2 H, m; 1.89 ppm, 2 H, s; 1.28 ppm, 6 H, m.

**EXAMPLE 294**



**(S)-2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl)butanamide**

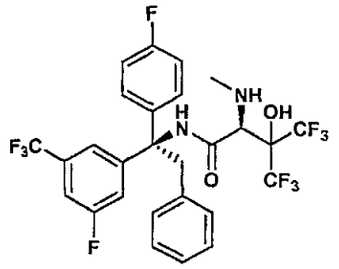
**Procedure 93**




**[00362]** To a solution of (S)-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (Example 292A, 25 mg, 0.036 mmol) in THF (0.5 mL) was added TBAF (72 μL, 1.0 M solution in THF, 0.072 mmol). The reaction mixture was heated at 60 °C under microwave irradiation for 10 min. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Shimadzu-YMC ODS 5 μ column, 20 × 100 mm eluting with 30-100% ACN (90% in $H_2O$,

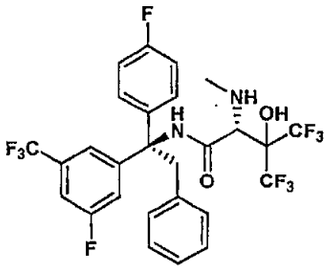
0.1%TFA) gradient over 18 min with flow rate 20 mL/min and UV detection at 220 nm). (S)-2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl)butanamide (Example 294) was eluted at a retention time of 17.28 min and was isolated as a clear oil (14 mg, yield 55%). The stereochemistry of (S)-2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl)butanamide (Example 294) was assigned arbitrarily. LCMS: RT = 2.22 min [M+H] 710.39 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.18 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 7.26 ppm, 1 H, m; 7.21 ppm, 3 H, m; 7.07 ppm, 1 H, m; 6.96 ppm, 1 H, d, *J*=8.79 Hz; 6.78 ppm, 4 H, m; 6.64 ppm, 2 H, d, *J*=7.15 Hz; 6.50 ppm, 1 H, s; 5.87 ppm, 1 H, tt, *J*=52.97, 2.61, 2.47 Hz; 5.10 ppm, 1H, d, *J*=46.17Hz; 4.41 ppm, 1 H, dt, *J*=12.09, 6.05 Hz; 3.97 ppm, 1 H, d, *J*=13.19 Hz; 3.58 ppm, 1 H, d, *J*=13.19 Hz; 1.30 ppm, 6 H, t, *J*=6.32 Hz.

**EXAMPLE 295A**



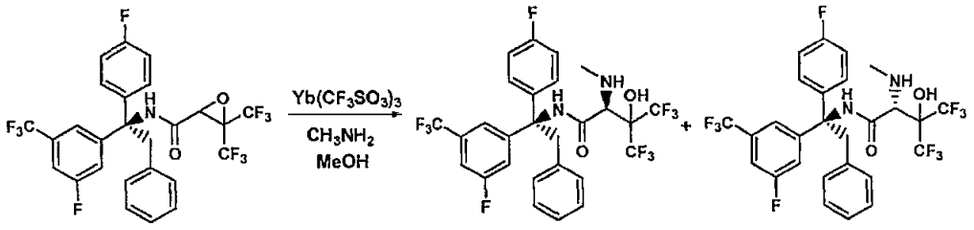

**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(methylamino)-3-(trifluoromethyl)butanamide**

## EXAMPLE 295B



**(R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(methylamino)-3-(trifluoromethyl)butanamide**

### Procedure 94




**[00363]** To a mixture of diastereomers of N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (40 mg, 0.069 mmol), prepared as described in Procedure 90 and 91, was added $Yb(CF_3SO_3)_3$ (10 mg) and methylamine in MeOH (0.2 mL, 2 M solution in MeOH). The reaction was heated at 60 °C under microwave irradiation for 10 min and then concentrated under reduced pressure. The residue was diluted with EtOAc (25 mL) and washed with saturated $Na_2CO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC Shimadzu-YMC-ODS-A 5µ column, 20 × 100 mm eluting with 30-100% MeOH (90% in $H_2O$, 0.1%TFA) gradient over 30 min with flow rate 20 mL/min and UV detection at 220 nm.

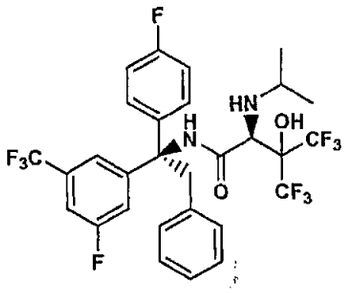
**[00364]** (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(methylamino)-3-(trifluoromethyl)butanamide (Example 295A) was eluted at a retention time of 22.96 min and isolated as a clear oil (4 mg, yield 9%). LCMS: RT = 4.17 min [M+H] 615.3

(Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 10 mM $NH_4OAc$; 4 mL/min, monitoring at 220 nm); HPLC: RT = 3.87 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm); NMR: 400 MHz $^1H$ ($CDCl_3$) 9.24 ppm, 1 H, s; 7.54 ppm, 1 H, s; 7.30 ppm, 3 H, m; 7.20 ppm, 3 H, m; 7.01 ppm, 2 H, t, *J*=8.35 Hz; 6.85 ppm, 2 H, m; 6.60 ppm, 2 H, d, *J*=7.03 Hz; 4.29 ppm, 1 H, d, *J*=12.74 Hz; 3.47 ppm, 1 H, d, *J*=12.74 Hz; 3.32 ppm, 1 H, s; 2.32 ppm, 3 H, s.

**[00365]** (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(methylamino)-3-(trifluoromethyl)butanamide (Example 295B) was eluted at a retention time of 23.45 min and isolated as a clear oil (5 mg, yield 11%). LCMS: 4.16 min [M+H] 615.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 10 mM $NH_4OAc$; 4 mL/min, monitoring at 220 nm); HPLC: RT = 3.93 min, Purity 92% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 9.06 ppm, 1 H, s; 7.30 ppm, 2 H, m; 7.23 ppm, 3 H, d, *J*=5.71 Hz; 7.17 ppm, 2 H, t, *J*=7.25 Hz; 7.08 ppm, 2 H, t, *J*=8.57 Hz; 7.00 ppm, 1 H, m; 6.91 ppm, 1 H, d, *J*=10.11 Hz; 6.60 ppm, 2 H, d, *J*=7.03 Hz; 4.14 ppm, 1 H, m; 3.98 ppm, 1 H, s; 3.52 ppm, 2 H, m; 3.39 ppm, 2 H, m; 2.37 ppm, 3 H, s.

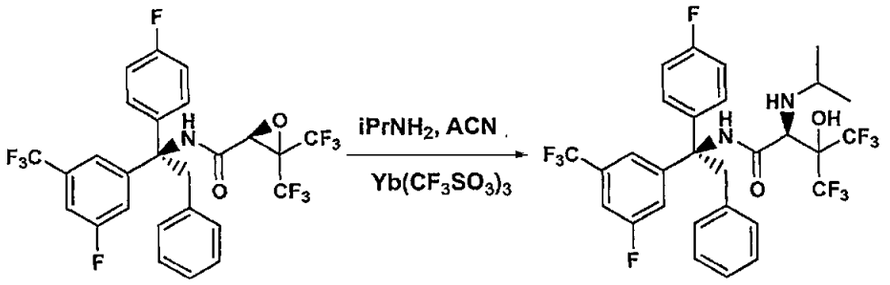
**[00366]** The stereochemistry of (S)-4,4,4-Trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(methylamino)-3-(trifluoromethyl)butanamide (Example 295A)and (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(methylamino)-3-(trifluoromethyl)butanamide isomer B (Example 295B)was assigned arbitrarily.

**EXAMPLE 296**



**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(isopropylamino)-3-(trifluoromethyl)butanamide**

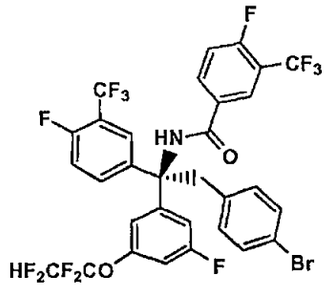
**Procedure 95**




**[00367]** To a solution of (S)-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl)oxirane-2-carboxamide (20 mg, 0.034 mmol), prepared as described in Procedure 90 and 91, in ACN (0.5 mL) was added $Yb(CF_3SO_3)_3$ (10 mg) and isopropylamine (10 μL, 0.1 mmol). The reaction mixture was heated at 60 °C under microwave irradiation for 10 min and then concentrated under reduced pressure. The residue was diluted with EtOAc (25 mL) and the organic layer was washed by saturated $Na_2CO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC Shimadzu-YMC-ODS-A 5μ column, 20 × 100 mm eluting with 30-100% MeOH (90% in $H_2O$, 0.1%TFA) gradient over 30 min with flow rate 20 mL/min and UV detection at 220 nm. (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(isopropylamino)-3-(trifluoromethyl)butanamide (Example 296) was eluted at a retention time of 27.36 min and isolated as a clear oil (12 mg, yield 54%). LCMS:

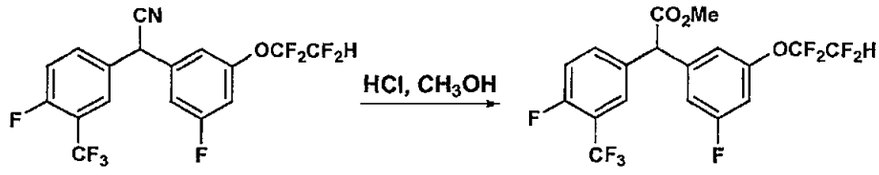
RT = 2.15 min [M+H] 643.4 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.293 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). NMR: 400 MHz $^1H$ ($CDCl_3$) 9.23 ppm, 1 H, s; 7.77 ppm, 1 H, s; 7.30 ppm, 3 H, m; 7.20 ppm, 1 H, m; 7.14 ppm, 2 H, t, *J*=7.25 Hz; 7.02 ppm, 2 H, t, *J*=8.35 Hz; 6.93 ppm, 1 H, d, *J*=4.83 Hz; 6.60 ppm, 2 H, d, *J*=7.03 Hz; 4.29 ppm, 1 H, d, *J*=13.18 Hz; 3.51 ppm, 1 H, d, *J*=5.27 Hz; 3.47 ppm, 1 H, d, *J*=12.74 Hz; 2.74 ppm, 1 H, m; 1.87 ppm, 1 H, s; 1.04 ppm, 3 H, d, *J*=6.15 Hz; 0.71 ppm, 3 H, d, *J*=6.15 Hz. The stereochemistry of (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(isopropylamino)-3-(trifluoromethyl)butanamide (Example 296) was assigned arbitrarily.

**EXAMPLE 297**




**(R)-N-(2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

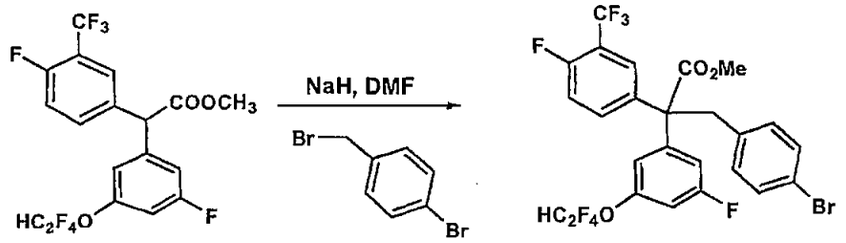
**Procedure 96**




**[00368]** A solution of 2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)acetonitrile prepared as described in Procedure 3, 4 and 73 (72% yield, 453 mg, 1.1 mmol) in MeOH (18 mL) was cooled to 0 °C and

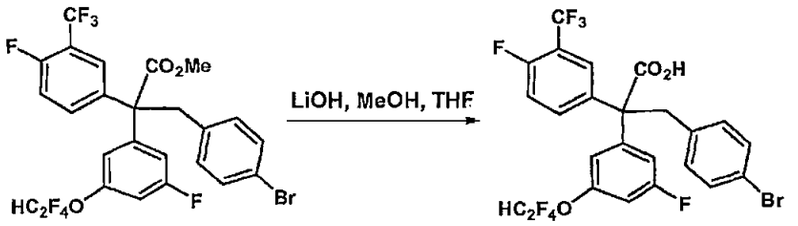
saturated with HCl gas. The resulting solution was heated at reflux overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and sat. NaCl. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by ISCO (40 g silica gel column, 0-40 % EtOAc/hexane over 50 min) to yield methyl 2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)acetate as a colorless oil (394 mg, 80% yield). LCMS: RT = 2.05 min [M+H] 446.97 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.%TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.22 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm); 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 (1 H, d, *J*=6.59 Hz), 7.47 - 7.51 (1 H, m), 7.19 (1 H, t, *J*=9.23 Hz), 6.9-6.97 (3 H, m), 5.76-6.03 (1 H, m), 3.78 (3 H, s).

**Procedure 97**



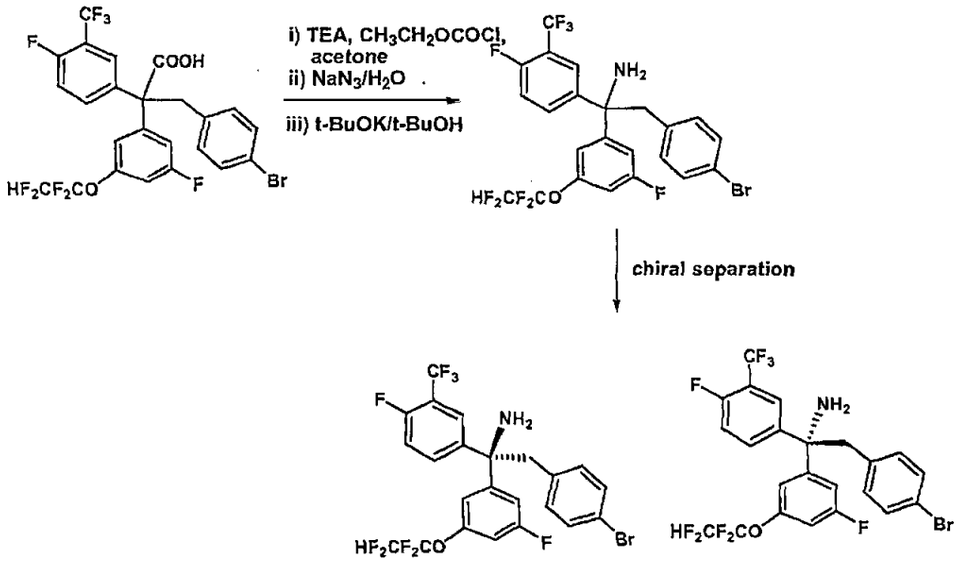

**[00369]** To a suspension of NaH (60% in oil, 66 mg, 1.65 mmol) in DMF (3 mL) at 0 °C was added a solution of methyl 2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)acetate (600 mg, 1.34 mmol) in one portion. The reaction mixture was stirred at 0 °C for 10 min followed by addition of a solution of 4-bromobenzylbromide (343 mg, 1.37 mmol) in DMF (2 mL). The reaction was stirred at 0 °C for 5 min and quenched by the addition of saturated $NH_4Cl$. The mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give methyl 3-(4-bromophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)propanoate as a colorless oil (865 mg, 100% yield). LCMS:

RT = 2.26 min, no ionization (Phenomenex Luna C18 4.6x30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.48 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm); 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.33 (1 H, m), 7.21-7.27 (4 H, m), 7.11 (1 H, t, *J*=9.23 Hz), 6.94 (1 H, d, *J*=8.79 Hz), 6.82 (1 H, d, *J*=9.67 Hz), 6.80 (1 H, s), 6.52 (2 H, d, *J*=8.35 Hz), 5.87 (1 H, t, *J*=53.2 Hz), 3.75 (3 H, s), 3.56 - 3.66 (2 H, m).




**[00370]** A mixture of methyl 3-(4-bromophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)propanoate (865 mg, 1.34 mmol) in MeOH (10 mL)/THF (20 mL) and LiOH (2 N, 10 mL) was stirred at rt overnight. The reaction mixture was made acidic by addition of 1 N HCl to pH = 1~2 and concentrated. The resulting residue was partitioned between EtOAc and sat. NaCl. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by ISCO (40 g siligel column, 0-10% MeOH/DCM over 30 min) to yield 3-(4-bromophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)propanoic acid as a colorless oil (650 mg, 81% yield). LCMS: RT = 2.17 min [M+H] 600.88 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.%TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.45 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm).

**Procedure 98**

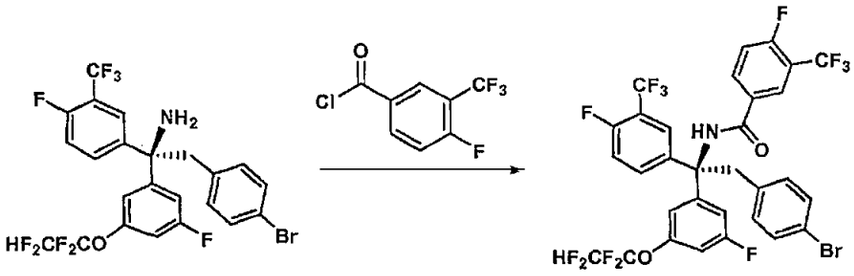



**[00371]** At 0 °C to a solution of 3-(4-bromophenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)propanoic acid (1.59 g, 2.64 mmol) in acetone (30 mL) was added TEA (442 μL, 3.17 mmol) followed by ethyl chloroformate (303 μL, 3.17 mmol). The reaction mixture was stirred at 0 °C for 45 min and $NaN_3$ (343 mg, 5.28 mmol) was added. The reaction was stirred at 0 °C for 1 h, quenched by the addition of water and the aqueous layer was extracted with toluene (3 x 30 mL). The combined organic layers were washed with sat. NaCl, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was diluted with toluene (10 mL) and heated at 90 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in t-BuOH/THF (1:1, 20 mL) and treated with t-BuOK/t-BuOH (1 N, 13.2 mL, 13.2 mmol). The reaction mixture was stirred at rt overnight, then heated at 85 °C for 3 h. The reaction mixture was quenched by the addition of water and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. NaCl, dried over magnesium sulfate, filtered and concentrated. The residue was purified by ISCO (40 g siligel column, 0-40% EtOAc/hexane over 40 min to yield 2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethanamine as a colorless oil (1.2 g, 82% yield). LCMS: RT = 1.82 min [M+H] 556.8 (Phenomenex Luna C18 4.6 x 30mm column,

eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm). 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.61 (1 H, d, *J*=6.15 Hz), 7.48 - 7.53 (1 H, m), 7.30 (1 H, d, *J*=7.91 Hz), 7.15 (1 H, t, *J*=9.23 Hz), 6.96 - 7.00 (2 H, m), 6.89 (1 H, d, *J*=8.79 Hz), 6.61 (2 H, d, *J*=7.91 Hz), 5.89 (1 H, t, *J*=53 Hz), 3.49 (1 H, d, *J*=13.6 Hz), 3.43 (1 H, d, *J*=13.6 Hz), 1.50 -1.65 (2 H, m).

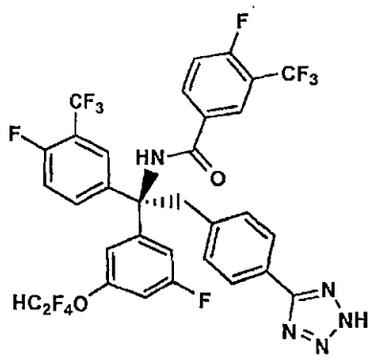
**[00372]** 2-(4-Bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethanamine (racemic, 510 mg) was subjected to chiral preparative HPLC separation (chiral OD 10 micron 4.6 x 250 mm column, eluting with 20% iPA/heptane/0.1% DEA) to give (R)-2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethanamine (211 mg) as a colorless oil and (S)-2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethanamine (195 mg) as colorless oil. For (R)-2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethanamine: chiral analytical HPLC: RT = 6.0 min, 100% ee (chiral OD 10 micron 4.6x250 mm column, eluting with 20%IPA/heptane/0.1%DEA, flow rate 1 mL/min, wavelength 220 nm); LCMS: RT = 1.82 min [M+H] 556.8 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.61 (1 H, d, *J*=6.15 Hz), 7.48 - 7.53 (1 H, m), 7.30 (1 H, d, *J*=7.91 Hz), 7.15 (1 H, t, *J*=9.23 Hz), 6.96 - 7.00 (2 H, m), 6.89 (1 H, d, *J*=8.79 Hz), 6.61 (2 H, d, *J*=7.91 Hz), 5.89 (1 H, t, *J*=53 Hz), 3.49 (1 H, d, *J*=13.6 Hz), 3.43 (1 H, d, *J*=13.6 Hz), 1.50 -1.65 (2 H, m). For (S)-2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethanamine isomer B: chiral analytical HPLC: RT = 7.5 min, 100% ee (chiral OD 10 micron 4.6 x 250 mm column, eluting with 20% IPA/heptane/0.1% DEA, flow rate 1 mL/min, wavelength 220 nm); LCMS: RT = 1.82 min [M+H] 556.8 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.61 (1 H, d, *J*=6.15 Hz), 7.48 - 7.53 (1 H, m), 7.30 (1 H, d, *J*=7.91 Hz), 7.15 (1 H, t, *J*=9.23 Hz), 6.96 - 7.00 (2 H, m), 6.89 (1

H, d, *J*=8.79 Hz), 6.61 (2 H, d, *J*=7.91 Hz), 5.89 (1 H, t, *J*=53 Hz), 3.49 (1 H, d, *J*=13.6 Hz), 3.43 (1 H, d, *J*=13.6 Hz), 1.50 -1.65 (2 H, m).



**[00373]** Following Procedure 7, (R)-N-(2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 297) was prepared as a white foam (471 mg, 88% yield). LCMS: RT = 2.25 min [M+H] 761.8 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.52 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm); 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (1 H, dd, *J*=6.59, 2.20 Hz), 7.81 - 7.85 (1 H, m), 7.39 - 7.44 (2 H, m), 7.30 – 7.34 (2 H, m), 7.21 (1 H, t, *J*=9.45 Hz), 6.99 (1 H, d, *J*=8.79 Hz), 6.79 - 6.84 (2 H, m), 6.57 (1 H, s), 6.55 (2 H, d, *J*=8.35 Hz), 5.89 (1 H, t, *J*=54 Hz), 3.95 (1 H, d, *J*=13.2 Hz), 3.86 (1 H, d, *J*=13.2 Hz).

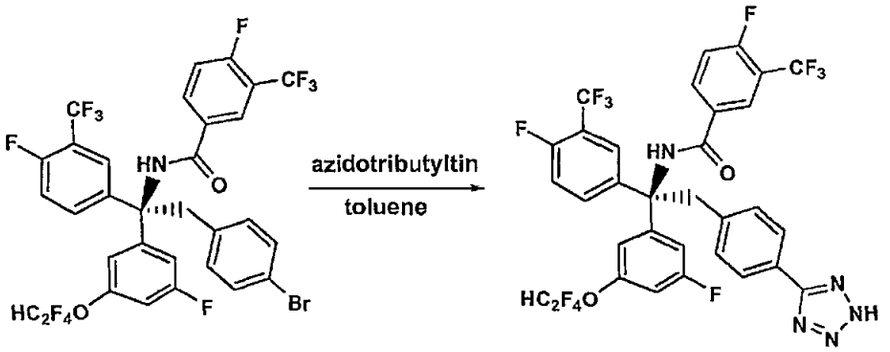
**EXAMPLE 298**



**(R)-N-(2-(4-(2H-tetrazol-5-yl)phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-**

**(3-fluoro-5-(1,1,2,2-tetrafluoroethyl)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

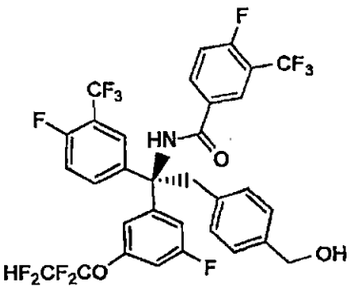
**Procedure 99**




**[00374]** A mixture of (R)-N-(2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 297, 20 mg, 0.028 mmol) and azidotributyltin (38 μL, 0.14 mmol) in toluene was heated at 100 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by ISCO (4 g silica gel column, 0-10% MeOH/DCM) to give (R)-N-(2-(4-(2H-tetrazol-5-yl)phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethyl)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 298) as a white solid (11 mg, 52% yield). LCMS: RT = 2.07 min [M+H] 752.3 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.26 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm). 1H NMR (400 MHz, $CD_3OD$) δ ppm 8.98 (1 H, s), 7.95 – 7.98 (2 H, m), 7.71 (2 H, d, *J*=8.35 Hz), 7.49 (1 H, dd, *J*=7.47, 3.95 Hz), 7.34 - 7.42 (2 H, m), 7.22 (1 H, t, *J*=9.45 Hz), 7.04 (1 H, d, *J*=10.11 Hz), 6.94 - 6.98 (2 H, m), 6.84 (2 H, d, *J*=8.35 Hz), 6.18 (1 H, t, *J*=52.3 Hz), 4.11 (1H, d, *J*=12.7), 4.11 (1H, d, *J*=12.7).

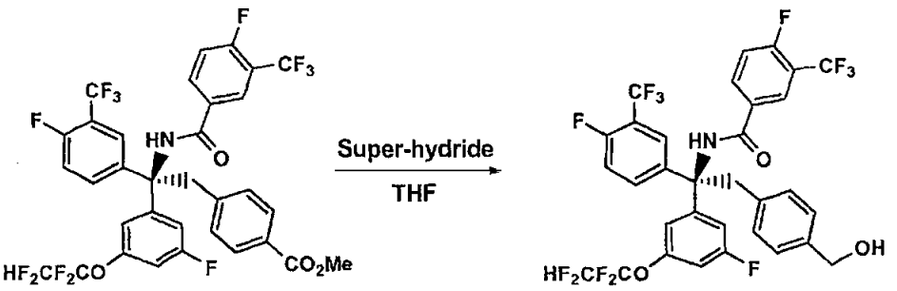
408

**EXAMPLE 299**



**(R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide**

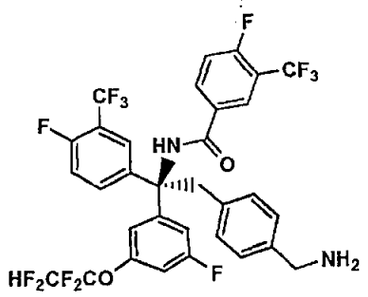
**Procedure 100**




**[00375]** To a solution of (R)-methyl 4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)benzoate prepared as described in Procedure 96, 97, 98, 56 and 57 (29 mg, 0.039 mmol) in THF at -78 °C was added a solution of lithium triethylborohydride (1.0 M in THF, 0.5 mL, 0.5 mmol). The resulting mixture was stirred at -78 °C for 1.5 h. The reaction was quenched by addition of 1 N NaOH (1 mL) and the aqueous layer was extracted with EtOAc (15 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by ISCO (12 g silica gel column, 0-50% EtOAc/hexane over 30 min) to yield (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide (Example 299) as a colorless film (22 mg, 79% yield). LCMS: RT = 2.10 min [M+H] 714.31 (Phenomenex Luna C18 4.6 x 30mm column,

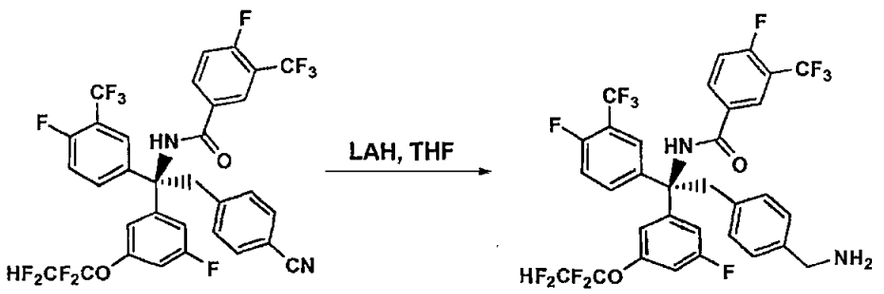
eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.0 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm); 1H NMR (400 MHz,$CDCl_3$) δ ppm 7.98 – 7.80 (1 H, m), 7.85 - 7.89 (1 H, m), 7.39 - 7.43 (3 H, m), 7.31 (1 H, t, *J*=9.23 Hz), 7.19 - 7.27 (1 H, m), 6.99 (1 H, d, *J*=8.79 Hz), 6.76 - 6.83 (5 H, m), 5.89 (1 H, t, *J*=53.0 Hz), 4.16 (1 H, d, *J*=13.18 Hz), 4.02 (1 H, d, *J*=13.18 Hz).

**EXAMPLE 300**




**(R)-N-(2-(4-(aminomethyl)phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

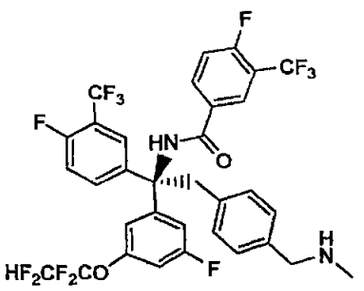
**Procedure 101**




**[00376]** To a solution of (R)-N-(2-(4-cyanophenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide, prepared as described in Procedure 56, (77% yield, 20 mg, 0.02 mmol) in THF (1.5 mL) at rt was added LAH (1.0 M in THF). The reaction mixture was stirred at rt for 5 h, then quenched by addition of 2 N LiOH.

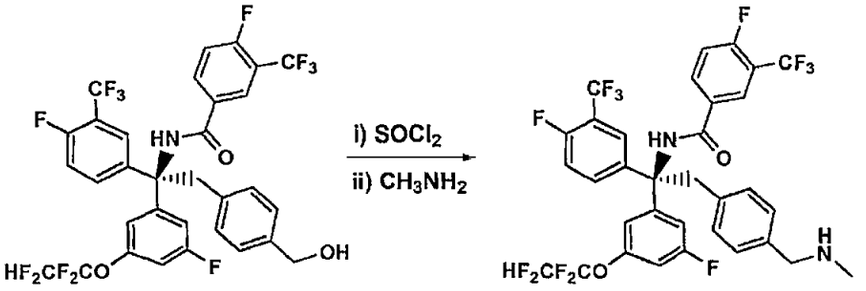
The solid was removed by filtration and the filtrate was concentrated. The resulting residue was purified by prep HPLC (YMC Sunfire 5μ C18 30 x 100 mm column, eluting with 20-90% MeOH/$H_2O$ containing 0.1% TFA, 10 min gradient, flow rate 40 mL/min, wavelength 220 nm) to provide (R)-N-(2-(4-(aminomethyl)phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 300) as a colorless film (5 mg, 36% yield). LCMS: RT = 1.8 min [M+H] 713.26 (Phenomenex Luna C18 4.6 x 30 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.31 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm). 1H NMR (400 MHz, $CD_3OD$) δ ppm 7.95 (1 H, d, *J*=6.59 Hz), 7.46 -7.48 (1 H, m), 7.36 7.41 (2 H, m), 7.22 (1 H, t, *J*=9.45 Hz), 7.16 (2 H, d, *J*=7.91 Hz), 6.99 (2 H, dd, *J*=16.48, 9.45 Hz), 6.93 (1 H, s), 6.73 (2 H, d, *J*=7.91 Hz), 6.21 H, t, *J* = 49.7 Hz), 4.01 - 4.06 (1 H, m), 3.93 - 3.99 (3 H, m).

**EXAMPLE 301**



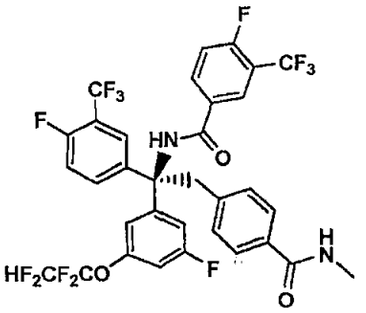

**(R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-((methylamino)methyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide**

**Procedure 102**



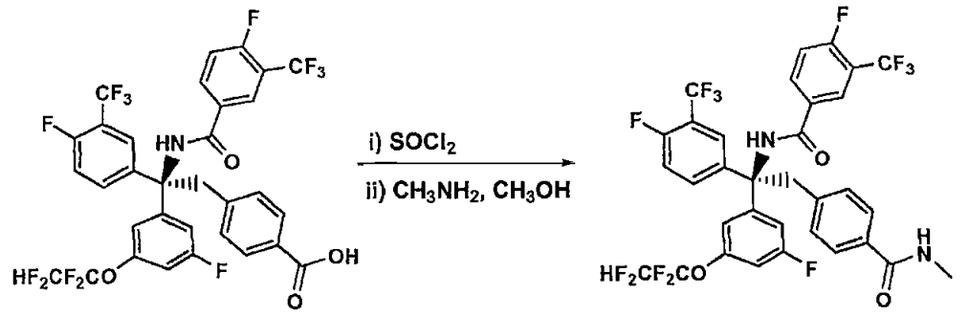

**[00377]** A solution of (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide (Example 299, 20 mg, 0.028 mmol) in $SOCl_2$ was stirred at rt overnight. The reaction mixture was concentrated and the residue was treated with a solution of methyl amine in methanol (1.0 M, 2.0 mL, 2.0 mmol) at rt overnight. The solvent was removed and the residue was purified by prep HPLC (YMC Sunfire 5μ C18 30 x 100mm column, eluting with 20-90% MeOH/$H_2O$ containing 0.1% TFA, 10 min gradient, flow rate 40 mL/min, wavelength 220 nm) to provide (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-((methylamino)methyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide (Example 301) as a white solid (13 mg, 65% yield). LCMS: RT = 2.02 min [M+H] = 727.48 (Phenomenex Luna C18 4.6 x 30 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 3.11 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm). 1H NMR (400 MHz, $CD_3OD$) δ ppm 7.57 - 8.06 (2 H, m), 7.48 – 7.57 (1 H, m), 7.43 - 7.49 (2 H, m), 7.30 (1 H, t, *J*=9.45 Hz), 7.25 (2 H, d, *J*=7.91 Hz), 7.00 - 7.10 (3 H, m), 6.82 (2 H, d, *J*=8.35 Hz), 6.29 (1 H, t, *J*=46.6 Hz), 4.03 - 4.15 (4 H, m), 2.65 (3 H, s).

**EXAMPLE 302**



**(R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(methylcarbamoyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide**

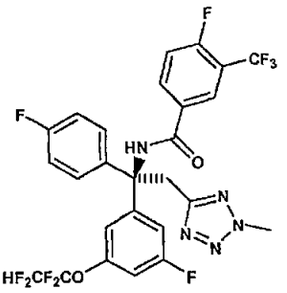
**Procedure 103**




**[00378]** A solution of (R)-4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)benzoic acid, prepared as described in Procedure 97, 98, 99 and 100, (65 mg, 0.09 mmol) in $SOCl_2$ was heated at 60 °C overnight. The reaction mixture was concentrated and 25 mg of the resulting residue was treated with a solution of methyl amine in methanol (1.0 M, 2.0 mL, 2.0 mmol) at rt overnight. The solvent was removed and the residue was purified by ISCO (12 g column, 0-20% EtOAc/hexane) to yield (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(methylcarbamoyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide (Example 302) as a white solid (14 mg, 85% yield). LCMS: RT = 2.16 min [M+H] 741.55 (Phenomenex Luna C18 4.6 x 30 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.0 min

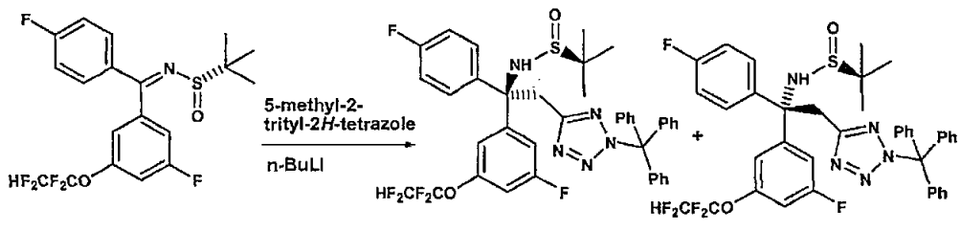
(Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.97 (1 H, d, *J*=5.71 Hz), 7.81 - 7.86 (1 H, m), 7.50 (2 H, d, *J*=7.91 Hz), 7.43 (2 H, d, *J*=5.27 Hz), 7.25 - 7.31 (1 H, m), 7.19 (1 H, t, *J*=9.45 Hz), 6.97 (1 H, d, *J*=8.35 Hz), 6.82 (2 H, d, *J*=4.83 Hz), 6.74 (2 H, d, *J*=7.91 Hz), 6.05 (1 H, d, *J*=4.83 Hz), 5.88 (1 H, t, *J*=52.1), 4.04 (1 H, d, *J*=13.2), 3.95 (1 H, d, *J*=13.2), 2.94 (3 H, d, *J*=4.83 Hz).

**EXAMPLE 303**



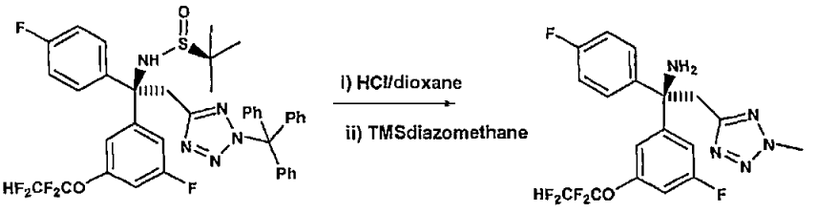
**(*R*)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2-methyl-2H-tetrazol-5-yl)ethyl)-3-(trifluoromethyl)benzamide**

**Procedure 104**

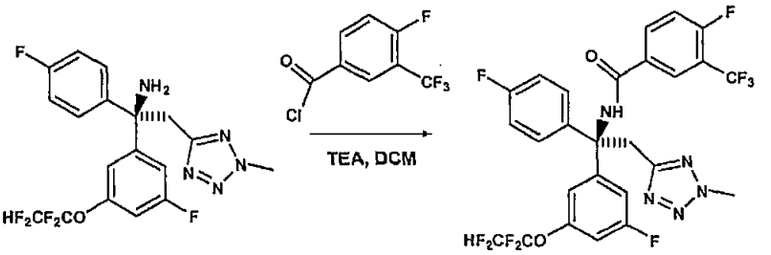



**[00379]** To a solution of 5-methyl-2-trityl-2H-tetrazole (0.90 g, 2.76 mmol) in dry THF (20 mL) at -78 °C under argon was added dropwise n-BuLi (2.5 M in hexane, 1.2 mL, 3 mmol). The resulting solution was stirred at -78 °C for 1 h, followed by the dropwise addition of a solution of (*R*)-N-((3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(4-fluorophenyl)methylene)-2-methylpropane-2-sulfinamide, prepared as described in Procedure 3, 4 and 5, (0.40 g, 0.91 mmol) in THF (5 mL). The reaction mixture was stirred at -78 °C to -70 °C overnight. The reaction mixture was quenched by addition of sat. $NH_4Cl$ and the aqueous layer was

extracted with $Et_2O$ (2 x) and the combined organic layers were washed with $H_2O$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by ISCO flash chromatography (silica gel, hexanes/EtOAc) to give (R)-N-((S)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2-trityl-2H-tetrazol-5-yl)ethyl)-2-methylpropane-2-sulfinamide as the fast eluting diastereomer (90 mg, 13% yield) and (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2-trityl-2H-tetrazol-5-yl)ethyl)-2-methylpropane-2-sulfinamide as the slow eluting diastereomer (85 mg, 12% yield).

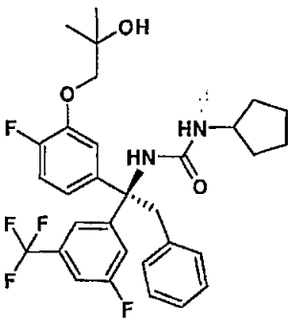



**[00380]** To a solution of (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2-trityl-2H-tetrazol-5-yl)ethyl)-2-methylpropane-2-sulfinamide (60 mg, 0.079 mmol) in MeOH (3 mL) was added 4 N HCl in dioxane (1 mL). The reaction mixture was stirred at room temperature for 20 min, then concentrated to yield (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2H-tetrazol-5-yl)ethanamine. LCMS: RT = 2.66 min [M+H] 418.55 (Phenomenex Luna C18 4.6 x 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 4 min gradient, flow rate 4 mL/min, wavelength 220 nm). To a solution of ((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2H-tetrazol-5-yl)ethanamine in THF (3 mL) and MeOH (0.5 mL) was added (diazomethyl)trimethylsilane (2.0 M in hexanes, 0.05 mL). After stirring at room temperate for 20 min, the reaction mixture was concentrated and purified by ISCO flash column chromatography (silica gel, EtOAc) to give ((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2-methyl-2H-tetrazol-5-yl)ethanamine (10 mg, yield: 30%). LCMS: RT = 2.83 min [M+H] 432.57 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).



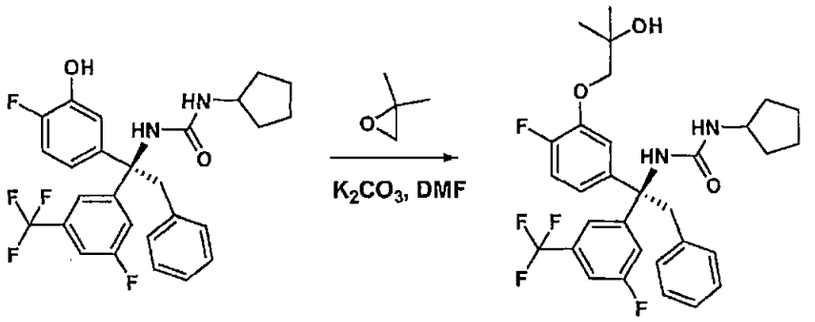

**[00381]** Following Procedure 7, ((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(2-methyl-2H-tetrazol-5-yl)ethanamine (Example 303) was obtained (10 mg, yield 67%). LCMS: RT = 3.86 min [M+H] 622.01 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) ppm 8.30 (m, 2 H), 8.19 (m, 1 H), 7.37(m, 3 H), 7.05 (m, 4 H), 6.92 (d, *J*=8.6 Hz, 1 H), 5.89 (tt, J=53.05, 3.03 Hz, 1 H), 4.26 (s, 3 H), 4.09 (AB, *J*=15.2 Hz, 2 H).

**EXAMPLE 304**



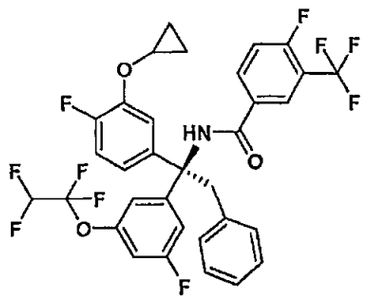

**(R)-1-cyclopentyl-3-(1-(4-fluoro-3-(2-hydroxy-2-methylpropoxy)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea**

**Procedure 105**



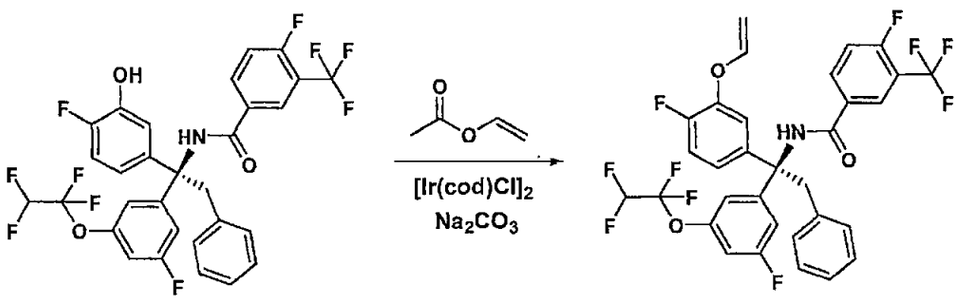

**[00382]** To a solution of (R)-1-cyclopentyl-3-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea, prepared as described in Procedure 59, (20 mg, 0.039 mmol) in DMF (0.1 mL) was added $K_2CO_3$ (12 mg, 0.086 mmol), followed by 2,2-dimethyloxirane (28 mg, 0.39 mmol). The resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered and the solid was washed with EtOAc. The filtrate was washed with $H_2O$, sat. NaCl and dried over $Na_2SO_4$ and filtered. The organic solvent was evaporated under reduced pressure and the residue was purified by Prep HPLC (phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford (R)-1-cyclopentyl-3-(1-(4-fluoro-3-(2-hydroxy-2-methylpropoxy)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea (Example 304) as white lyophillate (11 mg, 56% yield). LCMS: RT = 4.066 min [M+H] 577.3 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm (retention time, column type, size, solvent, flow rate, gradient). NMR: 400MHz $^1H$ ($CD_3OD$) ppm 1.27 (d, *J*=2.20 Hz, 6 H), 1.32 - 1.49 (m, 2 H), 1.54 - 1.76 (m, 4 H), 1.81 - 1.98 (m, 2 H), 3.53 (d, *J*=9.23 Hz, 1 H), 3.69 (d, *J*=9.23 Hz, 1 H), 3.78 (d, *J*=12.74 Hz, 1 H), 3.91 (t, *J*=6.15 Hz, 1 H), 4.02 (d, *J*=12.74 Hz, 1 H), 6.63 - 6.70 (m, 1 H), 6.72 - 6.79 (m, 3 H), 7.01 (dd, *J*=10.99, 8.79 Hz, 1 H), 7.09 - 7.20 (m, 3 H), 7.27 - 7.42 (m, 3 H).

## EXAMPLE 305



**(R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

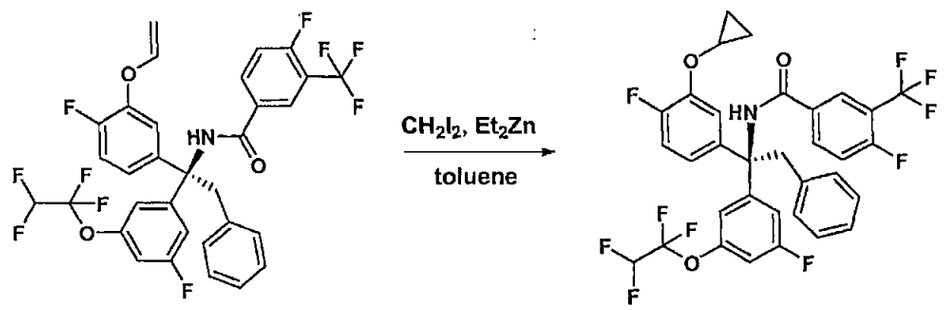
**Procedure 106**




**[00383]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264, 100 mg, 0.158 mmol) in toluene (0.2 ml) was added $Na_2CO_3$ (25 mg, 0.235 mmol) and catalystical amount of $[Ir(cod)Cl]_2$ (2 mg), followed by vinyl acetate (68 mg, 0.79 mmol). The reaction mixture was stirred at 100 °C for 16 h. The resulting mixture was filtered and the solid was washed with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with 1 N NaOH, $H_2O$ and dried over $Na_2SO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column using 0 to 60% EtOAc in hexane to afford (R)-4-fluoro-N-(1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide eluting out at 20% EtOAc in hexane as colorless oil (80 mg, 77%). LCMS: RT = 2.237 min [M+H] 658.3 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm. NMR: 400MHz

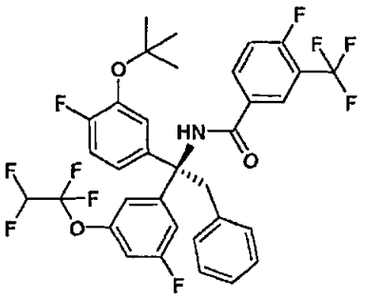
$^1$H ($CD_3OD$) ppm 3.87 (d, *J*=12.74 Hz, 1 H), 4.05 - 4.15 (m, 1 H), 4.35 (dd, *J*=5.93, 1.98 Hz, 1 H), 4.55 (dd, *J*=13.84, 1.98 Hz, 1 H), 6.12 - 6.41 (m, 1 H), 6.48 (dd, *J*=13.62, 6.15 Hz, 1 H), 6.72 (d, *J*=7.03 Hz, 2 H), 6.87 - 7.24 (m, 9 H), 7.37 - 7.51 (m, 1 H), 7.88 - 8.04 (m, 2 H).

**Procedure 107**



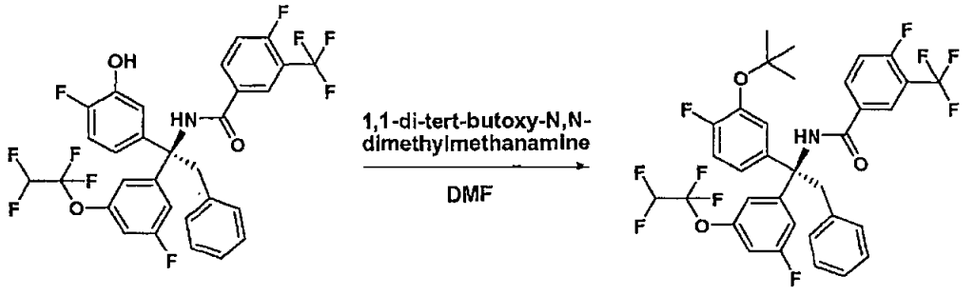

**[00384]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (66 mg, 0.10 mmol) in 0.5 ml toluene was added $Et_2Zn$ (1 N, 0.2 ml, 0.2 mmol), followed by $CH_2I_2$ (16 ml, 0.2 mmol). The reaction mixture was stirred at 120 °C for 3 h. The reaction mixture was quenched by addition of 1 N HCl and the aqueous layer was extracted with $CH_2Cl_2$. The organic layer was washed with sat. $NaHCO_3$ and concentrated under reduced pressure. The resulting residue was purified by ISCO silica gel column using 0 to 50% to EtOAc in hexane as eluting solvents and Prep HPLC (phenomenex AXIA Luna 75X30 mm, 5u column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford (R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 305) as white lyophillate (36 mg, 52% yield). LCMS: RT = 4.268 min [M+H] 672.3 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. NMR: 400MHz $^1$H ($CDCl_3$) ppm 0.45 - 0.73 (m, 4 H), 3.51 - 3.59 (m, 1 H), 3.76 (d, J=13.18 Hz, 1 H), 4.22 (d, J=12.74 Hz, 1 H), 6.13 - 6.44 (m, 1 H), 6.66 - 6.76 (m, 3 H), 6.97 - 7.08 (m, 3 H), 7.10 - 7.23 (m, 5 H), 7.42 - 7.50 (m, 1 H), 7.95 - 8.03 (m, 2 H).

**EXAMPLE 306**



**(R)-N-(1-(3-tert-butoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

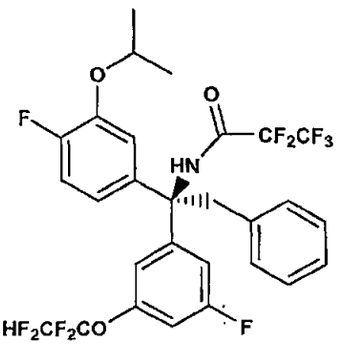
**Procedure 108**




**[00385]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264, 50 mg, 0.079 mmol) in DMF (0.2 mL) was added 1,1-di-tert-butoxy-N,N-dimethylmethanamine (100 μL, 0.49 mmol). The reaction mixture was stirred at 110 °C for 5 h. The reaction mixture was concentrated and purified by prep HPLC (phenomenex AXIA Luna 75 X 30 mm, 5 μ column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford (R)-N-(1-(3-tert-butoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 306) as white lyophillate (46 mg, 81% yield). LCMS: RT = 4.341 min [M+H] 688.2 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. NMR: 400MHz $^1H$ ($CDCl_3$) ppm 1.22 (s, 9 H), 3.89

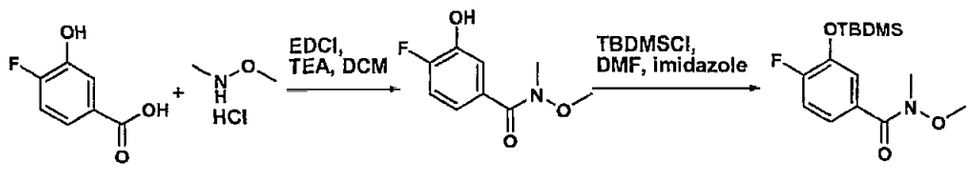
(s, 1 H), 4.06 (d, J=13.19 Hz, 1 H), 6.08 - 6.42 (m, 1 H), 6.73 (d, J=7.15 Hz, 2 H), 6.91 - 7.21 (m, 9 H), 7.39 - 7.44 (m, 1 H), 7.94 - 8.00 (m, 2 H).

**EXAMPLE 307**




**(R)-2,2,3,3,3-pentafluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)**

**Procedure 109**

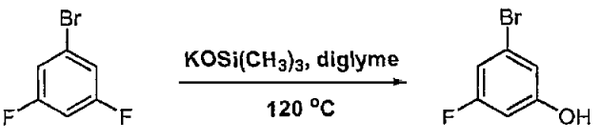



**[00386]** To a solution of 4-fluoro-3-hydroxybenzoic acid (1.49 g, 9.55 mmol) in DCM (40 mL) was added TEA (1.2 mL, 8.61 mmol) followed by N,O-dimethylhydroxylamine hydrochloride (1.12 g, 11.5 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with DCM, washed with water twice, dried over $Na_2SO_4$, filtered and concentrated to yield 4-fluoro-3-hydroxy-N-methoxy-N-methylbenzamide as a colorless oil (1.90 g, 100% yield). LCMS: RT = 0.89 min [M+H] 200.10 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

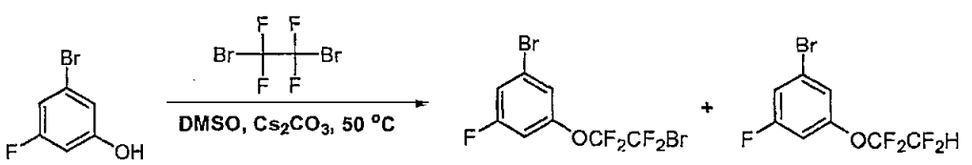
**[00387]** To a solution of 4-fluoro-3-hydroxy-N-methoxy-N-methylbenzamide (1.90 g, 9.55 mmol) in DMF (8 mL) was added imidazole (740 mg, 10.8 mmol) and TBDMSCl (1.62 g, 10.8 mmol) at room temperature. The reaction mixture was stirred for 48 h and quenched with saturated $NaHCO_3$. The solution was extracted

with ether (3 x) and the combined ether portions washed with LiCl (10%), dried over $Na_2SO_4$, filtered and concentrated. The resulted colorless oil was purified by ISCO chromatography (120 g column) using hexanes/EtOAc (0-100% over 30 min) to give 3-(tert-butyldimethylsilyloxy)-4-fluoro-N-methoxy-N-methylbenzamide (RT = 10-12 minutes) as a colorless oil (2.00 g, 67% yield). LCMS: RT = 2.06 min [M+H] 314.22 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) 7.26 ppm, 2 H, m; 7.02 ppm, 1 H, m; 3.50 ppm, 3 H, s; 3.31 ppm, 3 H, s; 0.97 ppm, 9 H, s, 0.16 ppm, 6H, s.

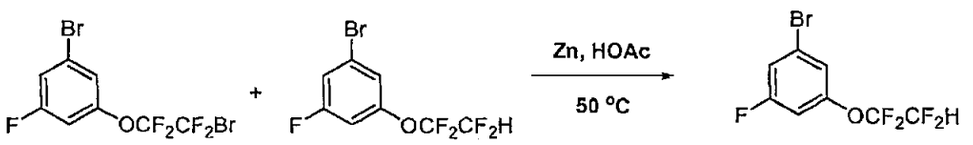
**Procedure 110**




**[00388]** To a $N_2$ flushed, 2 L four necked flask equipped with a mechanical stirrer, a condenser, temperature controller and a $N_2$ inlet, was added potassium trimethylsilanolate (225.0 g, 1.75 mol, tech. purify 90%), 1-bromo-3,5-difluorobenzene (96.5 g, 0.5 mol) and diglyme (300 mL). The reaction mixture was heated to 120 °C under $N_2$ for 5 h. After cooling to rt, the heating mantle was replaced with an ice bath. The reaction mixture was acidified with 3 N HCl solution (600 mL) below 30 °C. TBME (1 L) was added and the resulting mixture was stirred below 20 °C for 30 min then transferred to a 5 L separatory funnel. The organic layer was separated and washed with water (3 X 500 mL), sat. NaCl (500 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude reddish product (145.0 g). The crude material was then distillated at 52 – 55 °C / 0.1 mm Hg to yield 3-bromo-5-fluorophenol as a slightly yellow oil (88.0 g, 92% yield). $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.34 (s, H), 6.47-6.52 (m, 1H), 6.77-6.83 (m, 2 H).

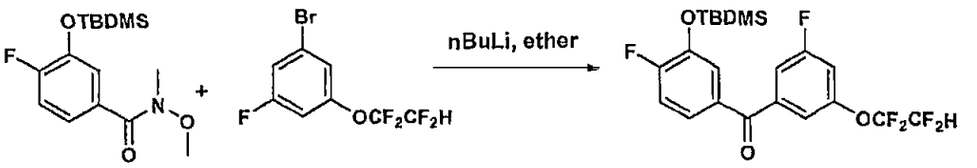


**[00389]** To a flame dried, 1 L, three necked round bottom flask (1 L) equipped with a temperature controller, a mechanical stirrer, a condenser and a $N_2$ inlet was charged 3-bromo-5-fluorophenol (57.3 g, 300 mmol), 1,2-dibromotetrafluoroethane (156.0 g, 600 mmol), dry DMSO (300 mL) and $Cs_2CO_3$ (146.6 g, 450 mmol) under $N_2$. The reaction mixture was heated to 50 °C for 5 h. After cooling to rt, water (300 mL) and hexane (300 mL) were added. The resulting mixture was stirred at rt for 30 min. The organic phase was separated and the aqueous layer was extracted with hexane (300 mL). The combined organic extracts were washed with water (500 mL), sat. NaCl (500 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give 1-bromo-3-(2-bromo-1,1,2,2-tetrafluoroethoxy)-5-fluorobenzene (104.2 g, 94% yield) containing 5% of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (5.2 g). 1-Bromo-3-(2-bromo-1,1,2,2-tetrafluoroethoxy)-5-fluorobenzene: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.91-6.94 (m, 1H), 7.18-7.23 (m, 2 H).

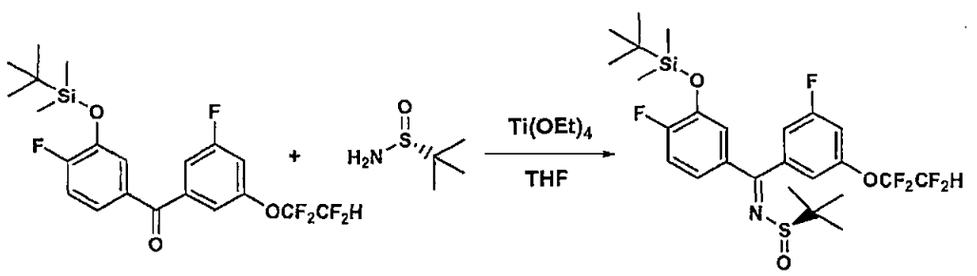



**[00390]** To a 1 L four necked round bottom flask equipped with a temperature controller, a mechanical stirrer, and a $N_2$ inlet, was added 1-bromo-3-(2-bromo-1,1,2,2,-tetrafluoro-ethoxy)-5-fluorobenzene (104.0 g, 281 mmol) and 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (5.2 g, 18 mmol), acetic acid (300 mL). The reaction mixture was then heated to 50 °C. Zinc dust (91.9 g, 1.405 mol) was added portion wise. The reaction mixture was stirred at 50 °C for 1 h and allowed to cool to rt. Water (300 mL) and hexane (300 mL) were added. The resulting mixture was stirred at rt for 30 min. The organic phase was separated and the aqueous layer was extracted with hexane (2 x 300 mL). The combined organic extracts were washed with water (500 mL), sat. NaCl (500 mL), dried over MgSO4, filtered and concentrated in vacuo to yield 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene as a slightly yellow liquid (71 g, 87% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 5.87 (tt, J = 52.7 and 2.9 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 7.16-7.18 (m, 2 H).

**Procedure 111**



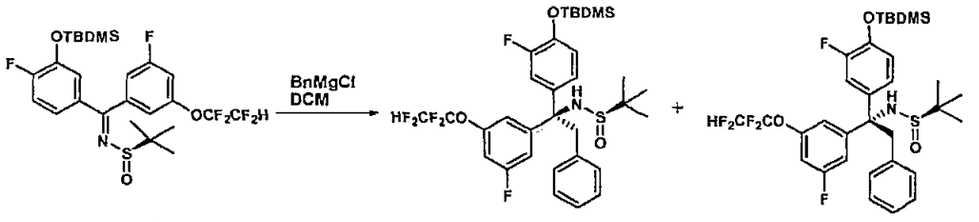

**[00391]** At -78 °C under argon, to a solution of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (2.04 g, 7.01 mmol) in anhydrous ether (20 mL) was added nBuLi (3.5 mL, 2.0 M in cyclohexane, 7.0 mmol) dropwise and the reaction mixture was stirred for 1 h. 3-(Tert-butyldimethylsilyloxy)-4-fluoro-N-methoxy-N-methylbenzamide (2.00 g, 6.38 mmol) was added in one portion and the reaction mixture was stirred at -78 °C for 1.5 h. The pale yellow solution was poured into 1 N HCl aqueous solution (30 mL) and ether (30 mL) was used to rinse the reaction flask. The aqueous phase was separated and extracted with ether (20 mL). The combined ether portions were dried over $Na_2SO_4$, filtered and concentrated. The resulting oil was purified by ISCO chromatography (120 g column) using hexanes/EtOAc (0-100% over 30 min) to give (3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone at a retention time of 7 min (2.11 g, 71% yield). LCMS: RT = 2.41 min [M+H] 465.19 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) 7.33 ppm, 3 H, m; 7.28 ppm, 1 H, m; 7.11 ppm, 2 H, m; 5.86 ppm, 1 H, t, J=53.39 Hz; 0.95 ppm, 9 H, s; 0.15 ppm, 6 H, s.




**[00392]** A round bottom flask was charged with (3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone (2.09 g, 4.50 mmol), (R)-2-methylpropane-2-sulfinamide (653 mg, 5.4 mmol), $Ti(OEt)_4$ (1.54 g,

6.76 mmol) and anhydrous THF (40 mL). The resulting solution was heated at 75 °C under argon for 14 h. The solvents were removed and the residue was diluted with ether (50 mL) and sat. NaCl (20 mL). The resulting mixture was filtered through a glass frit and the filtrate transferred to a separatory funnel. The organic portion was separated and the aqueous extracted with ether (2 x 20 mL). The combined organic portions were dried over $Na_2SO_4$, filtered and concentrated. The residue was dissolved in hexane:EtOAc and purified by ISCO chromatography (2 × 120 g column) using hexanes/EtOAc (0-100% over 30 min) to yield (R)-N-((3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide at a retention time of 14 min (2.05 g, 80% yield) LCMS: RT = 2.37 min [M+H] 568.24 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). NMR: 400MHz $^1H$ ($CDCl_3$) 7.36 ppm, 1 H, m; 7.11 ppm, 5 H, m; 5.90 ppm, 1 H, t, *J*=52.73 Hz; 0.97 ppm, 9 H, s; 0.18 ppm, 6 H, s.

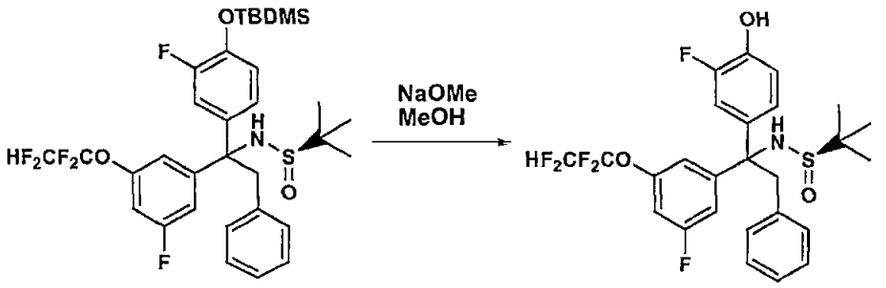
**Procedure 112**




**[00393]** At -78 °C to a solution of (R)-N-((3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (1.0 g, 1.76 mmol) in DCM (50 mL) was added $BF_3{\cdot}Et_2O$ (0.77 mL, 3.52 mmol) via syringe. After 5 min, BnMgCl solution (3.5 mL, 1.0 M solution in ether, 3.5 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. An additional portion of BnMgCl (3.5 mL, 1.0 M solution in ether, 3.5 mmol) was added dropwise and the reaction was stirred for an additional 1 h at -78 °C. The reaction mixture was poured into saturated NaCl (50 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and

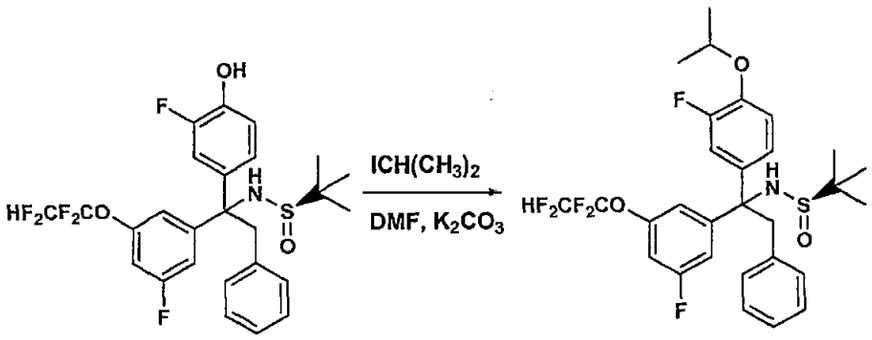
concentrated. The resulting oil was purified by ISCO chromatography (120 g column) using hexanes/EtOAc (0-100% over 30 min) to give an approximate 4:1 mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide and (S)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide at a retention time of 12 min (824 mg, 71% yield) LCMS: RT = 2.43 min [M+H] 660.39 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). The diastereomeric ratio of the product was determined to be 4:1 by Chiral HPLC analysis (Chiralcel® AD, 90:10 heptane :*i*-PrOH, 1 mL / min, 254 nm, RT (minor)= 4.43 min, PA=17%; RT (major) = 19.28 min, PA=71%) and the diastereomeric mixture was taken on directly to the next step, Procedure 112, or the diastereomers were separated as described in Procedure 114. NMR: 400MHz $^1H$ ($CDCl_3$) 7.30 ppm, 2 H, m; 7.06 ppm, 5 H, m; 6.85 ppm, 2 H, m; 6.76 ppm, 1 H, m; 6.62 ppm, 2 H, m; 5.79 ppm, 1 H, m; 4.13 ppm, 1H, s; 3.84 ppm, 1 H, m; 3.47 ppm, 1 H, m; 1.12 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6 H, d, *J*=4.39 Hz.

**Procedure 113**

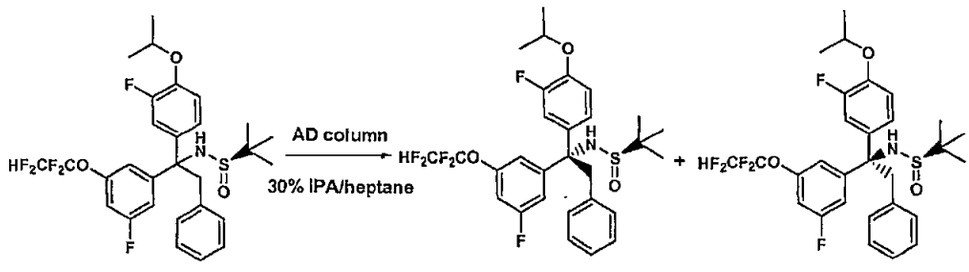



**[00394]** At room temperature a solution of NaOMe (5 mL, 0.5 M solution in MeOH) was added to the 4:1 diastereomeric mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (801 mg, 1.22 mmol). The reaction mixture was stirred for 15 minutes, MeOH was removed then the residue dissolved in EtOAc (50 mL) and transferred to a separation funnel. HCl (20 mL, 1.0 N solution) was added and the EtOAc layer was separated. The

aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to yield (R)-N-(1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a white foam (578 mg, 87% yield). LCMS: RT = 1.987 min [M+H] 546.35 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).



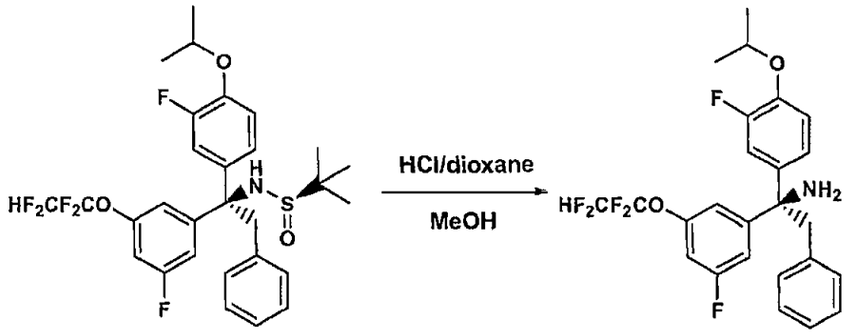

**[00395]** At rt to a solution of (R)-N-(1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (578 mg, 1.06 mmol) in DMF (10 mL) was added $K_2CO_3$ (800 mg, 5.80 mmol) and the slurry was stirred vigorously. 2-Iodopropane (220 mg, 1.27 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with ether (50 mL), washed successively with 10% LiCl (2 × 20 mL) and water (20 mL). The organic portion was dried over $Na_2SO_4$, filtered and concentrated to yield (R)-N-(1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a pale orange foam (780 mg, 100% yield).



**[00396]** The diastereomeric mixture of (R)-N-(1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (780 mg, 1.06 mmol crude) was separated by Chiral preparative HPLC chiralpak AD 20μ column, 5 × 50 cm, eluting with 30% IPA/Heptane with flow rate 50 mL/min.

**[00397]** (R)-N-((S)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 17 min and isolated as a colorless oil (101 mg, yield 16%). LCMS: RT = 2.128 min [M+H] 588.38 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); Chiral HPLC: RT = 4.35 min, ee 100% (Diacel Chiralpak AD 10μ column, 4.6 × 250 mm isocratic elution with IPA (20%) and heptane; 1 mL/min, monitoring at 254 nm).

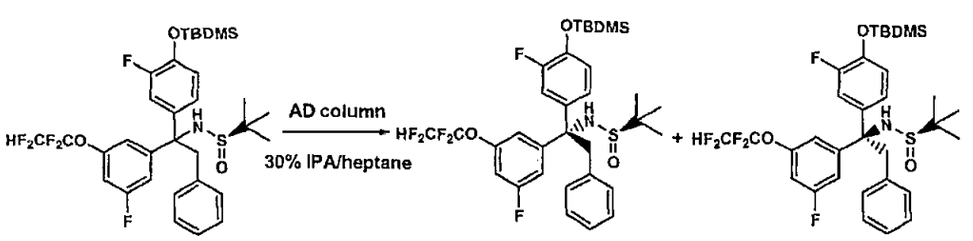
**[00398]** (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 39 min and isolated and was isolated as a colorless oil (398 mg, yield 64%). LCMS: RT = 2.138 min [M+H] 588.38 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); Chiral HPLC: RT = 9.98 min, ee 100% (Diacel Chiralpak AD 10 μ column, 4.6 × 250 mm isocratic elution with IPA (20%) and heptane; 1 mL/min, monitoring at 254 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.08 ppm, 5 H, m; 6.84 ppm, 2 H, d, *J*=7.47 Hz; 6.77 ppm, 2 H, d, *J*=7.47 Hz; 6.63 ppm, 2 H, m; 5.79 ppm, 1 H, t, *J*=52.95 Hz; 4.33 ppm, 1 H, m; 4.15 ppm, 1 H, s; 3.92 ppm, 1 H, d, *J*=12.30 Hz; 3.48 ppm, 1 H, d, *J*=12.30 Hz; 1.22 ppm, 3 H, d, *J*=6.15 Hz; 1.18 ppm, 3 H, d, *J*=5.71 Hz; 1.14 ppm, 9 H, s.




**[00399]** To a solution of (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (398 mg, 0.678 mmol) in MeOH (1.5 mL) was added HCl (1.5 mL, 4 M solution in dioxane) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with ether (50 mL) and the organic layer was washed with sat. $NaHCO_3$ (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine as a colorless oil (334 mg, 100% yield). LCMS: RT = 1.76 min [M-$NH_2$] 467.24 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.04 min, Purity 95% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.15 ppm, 3 H, m; 6.99 ppm, 4 H, m; 6.89 ppm, 1 H, m; 6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=6.15 Hz; 5.87 ppm, 1 H, m; 4.42 ppm, 1 H, m; 3.47 ppm, 2 H, s; 1.27 ppm, 6 H, dd, *J*=7.91,6.15 Hz.

**[00400]** An alternative route used to prepare (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine was as follows:

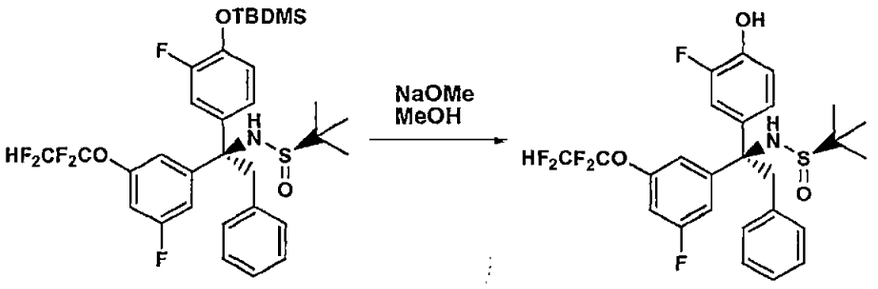
**Procedure 114**



**[00401]** The diastereomer mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (1.14 g, 1.73 mmol) was separated by Chiral preparative HPLC chiralpak AD 20μ column, 5 × 50 cm, eluting with 30% IPA/Heptane with flow rate 50 mL/min.

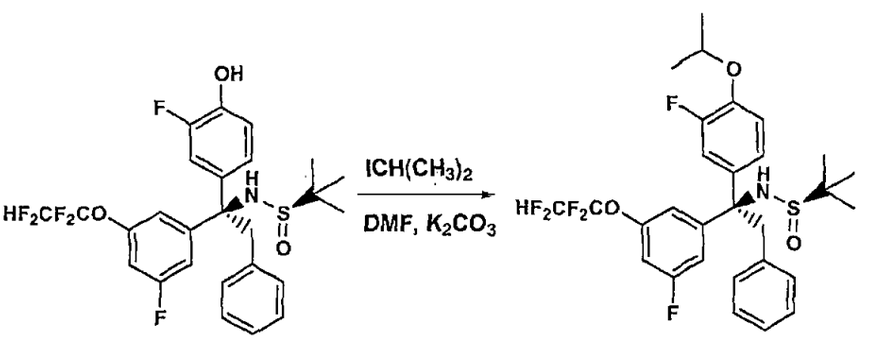
**[00402]** (R)-N-((S)-1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 19 min (114 mg, yield 10%). LCMS: RT = 2.45 min [M+H] 660.41 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**[00403]** (R)-N-((R)-1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 36 min (634 mg, yield 56%). LCMS: RT = 2.41 min [M+H] 660.39 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); Chiral HPLC: RT = 8.54 min, ee 100% (Diacel Chiralpak AD 10μ column, 4.6 × 250 mm isocratic elution with IPA (20%) and heptane; 1 mL/min, monitoring at 254 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.03 ppm, 5 H, m; 6.84 ppm, 2 H, m; 6.74 ppm, 1 H, d, *J*=8.79 Hz; 6.66 ppm, 1 H, dd, *J*=8.13, 1.98 Hz; 6.61 ppm, 2 H, m; 5.76 ppm, 1 H, m; 4.12 ppm, 1 H, s; 3.90 ppm, 1 H, d, *J*=12.74 Hz; 3.46 ppm, 1 H, d, *J*=12.30 Hz; 1.11 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6 H, d, *J*=4.83 Hz.

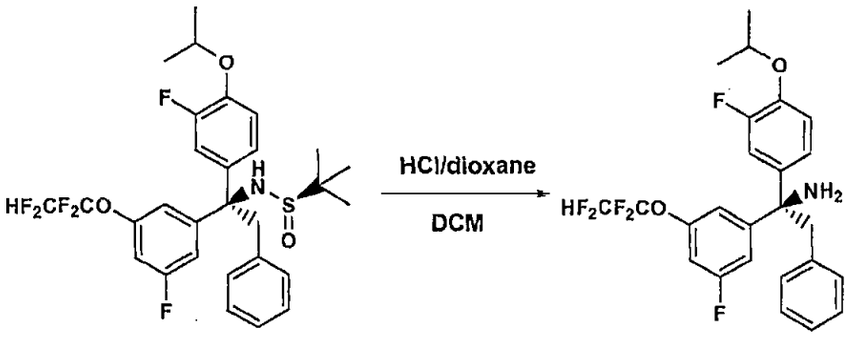



**[00404]** (R)-N-((R)-1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was prepared from (R)-N-((R)-1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-

sulfinamide as described in Procedure 112 in quantitative yield. LCMS: RT = 1.998 min [M+H] 546.28 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). HPLC: RT = 3.83 min, Purity 98% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.61 ppm, 1 H, s; 7.40 ppm, 1 H, dd, *J*=8.13, 1.98 Hz; 7.13 ppm, 3 H, m; 6.99 ppm, 1 H, dd, *J*=10.33, 8.57 Hz; 6.84 ppm, 3 H, m; 6.68 ppm, 2 H, m; 6.61 ppm, 1 H, m; 5.85 ppm, 1 H, tt, *J*=52.95, 2.64 Hz; 4.30 ppm, 1 H, s; 4.02 ppm, 1 H, d, *J*=12.30 Hz; 3.50 ppm, 1 H, d, *J*=12.30 Hz; 1.24 ppm, 9 H, s.

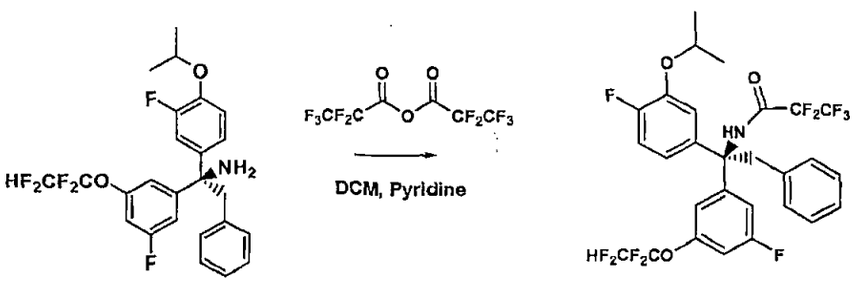



**[00405]** (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was prepared from (R)-N-(1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as described in Procedure 6 in 78% yield. LCMS: RT = 2.17 min [M+H] 588.17 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm) HPLC: RT = 4.20 min, Purity 95% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.10 ppm, 2 H, m; 6.87 ppm, 4 H, m; 6.70 ppm, 2 H, m; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 4.31 ppm, 1 H, s; 3.98 ppm, 1 H, d, *J*=12.74 Hz; 3.56 ppm, 1 H, d, *J*=12.74 Hz; 1.30 ppm, 3 H, d, *J*=5.71 Hz; 1.25 ppm, 3 H, d, *J*=6.15 Hz; 1.22 ppm, 9 H, s.




**[00406]** (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine was prepared from (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as described in Procedure 6 in 97% yield. LCMS: RT = 1.83 min [M-$NH_2$] 467.24 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.17 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.01 ppm, 3 H, m; 6.92 ppm, 2 H, m; 6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=7.03 Hz; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 3.49 ppm, 2 H, s; 1.25 ppm, 6 H, m.

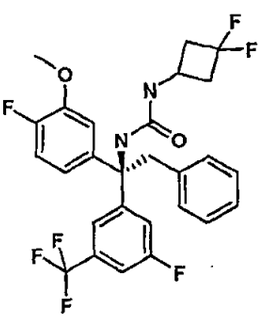
**Procedure 115**




**[00407]** At rt, to a solution of (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine (25 mg, 0.05 mmol) in anhydrous DCM (0.5 mL) was added pyridine (1 drop) and 2,2,3,3,3-pentafluoropropanoic anhydride (19 mg, 0.08 mmol). The resulting solution was stirred for 5 min, diluted with MeOH (0.5 mL) and purified by preparative HPLC

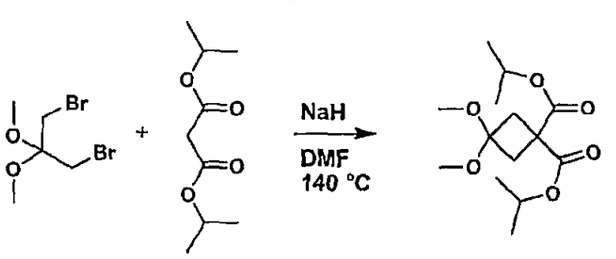
(YMC Sunfire 30 x 100 mm column, eluting with 10-90% MeOH/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm). (R)-2,2,3,3,3-pentafluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)propanamide (Example 307) was isolated as a colorless oil (7 mg, 21% yield) at a retention time of 11.84 min. LCMS: RT = 2.19 min [M+H] 630.32 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.21 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1$H ($CDCl_3$) 7.25 ppm, 3 H, m; 7.03 ppm, 1 H, t, J = 8.0 Hz; 6.86 – 6.97 ppm, 4 H, m; 6.66 ppm, 2 H, d, *J*=8.0 Hz; 6.58 ppm, 2 H, d, *J*=8.0 Hz; 5.87 ppm, 1 H, d, J = 57.8 Hz; 4.32 ppm, 1 H, sept, *J*=8.0 Hz; 3.93 ppm, 1 H, d, *J*=12.0 Hz; 3.68 ppm, 1 H, d, *J*=12.0 Hz; 1.28 ppm, 3 H, d, *J*=8.0 Hz; 1.22 ppm, 3 H, d, *J*=8.0 Hz.

**EXAMPLE 308**



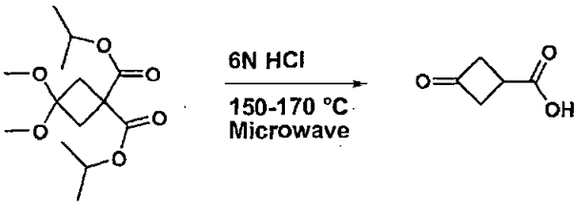
**(R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea**

**Procedure 116**



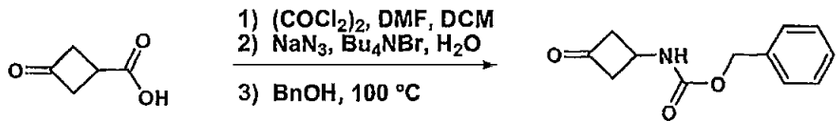
**[00408]** To a suspension of sodium hydride (60% in mineral oil, 3.7 g, 92 mmol) in dry DMF (32 mL) under nitrogen was added dropwise diisopropyl malonate (16 mL, 84 mmol) and the temperature was maintained below 0 °C. On cessation of hydrogen evolution, 1,3-dibromo-2,2-dimethoxypropane (11.0 g, 42 mmol) was added at rt and the reaction mixture was heated at 140 °C for 24 h. The cooled mixture was poured into saturated ammonium chloride (100 mL) and extracted with hexane (3 x 75 mL). The combined organic extracts were washed with water (100 mL), sat. $NaHCO_3$ (50 mL), dried over magnesium sulfate and the solvent was evaporated to give 17.42 g of pale yellow oil. Distillation of the residue through Vigreux column with an air condenser and further purification by an Analogix silica column (12 g, 20% ethyl acetate in hexane) afforded diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (6.2 g, 51 % yield). LCMS: RT = 3.26 min, No parent ion (Phenominex, Luna C18, 4.6 X 50 mm, 4 min gradient from 10% methanol, 90% water, 0.1% TFA to 90% methanol, 10% water, 0.1% TFA); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 5.06 (2 H, dq), 3.15 (6 H, s), 2.69 (4 H, s), 1.24 (12 H, d, *J*=6.0 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 170.34 (2 C, s), 98.50, 69.03 (2 C, s), 48.59 (2 C, s), 45.01, 39.63 (2 C, s), 21.47 (4 C, s).

**Procedure 117**



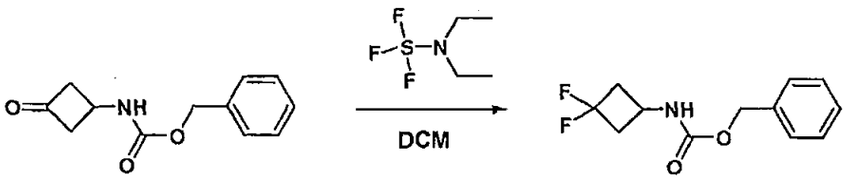

**[00409]** A solution of diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (2.2 g, 7.63 mmol) in HCl (6 N, 6 mL) was heated at 155-160 °C under microwave irradiation for 60 min. The reaction mixture was diluted with ether (150 mL) and vigorously stirred over the weekend. The ether layer was dried with $MgSO_4$, filtered and concentrated to give 3-oxocyclobutanecarboxylic acid (1.0 g, 118 % yield) as a brown solid. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 10.80 (1 H, br. s.), 3.43 - 3.51 (2 H, m), 3.26 - 3.40 (3 H, m); $^{13}$C NMR (126 MHz, CDCl3) δ ppm 203.14, 180.17, 51.64 (2 C, s), 27.32 (1 C, s).

**Procedure 118**



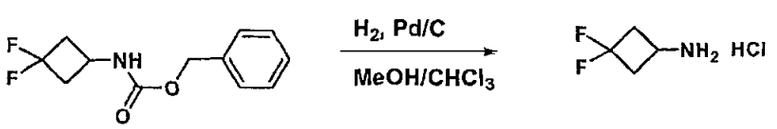

[00410] To a solution of 3-oxocyclobutanecarboxylic acid (3.34 g, 29.2 mmol) in dichloromethane (29 mL) at 0 °C was added oxalyl chloride (19.0 mL, 38.0 mmol) followed by DMF (0.057 mL, 0.731 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane (15 mL). At 0 °C, to the resulting solution was added sodium azide (3.23 g, 49.7 mmol) in water (7 mL) followed by tetrabutylammonium bromide. The reaction mixture was vigorously stirred for 2 h. The aqueous phase was separated and extracted with dichloromethane (2 x 40 mL). The combined organic portions were dried over $MgSO_4$, filtered rapidly and benzyl alcohol (30.4 ml, 292 mmol) was added and the solvent volume was reduced under reduced pressure. The reaction mixture was heated at 95 °C for 1 h. Benzyl alcohol was removed under reduced pressure and the residue oil was purified by ISCO flash chromatography (80 g column, hexane/ethyl acetate) to give benzyl 3-oxocyclobutylcarbamate as a pale yellow solid (693 mg, 11% yield). HPLC: RT = 1.16 min, 90% pure (Phenomenex, Onyx C18, 4.6 X 100 mm, 2 min gradient from 10% MeCN, 90% water, 0.1% TFA to 90% MeCN, 10% water, 0.1% TFA); LCMS: RT = 2.37 min, 75% purity, [M+H] 220.1 (Phenominex, Luna C18, 4.6 X 50 mm, 4 min gradient from 10% methanol, 90% water, 0.1% TFA to 90% methanol, 10% water, 0.1% TFA); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 - 7.38 (5 H, m), 5.27 (1 H, d, *J*=3.3 Hz), 5.12 (2 H, s), 4.33 (1 H, d, *J*=5.5 Hz), 3.40 (2 H, dd, *J*=13.2, 6.6 Hz), 3.08 (2 H, d, *J*=14.3 Hz). $^{13}$C NMR (101 MHz, $CDCl_3$) δ ppm 204.50, 155.87, 136.06, 128.56 (2 C, s), 128.28, 128.13 (2 C, s), 66.97, 54.59 (2 C, s), 37.08.

**Procedure 119**



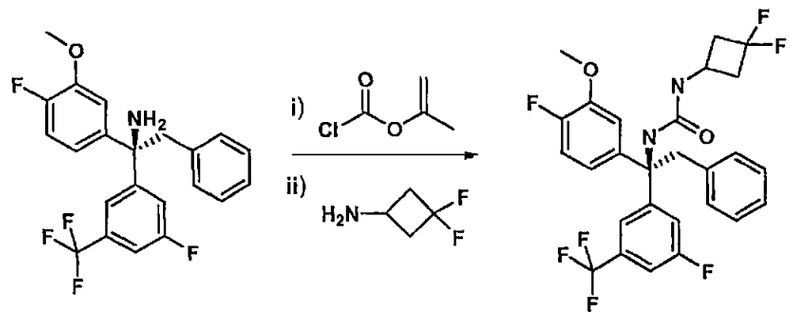

**[00411]** To a solution of benzyl 3-ocyclobutylcarbamate (2.58 g, 11.77 mmol) in dichloromethane (23.5 mL) at 0 °C to -5 °C was added dropwise DAST (4.66 mL, 35.3 mmol). The reaction mixture was stirred for 4.5 h at room temperature, then diluted with sat. NaCl at 0 °C and the aqueous layers were extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over MgSO4, filtered and concentrated. The resulting oil was purified by ISCO flash chromatography (120 g column, hexanes to ethyl acetate) to yield benzyl 3,3-difluorocyclobutylcarbamate (1.7 g, yield 60%). LCMS: RT = 2.95 min [M+H] 242.1 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 7.30 - 7.41 (5 H, m), 5.10 (2 H, br. s.), 4.99 (1 H, br. s.), 4.04 - 4.16 (1 H, m), 2.90 - 3.04 (2 H, m), 2.42 - 2.56 (2 H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 155.52, 136.07, 128.58 (2 C, s), 128.30, 128.18 (2 C, s), 66.97, 42.72 - 43.57 (1 C, m), 35.71 - 36.66 (2 C, m), the triplet for the difluorocarbon signal did not rise above baseline; $^{19}$F NMR (471 MHz, CDCl3) δ ppm -84.90 (1 F, d, *J*=195.8 Hz), -97.62 (1 F, d, *J*=201.5 Hz).

**Procedure 120**



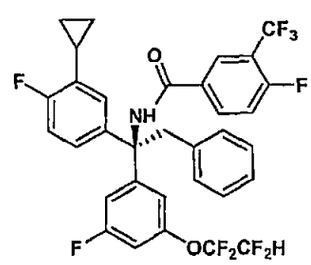

**[00412]** To a solution of benzyl 3,3-difluorocyclobutylcarbamate (1.86 g, 7.71 mmol) in methanol (49 mL) and chloroform (2 mL) was added 10% palladium on carbon (0.41 g, 0.39 mmol) and the slurry was subjected to balloon hydrogenation overnight. The reaction mixture was filtered, washed with methanol and HCl (1.0 M) in ether (1 mL) and the filtrate concentrated. The residue was triturated with ether, filtered, washed with ether and dried to give 3,3-difluorocyclobutanamine

hydrochloride as a pale yellow solid (1.01 g, 92 % yield). $^1$H NMR (400 MHz, DMSO-D6) δ ppm 8.48 (m, 3 H), 3.60 - 3.69 (m, 1 H), 2.72 - 3.02 (m, 4 H); $^{19}$F NMR (376 MHz, DMSO-D6) δ ppm -81.57 (1 F, d, *J*=189.6 Hz), -97.13 (1 F, ddd, *J*=198.8 Hz, 18.5 Hz).



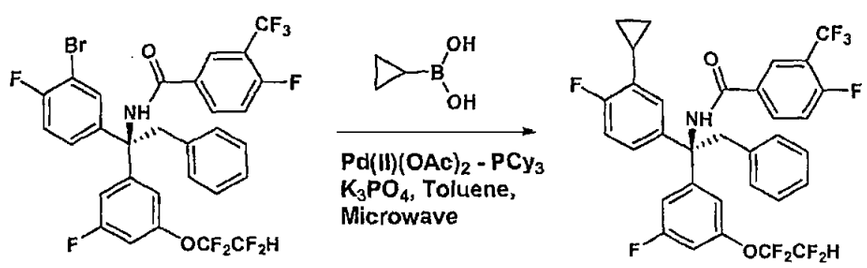

**[00413]** (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea (Example 308) was prepared as described in Procedure 10. LCMS: RT = 2.003 min [M+H] 639 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). HPLC: RT = 4.10 min, 100 % purity (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, Solvent) δ ppm 2.33 - 2.44 (m, 2 H), 2.86 - 2.97 (m, *J*=15.25, 7.83, 7.70, 3.30 Hz, 2 H), 3.63 - 3.72 (m, 3 H), 3.74 - 3.85 (m, 1 H), 3.93 - 4.03 (m, 1 H), 4.09 (d, *J*=7.15 Hz, 1 H), 6.62 - 6.69 (m, 1 H), 6.70 - 6.78 (m, 3 H), 7.00 (ddd, *J*=11.13, 8.11, 3.30 Hz, 1 H), 7.10 - 7.21 (m, 3 H), 7.29 - 7.40 (m, 3 H).

**EXAMPLE 309**



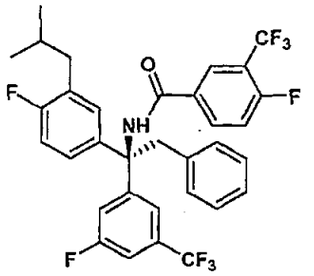

**(R)-N-(1-(3-cyclopropyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

**Procedure 121**



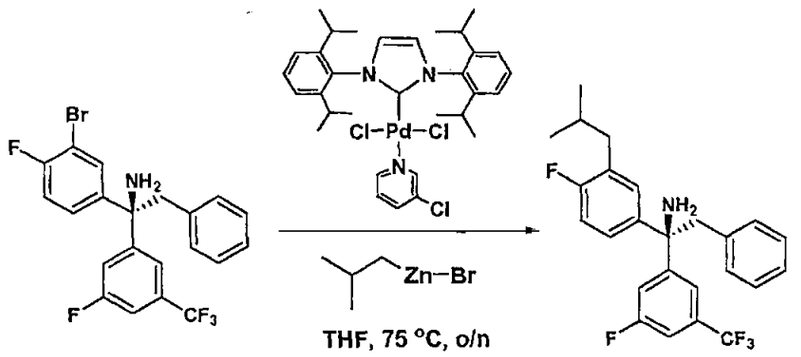

**[00414]** To a mixture of (S)-N-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide, prepared as described in Procedures 3, 62, 5, 6 and 7, (50 mg, 0.07 mmol), (50 mg, 0.07 mmol), cyclopropylboronic acid (6 mg, 0.07 mmol), palladium (II) acetate (1 mg, 0.004 mmol) and tricyclohexylphosphine (2 mg, 0.007 mmol) in toluene (2 mL) was added $K_3PO_4$ (0.072 mL, 0.22 mmol). The reaction mixture was heated at 100 °C under microwave irradiation for 15 min. The reaction mixture was filtered, concentrated and the resulting residue was purified by preparative HPLC (Sunfire-S5-C18 18 x 50mm column, eluting with 10-90% MeOH/$H_2O$ gradient over 8 min, with flow rate 20 mL/min and UV detection at 220 nm) to yield (R)-N-(1-(3-cyclopropyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 309, 14 mg, 30 % yield). LCMS: RT = 4.37 min [M+H] 656.38 (Waters Sunfire-S5-C18 4.6 x 50mm, eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 7.90 (1 H, dd, *J*=6.60, 1.92 Hz), 7.81 - 7.84 (1 H, m), 7.22 - 7.30 (5 H, m), 7.16 (2 H, t, *J*=7.56 Hz), 6.93 - 7.00 (4 H, m), 6.77 - 6.81 (1 H, m), 6.68 (2 H, d, *J*=7.42 Hz), 6.62 (1 H, s), 6.54 (1 H, dd, *J*=6.87, 2.47 Hz), 5.88 (1 H, t, *J*=52.73 Hz), 4.08 (1 H, d, *J*=13.20 Hz), 3.66 (1 H, d, *J*=13.20 Hz), 2.03 (1 H, ddd, *J*=13.75, 8.52, 5.22 Hz), 0.92 - 0.96 (2 H, m), 0.52 - 0.56 (1 H, m), 0.43 - 0.47 (1 H, m).

## EXAMPLE 310

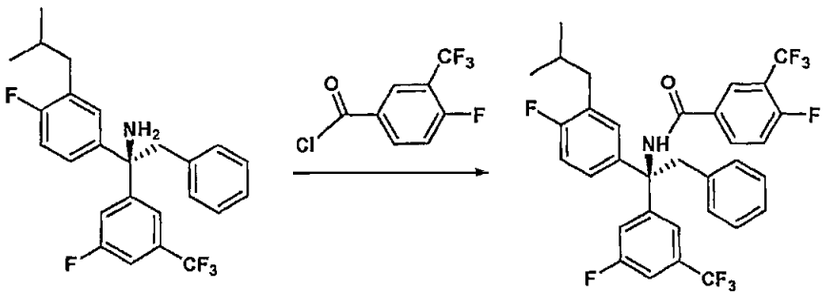


**(R)-4-fluoro-N-(1-(4-fluoro-3-isobutylphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

**Procedure 122**

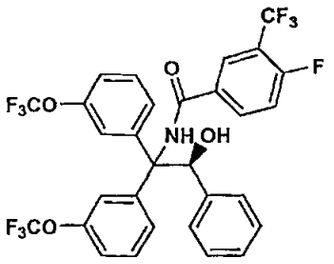



**[00415]** To a solution of [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (8 mg, 0.01 mmol) in NMP (0.5 mL) was added isobutylzinc(II) bromide in THF (0.5 M, 0.7 mL, 0.35 mmol) followed by (S)-1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethanamine, prepared as described Procedure 62, 5 and 6, (50 mg, 0.11 mmol) in anhydrous THF. The reaction mixture was heated at 75 °C overnight. The reaction mixture was diluted with EtOAc and the organic layer was washed with sat. $NH_4Cl$, dried over $Na_2SO_4$ and concentrated to yield (R)-1-(4-fluoro-3-isobutylphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethanamine. LCMS: RT = 3.62 min [M-$NH_2$] 417 (Waters Sunfire-S5-C18 4.6 x 50mm, eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).



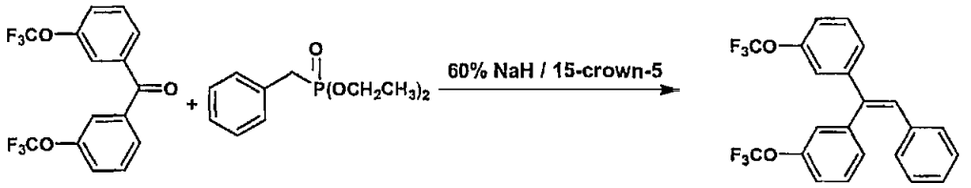
**[00416]** Following Procedure 7, (R)-4-fluoro-N-(1-(4-fluoro-3-isobutylphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 310) was prepared (13 mg, 18% yield). LCMS: RT = 4.68 min [M+H] 624.33 (Waters Sunfire-S5-C18 4.6 x 50mm, eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 7.89 (1 H, dd, *J*=6.46, 2.06 Hz), 7.82 (1 H, ddd, *J*=8.45, 4.61, 2.34 Hz), 7.37 (1 H, s), 7.22 - 7.30 (6 H, m), 7.16 (2 H, t, *J*=7.56 Hz), 6.98 (1 H, t, *J*=8.80 Hz), 6.87 - 6.90 (1 H, m), 6.83 (1 H, dd, *J*=6.74, 2.61 Hz), 6.71 (1 H, s), 6.69 (2 H, d, *J*=7.15 Hz), 4.07 (1 H, d, *J*=12.92 Hz), 3.78 (1 H, d, *J*=13.20 Hz), 2.47 - 2.52 (1 H, m), 2.40 - 2.45 (1 H, m), 1.80 (1 H, dt, *J*=13.54, 6.84 Hz), 0.85 (6 H, dd, *J*=9.62, 6.60 Hz).

**EXAMPLE 311**



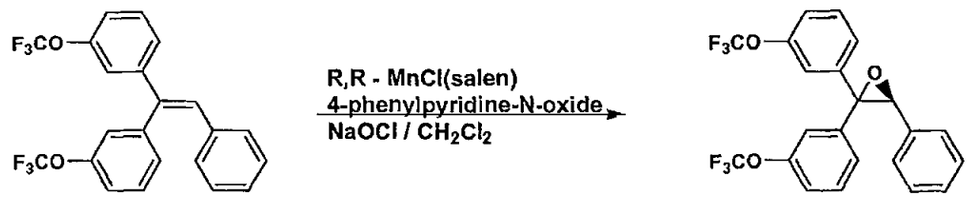
**(S)-4-fluoro-N-(2-hydroxy-2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(trifluoromethyl)benzamide**

**Procedure 123**




**[00417]** To a suspension of NaH (60% in oil, 0.24 g, 6 mmol) in dry THF (25 mL) under nitrogen was added 15-crown-5 (0.06 g). The suspension was cooled in an ice bath. Bis(3-(trifluoromethoxy)phenyl)methanone (2.10 g, 6 mmol ) and diethyl benzylphosphonate ( 1.37 g, 6 mmol ) were dissolved in THF (12 mL) and added to the suspension. The reaction mixture was stirred at ice bath temperature for 15 min, allowed to warm to rt and stirred overnight. The reaction mixture was poured into water and extracted with ether (2 x). The combined ether layers were washed with 10% $NaHSO_3$, sat. NaCl, dried over $K_2CO_3$, filtered and purified by ISCO using a gradient of 0-4% EtOAc / hexanes as eluent to give 3,3'- (2-phenylethene-1,1-diyl)bis((trifluoromethoxy)benzene) as a colorless oil (1.34 g, 53% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 (m, 2 H), 7.2 – 7.1 (m, 8 H), 7.04 ( s, 1 H), 7.0 – 6.97 (m, 3 H).

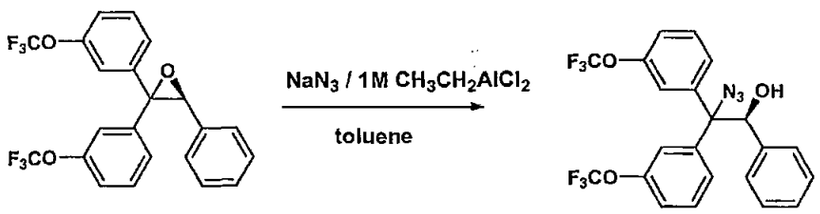
**Procedure 124**




**[00418]** A mixture of 3,3'- (2-phenylethene-1,1-diyl)bis((trifluoromethoxy)benzene) (1.30 g, 3.06 mmol), R,R-MnCl (salen) (0.40 g, 0.64 mmol), 4-phenylpyridine-N-oxide (0.22 g, 1.27 mmol) in $CH_2Cl_2$ (30 mL) was cooled in an ice bath. A cold bleach (6.2% NaOCl in water, 11.54 g, 9.52 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 48 h. The dark brown reaction mixture was diluted with $CH_2Cl_2$ and filtered through celite. The organic layer was separated, washed with water, sat. NaCl, dried over $MgSO_4$, filtered and concentrated to yield a dark brown oil. The resulting oil was purified by ISCO using a gradient of 0-7% EtOAc / hexanes to give (S) – 3-Phenyl-2,2-

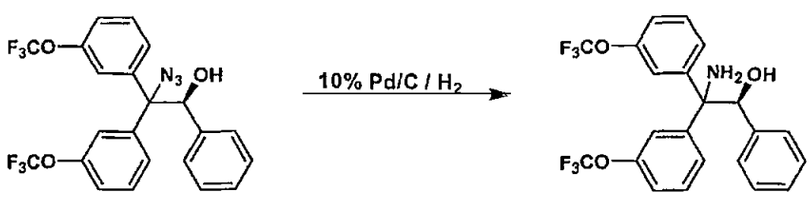
bis(trifluoromethoxy)phenyl)oxirane as a light yellow oil (0.96 g, 71% yield). HPLC: RT = 4.68 min ( Phenomenex Luna C18 5 u column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% phosphoric acid over a 4 minute gradient, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.4-7.0 (m, 13 H), 4.32 ( s, 1 H).

**Procedure 125**



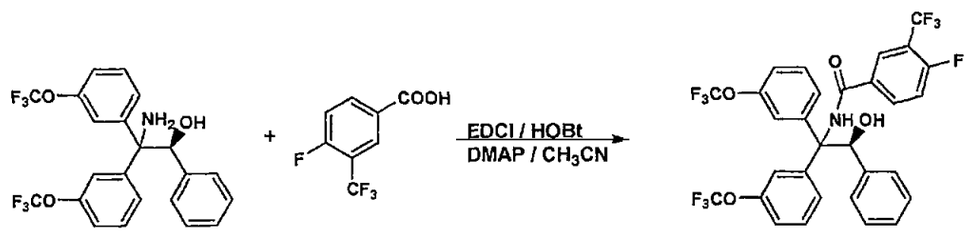

**[00419]** To a suspension of sodium azide (65 mg, 1 mmol) in toluene (9.1 mL) cooled at - 78 °C was added 1 M ethylaluminum dichloride (0.91 mL, 0.91 mmol). The reaction mixture was stirred for 4 h at - 78 °C. (S)-3-Phenyl-2,2-bis(trifluoromethoxy)phenyl)oxirane (0.2 g, 0.45 mmol) was dissolved in toluene (0.5 mL) and added dropwise via syringe. The reaction mixture was stirred at - 78 °C for 30 min and then allowed to warm to rt and stirred overnight. The reaction mixture was diluted with EtOAc (5 mL) and $NaN_3$ (1 g) and water (1 mL) were added and stirred for 1 h. The resulting mixture was filtered through a pad of sodium sulfate and the filtrate was concentrated to a yellow oil. The residue was purified by ISCO using a gradient of 0-30% EtOAc/hexane as eluent to give (S)-2-azido-1-phenyl-2,2-bis(3-(trifluoromethoxy)phenyl)ethanol as a light yellow oil (69 mg, 31% yield). HPLC: RT = 4.438 min ( Phenomenex Luna C18 5 u column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% phosphoric acid over a 4 minute gradient, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.5-7.0 (m, 13 H), 5.63 (d, 1 H), 2.35 (d, 1 H).

**Procedure 126**



[00420] A slurry of (S)-2-azido-1-phenyl-2,2-bis(3-(trifluoromethoxy)phenyl)ethanol (64 mg, 0.132 mmol) and 10% Pd on C (40 mg) in methanol (2 mL) was subjected to balloon hydrogenation overnight at rt. The reaction mixture was filtered through celite and the filtrate was concentrated to give (S)-2-amino-1-phenyl-2,2-bis(3-(trifluoromethoxy)phenyl)ethanol as a light yellow oil (53 mg, 87% yield). HPLC: RT = 3.40 min (Phenomenex Luna C18 5 u column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% phosphoric acid over a 4 minute gradient, monitoring at 220 nm). LCMS: [M+H] 458.1 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

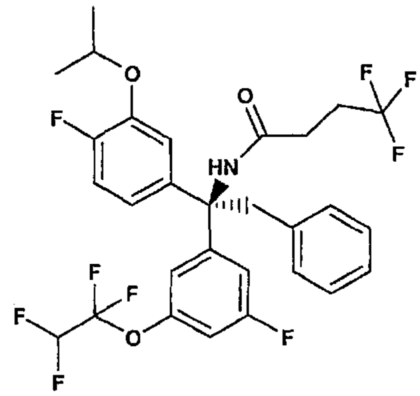
**Procedure 127**




[00421] A solution of (S)-2-amino-1-phenyl-2,2-bis(3-(trifluoromethoxy)phenyl)ethanol (44 mg, 0.096 mmol), 4-fluoro-3-(trifluoromethyl)benzoic acid (20 mg, 0.096 mmol), EDCI ( 28 mg, 0.14 mmol), HOBT (14 mg, 0.096mmol) and a catalytic amount of DMAP in acetonitrile (3 mL) was stirred for 24 h at rt. The reaction mixture was diluted with EtOAc and washed successively with 1 N HCl, 1 N NaOH, sat. NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC Shimadzu-YMC Sunfire 5 μ column, 30 × 100 mm eluting with 50-100% MeOH (90% in $H_2O$, 0.1% TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm. (S)-4-Fluoro-N-(2-hydroxy-2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl)ethyl)-3-(trifluoromethyl)benzamide (Example 311) was isolated as a colorless film (10 mg, 15% yield). HPLC: RT = 4.143 minutes ( Phenomenex Luna C18 5 u column eluting with 10-90% aqueous methanol containing 0.1% phosphoric acid over a 4 minute gradient monitoring at 220nm). LCMS: [M+H] 648.0 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing

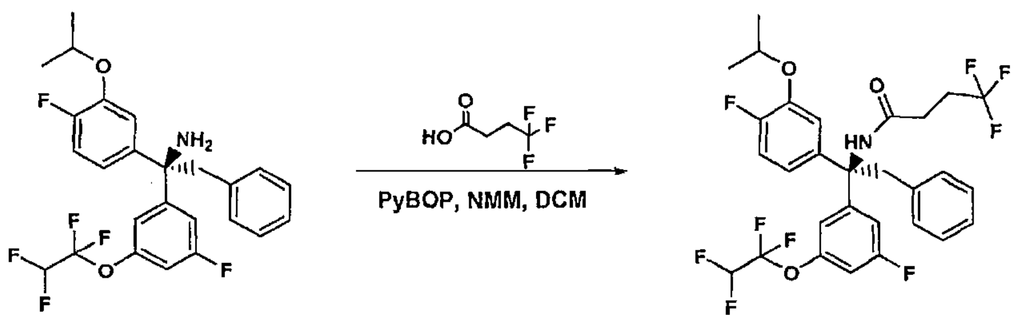
0.1% TFA; 5 mL/min, monitoring at 220 nm). [1]H NMR (400 MHz, $CDCl_3$) δ ppm 8.23 (m, 1 H), 7.37-6.9 (m, 15 H), 5.41 (s, 1 H).

**EXAMPLE 312**



**(R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide**

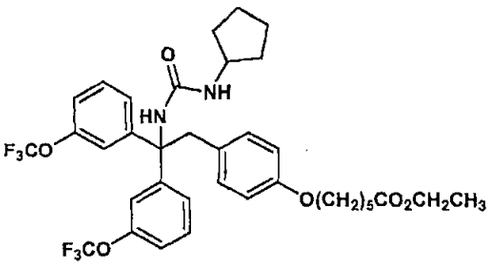
**Procedure 128**



**[00422]** To a solution of 4,4,4-trifluorobutyric acid (13 mg, 0.09 mmol) in DCM (0.8 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (52 mg, 0.1 mmol), (R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine (40 mg, 0.08 mmol), followed by NMM (28 μl, 0.25 mmol). The reaction mixture was stirred at room temperature for 16 h, then another 16 h at 60 °C. The reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with $H_2O$, dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC Phenomenex Luna C18 column, 30 X 50 mm eluting with 10-90% ACN/$H_2O$ over 10

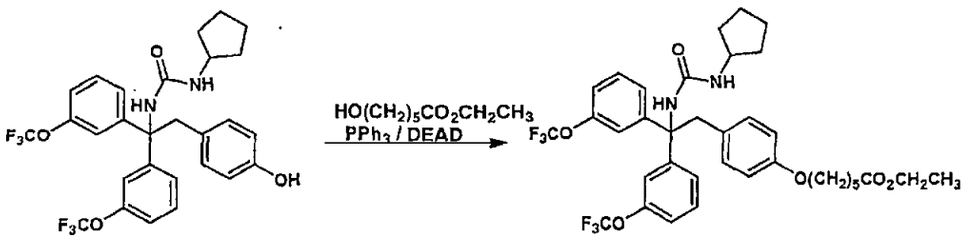
minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm; 40-100% ACN (90% in water, 0.1%TFA) gradient over 10 min with flow rate 40 mL/min and UV detection at 220 nm. (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2,-tetrafluoroethoxy) phenyl)-2-phenylethyl)butanamide (Example 312) was isolated as a lyophillate (27 mg, 55% yield). LCMS: RT = 2.15 min [M+H] 608.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.79 min, Purity 100% (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% ACN/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (d, *J*=6.05 Hz, 3 H), 1.24 (d, *J*=6.05 Hz, 3 H), 2.34 - 2.48 (m, 2 H), 2.51 - 2.61 (m, 2 H), 3.79 (d, *J*=13.19 Hz, 1 H), 3.98 (d, *J*=13.19 Hz, 1 H), 4.29 - 4.39 (m, 1 H), 6.12 - 6.44 (m, 1 H), 6.67 - 6.82 (m, 4 H), 6.91 - 7.07 (m, 4 H), 7.10 - 7.19 (m, 3 H), 8.29 (s, 1 H).

**EXAMPLE 313**




**Ethyl 6-(4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy)phenyl)ethyl)phenoxy)hexanoate**

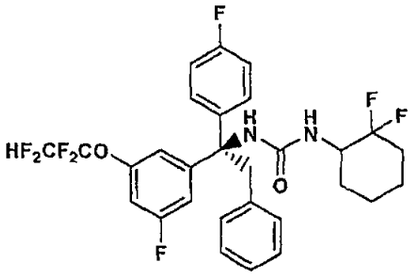
**Procedure 129**




**[00423]** To an oven-dried 3-necked 10 mL round-bottom flask under nitrogen was added 1-cyclopentyl-3-(2-(4-hydroxyphenyl)-1,1-bis(3-

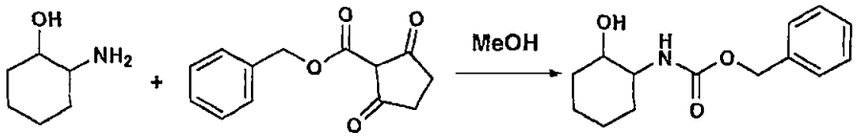
(trifluoromethoxy)phenyl)ethyl)urea, prepared as described in Procedure 11, 6, 2 and 59, (50 mg, 0.1 mmol ), triphenylphosphine (34 mg, 0.1 mmol), ethyl 6-hydroxyhexanoate (17 mg, 0.1 mmol ) and dry THF (0.5 mL ). The reaction mixture was cooled in an ice-methanol bath and diethylazodicarboxylate ( 23 mg, 0.13 mmol ) was added via syringe. The reaction was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated *in vacuo* and purified by ISCO silica gel chromatography using a gradient of 5-25% EtOAc / hexanes as eluent to yield ethyl 6-(4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy)phenyl)ethyl)phenoxy)hexanoate (Example 313) was isolated as a white solid (43 mg, 61% yield). HPLC: RT = 4.69 minutes ( Phenomenex Luna C18 5μ column 4.6 x 50 mm eluting with 10-90% aqueous methanol containing 0.1% phosphoric acid over a 4 minute gradient monitoring at 220 nm). LC/MS [M+H] 711.3 ( Phenomenex Luna C18 5μ column 4.6 x 30 mm eluting with 10-90% aqueous methanol containing 0.1% TFA over a 4 minute gradient monitoring at 220 nm). $^1$H NMR (400MHz , $CDCl_3$) δ ppm 7.33 (t, J= 7.9 Hz, 2 H), 7.20 (d, J= 7.9 Hz, 2 H), 7.12 (d, J= 7.9 Hz, 2 H), 7.07 (s, 2 H), 6.62 (d, J= 8.8 Hz, 2 H), 6.56 (d, J= 8.8 Hz, 2 H), 4.10 (q, J= 7.1 Hz, 2 H), 3.86 t, J = 6.1Hz, 2 H), 3.68 (s, 1 H), 3.62 (t, J= 6.6Hz, 1 H), 2.30-2.27 (m, 2 H), 1.82-1.14 (m, 17 H), 1.23 (t, J= 7.1Hz, 3 H).

**EXAMPLE 314**

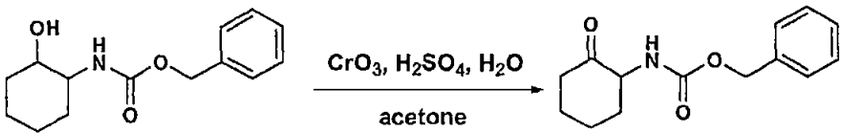



**1-(2,2-difluorocyclohexyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea**

**Procedure 130**

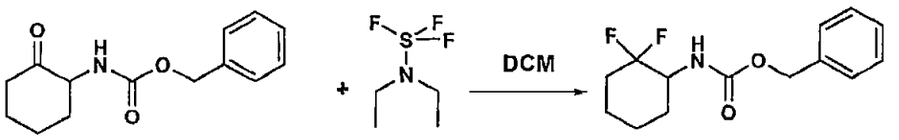



**[00424]** At 0 °C to a solution of benzyl 2,5-dioxocyclopentanecarboxylate (2.58 g, 10.35 mmol) in MeOH (20 mL) was added 2-aminocyclohexanol (1.25 g, 10.87 mmol). The reaction mixture was stirred at room temperature for 18 h and quenched with 0.25 N HCl (8 mL). MeOH was removed under vacuum and the aqueous layer was extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic layers were washed with sat. NaCl (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by ISCO chromatography (40 g column) using hexanes/EtOAc (0-5% over 15 min, 5-10% over 7 min) to give benzyl 2-hydroxycyclohexylcarbamate as a light yellow solid at a retention time of 11 - 13 min (2.15 g, 83% yield). HPLC: RT = 2.83 min, Purity 95% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.33 ppm, 5 H, m; 5.16 ppm, 1 H, m; 5.09 ppm, 2 H, s; 3.95 ppm, 1 H, s; 3.68 ppm, 1 H, m; 1.54 ppm, 8 H, m.

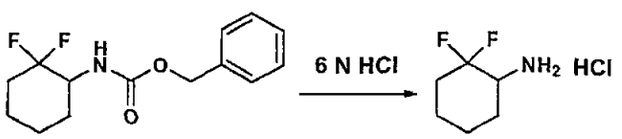



**[00425]** A mixture of $CrO_3$ (0.70 g) in concentrated $H_2SO_4$ (0.61 mL) was diluted with $H_2O$ to the volume of 6 mL. To a solution of benzyl 2-hydroxycyclohexylcarbamate (1.60 g, 6.43 mmol) in acetone (5.4 mL) at 0 °C was added Jones Reagent (5.51 mL, 1.17 M, 6.43 mmol) dropwise over 5 min. The reaction mixture was stirred at room temperature for 1.5 h, quenched with 20% aq. $K_2CO_3$ to pH = 8. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with sat. NaCl (20 mL), dried over $Na_2SO_4$, filtered and concentrated. The resulted crude yellow oil was purified by ISCO chromatography (40 g column) using hexanes/EtOAc (0-30% over 8 min, 30-45% over 10 min) to give benzyl 2-oxocyclohexylcarbamate as a colorless oil at a retention time of 8.5 - 11 min (1.26 g, 79% yield). HPLC: RT = 2.69 min, Purity

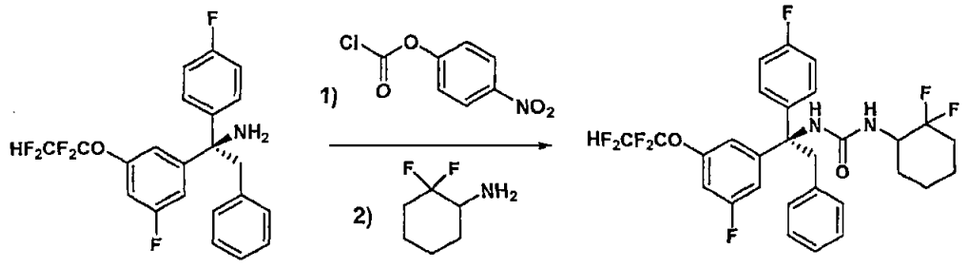
99% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). NMR: 400MHz $^1H$ ($CDCl_3$) 7.33 ppm, 5 H, m; 5.76 ppm, 1 H, s; 5.11 ppm, 2 H, m; 4.27 ppm, 1 H, m; 2.65 ppm, 1 H, dd, *J*=6.60, 2.75 Hz; 2.52 ppm, 1 H, m; 2.38 ppm, 1 H, m; 2.13 ppm, 1 H, m; 1.89 ppm, 1 H, m; 1.77 ppm, 1 H, m; 1.64 ppm, 1 H, m; 1.42 ppm, 1 H, m.




**[00426]** At room temperature to a solution of benzyl 2-oxocyclohexylcarbamate (294 mg, 1.19 mmol) in DCM (5 mL) was added DAST (0.5 mL, 3.92 mmol). The reaction mixture was stirred for 18 h, cooled to 0 °C and quenched by addition of sat. NaCl ( 1 mL). The aqueous phase was separated and extracted with DCM (3 × 8 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by ISCO chromatography (12 g column) using hexanes/EtOAc (0-30% over 15 min, 30-45% over 10 min) to give benzyl 2,2-difluorocyclohexylcarbamate as a brown oil at a retention time of 7 - 10 min (272 mg, 85% yield). HPLC: RT = 3.03 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm). NMR: 400MHz $^1H$ ($CDCl_3$) 7.34 ppm, 5 H, m; 5.12 ppm, 2 H, m; 4.99 ppm, 1 H, d, *J*=8.35 Hz; 3.93 ppm, 1 H, m; 2.18 ppm, 1 H, m; 2.04 ppm, 1 H, m; 1.77 ppm, 2 H, m; 1.46 ppm, 4 H, m.

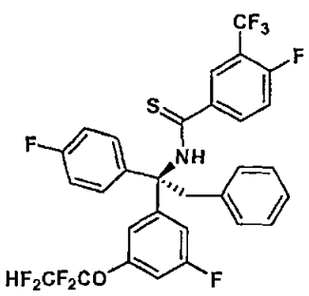



**[00427]** A solution of benzyl 2,2-difluorocyclohexylcarbamate (38 mg, 0.14 mmol) in 6 N HCl (2 mL) was heated at 100 °C for 2 h. The cooled reaction mixture was extracted with ether (3 × 1 mL) and the combined organic layers were concentrated to give 2,2-difluorocyclohexanamine hydrochloride as a light brown solid (23 mg, 96% crude).



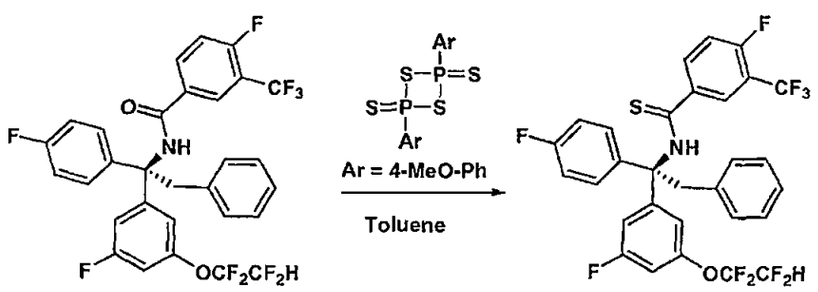
[00428] 1-(2,2-Difluorocyclohexyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea (Example 314) was prepared as described in Procedure 12 (43 mg, 60% yield). LC/MS: RT = 4.07 min [M+H] 587.3 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm).

## EXAMPLE 315



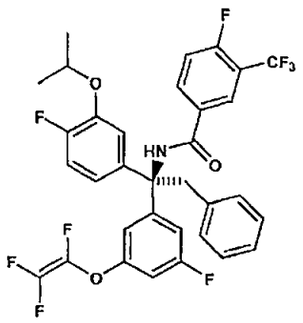
**(R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzothioamide**

### Procedure 131



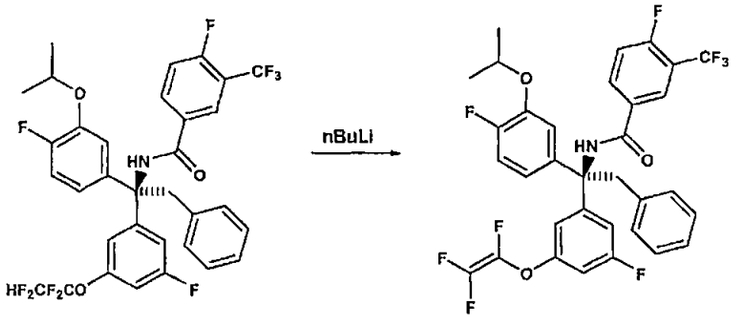
**[00429]** To a stirred solution of (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (105 mg, 0.17 mmol), prepared as described in Procedure 3, 4, 5, 6 and 7, in toluene (5.2 mL) was added Lawesson's reagent (83 mg, 0.20 mmol). The reaction mixture was heated at 110 °C. After 8 h, the reaction mixture was concentrated and the residue was purified by ISCO column chromatography (EtOAc/hexane 0-100%, $SiO_2$) to provide (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzothioamide (Example 315, 89 mg, 83% yield) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 7.92 (s, 1H), 7.74-7.72 (m, 1H), 7.68-7.66 (m, 1H), 7.22-6.86 (m, 11H), 6.72 (d, $J$ = 5 Hz, 2H), 5.92-5.70 (m, 1H), 4.36 (d, $J$ = 15 Hz, 1H), 3.82 (d, $J$ = 10 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 195 (C=S); LC/MS: RT = 4.393 min [M+H] 632.4 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeCN/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm).

**EXAMPLE 316**



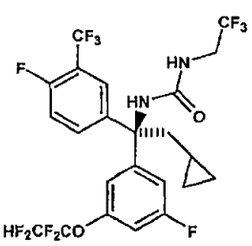

**(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,2,2-trifluorovinyloxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

**Procedure 132**




**[00430]** At -78 °C under argon, to a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (31 mg, 0.046 mmol), prepared as described in Procedure 3, 4, 5, 6, 7, 59 and 68, in dry THF (0.7 mL) was added nBuLi (2.5 M in hexane, 0.25 mL, 0.625 mmol) dropwise. The reaction mixture was allowed to warm to -5 °C over 1.5 h period. After stirring for total 2 h, the reaction mixture was quenched by addition of sat. $NH_4Cl$ and the aqueous phase was extracted with EtOAc and the organic layer was concentrated. The resulting residue was purified by reverse phase HPLC to give pure desired product (7 mg, 23% yield). LC-MS: RT = 4.19 min [M+H] 654.3 (Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, Methanol-$d_4$) δ ppm 8.85 (m, 1 H), 8.00 (m, 2 H), 7.47 (t, *J*=8.8 Hz, 1 H), 7.22 (m, 1 H), 7.15 (t, *J*=7.7 Hz, 2 H), 7.07 (m, 1 H), 7.01-6.94 (m, 2 H), 6.90 (m, 1 H), 6.88-6.83 (m, 2 H), 6.75 (m, 1 H), 4.01 (AB, *J*=12.9 Hz, 2 H), 1.27, 1.21 (d, *J*=6.1 Hz, 6 H).

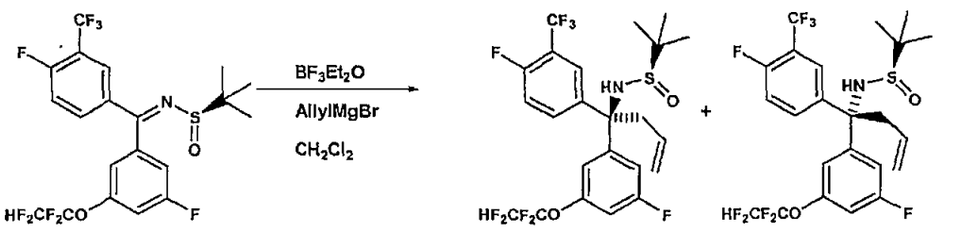
**EXAMPLE 317**



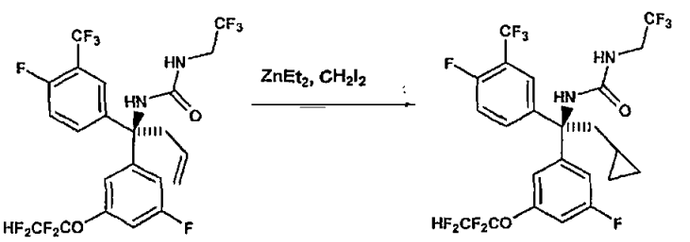

**(*R*)-1-(2-cyclopropyl-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea**

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**Procedure 133**



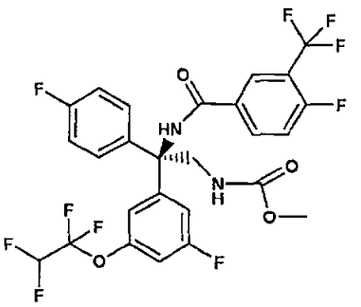

**[00431]** Following Procedure 14, (R)-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)but-3-enyl)-2-methylpropane-2-sulfinamide was prepared (1.9 g, 92% yield). The two diastereomers were separated via chiral AD column (20% isopropanol/heptanes/ /0.1%DEA) to give (R)-N-((S)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)but-3-enyl)-2-methylpropane-2-sulfinamide (1.02 g) as the fast eluting isomer and (R)-N-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)but-3-enyl)-2-methylpropane-2-sulfinamide (0.88 g) as the slow eluting isomer. (R)-N-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)but-3-enyl)-2-methylpropane-2-sulfinamide: LCMS: RT = 4.08 min [M+H] 548.2 (Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).




**[00432]** At 0 °C under argon, to a solution of (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)but-3-enyl)-3-(2,2,2-trifluoroethyl)urea (40 mg, 0.070 mmol), prepared as described in Procedure 6 and 10, in dry toluene (1 mL) was added diethyl Zinc (1.0 M in hexane, 1.2 mL, 1.2 mmol), followed by dropwise addition of diiodomethane (0.2 mL). The reaction mixture was gradually warmed to 110 °C, and heated at 110 °C for 1 h. After

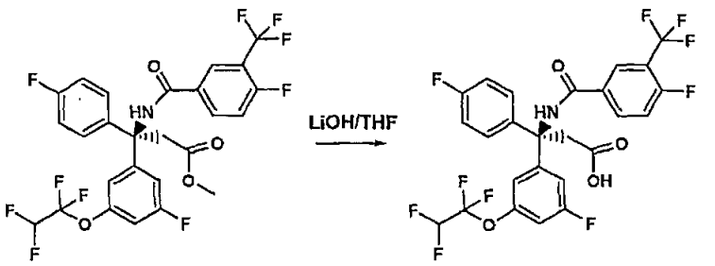
cooling, 1 N HCl was added and the reaction mixture was stirred at room temperature for 5 min. The reaction mixture was extracted with EtOAc and the organic layer was washed with $H_2O$, sat. $NaHCO_3$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by Prep HPLC (phenomenex AXIA Luna 75 x 30 mm, 5 u column eluting with 50-100% MeOH in $H_2O$ with 0.1% TFA, 40 mL/min, monitoring at 220 mn) to give (R)-1-(2-cyclopropyl-1-(4-fluoro-3-(trifluoromethyl)-phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea (Example 317) as white solid (13 mg, yield 32%). LCMS: RT = 3.26 min [M+H] 583.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 50-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (d, *J*=6.6 Hz, 1 H), 7.46 (m, 1 H), 7.12 (t, *J*=9.3 Hz, 1 H), 6.94-6.85 (m, 3 H), 5.84 (tt, *J*=52.8, 2.8 Hz, 1 H), 5.61 (br, s, 1 H), 4.78 (br, t, *J*=6.1 Hz, 1 H), 3.69 (m, 2 H), 2.31 (m, 2 H), 0.36 (m, 3 H), 0.00 (m, 2 H).

**EXAMPLE 318**

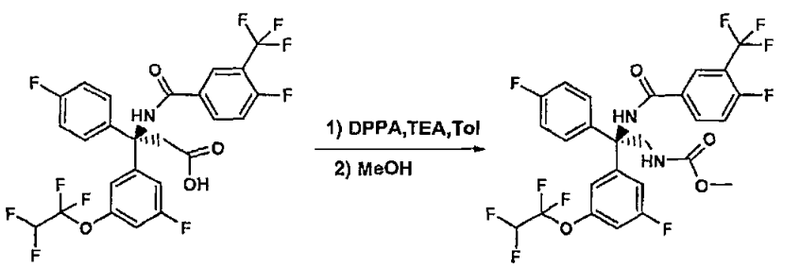


**(R)-methyl 3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(4-fluorophenyl)propanoate**

**Procedure 134**



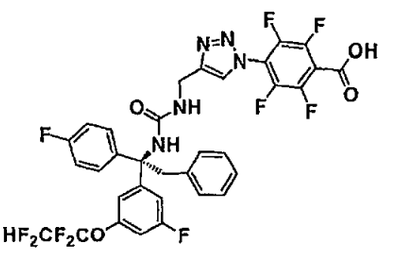

**[00433]** (R)-3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(4-fluorophenyl)propanoic acid was prepared as described in Procedure 3, 4, 5, 14, 6, 7 and 23 (32 mg, 79% yield). LCMS: 2.03 min [M+H] 584.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 3.70 (s, 2 H), 6.18 (t, *J*=53 Hz, 1 H), 6.97 (d, *J*=8.79 Hz, 1 H), 7.08 (t, *J*=8.79 Hz, 2 H), 7.14 (s, 1 H), 7.19 (d, *J*=10.44 Hz, 1 H), 7.34 - 7.50 (m, 3 H), 8.05 - 8.18 (m, 3 H).




**[00434]** To a solution of (R)-3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(4-fluorophenyl)propanoic acid (32 mg, 0.055 mmol) in toluene (0.5 mL) was added DPPA (18 mg, 0.066 mmol) and TEA (7 mg, 0.066 mmol). The reaction mixture was heated at 100 °C for 1 h followed by the addition of MeOH and TEA. The reaction was heated at 65 °C overnight. Excess $K_2CO_3$ was added and the reaction was heated to reflux for 3 h. The reaction mixture was concentrated and the resulting residue was purified by preparative HPLC (phenominex 30 x 100 mm column, 30-100% MeOH (90% in water, 0.1%TFA) gradient over 12 min with flow rate 40 mL/min and UV detection at 220 nm) to yield (R)-methyl 3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(4-fluorophenyl)propanoate (Example 318) as a white

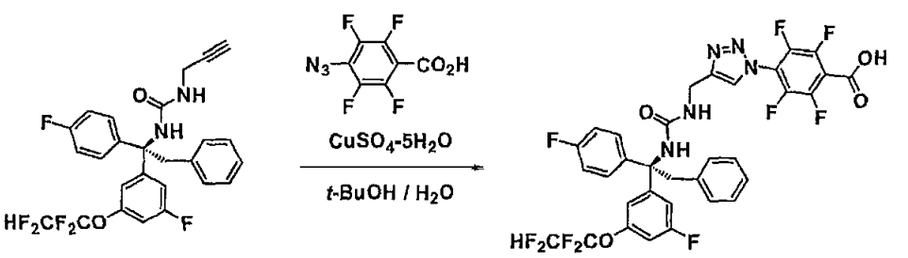
solid (5 mg, 15% yield). LCMS: RT = 3.92 min [M+H] 613.3 (4 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) ppm 3.74 (s, 3 H), 3.87 - 4.11 (m, 2 H), 4.89 (m, 1 H), 5.86 (t, 1 H), 6.95 (d, 1 H), 6.99 - 7.13 (m, 5 H), 7.28 - 7.40 (m, 3 H), 8.09 - 8.16 (m, 1 H), 8.26 (d, 1 H), 8.94 (s, 1 H).

**EXAMPLE 319**



**(R)-2,3,5,6-tetrafluoro-4-(4-((3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid**

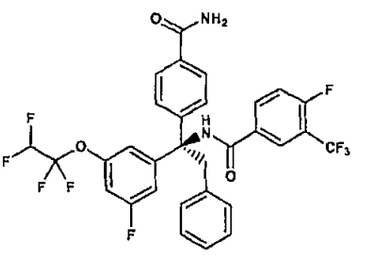
**Procedure 135**




**[00435]** To a suspension of (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(prop-2-ynyl)urea (5.0 mg, 0.01 mmol), prepared as described in Procedure 3, 4, 5, 6 and 12, in a 1:1 mixture of water and *tert*-butyl alcohol (100 μL) was added 4-azido-2,3,5,6-tetrafluorobenzoic acid (2.3 mg, 0.01 mmol), followed by sodium ascorbate (1 M solution in $H_2O$, 100 μL) and $CuSO_4 \cdot 5H_2O$ (1 mg). The reaction mixture was stirred vigorously overnight in a sealed vial. The reaction mixture was diluted with $H_2O$ and extracted with EtOAc (3 x). The combined organic portions were concentrated and

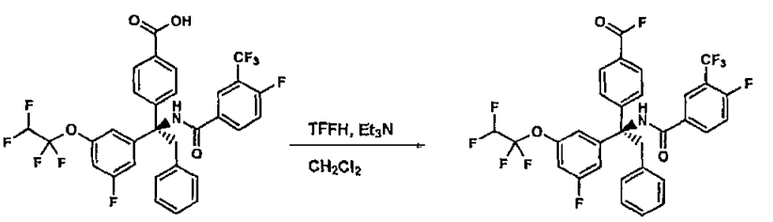
the residue was dissolved in MeOH and purified by preparative HPLC (Phenoma Onyx Monolithic 10 x 100mm; eluting with 10% -90% MeCN/$H_2O$ with 0.1% TFA, monitoring at 220 nm) to provide (R)-2,3,5,6-tetrafluoro-4-(4-((3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (Example 319, 5.7 mg, 78% yield). LC/MS: RT = 3.610 min [M+H] 742.3 (Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% $NH_4OAc$; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (500 MHz, MeOH-$d_4$) δ 8.02 (s, 1 H), 7.10-6.79 (m, 11 H), 6.53 (d, $J$ = 5Hz, 2 H), 6.27-6.04 (m, 1 H), 4.38-4.31 (m, 2 H), 3.81 (d, $J$ = 15Hz, 1 H), 3.73 (d, $J$ = 10Hz, 1 H).

## EXAMPLE 320



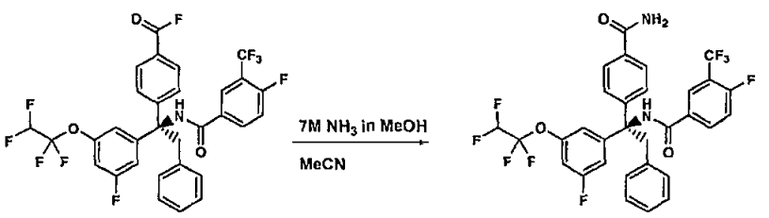
**(R)-N-(1-(4-carbamoylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

### Procedure 136



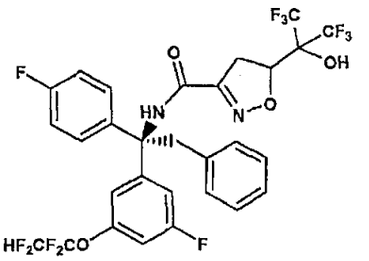

**[00436]** To a suspension of (R)-4-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzoic acid (224 mg, 0.4 mmol), prepared as described in Procedure 3, 4, 5, 6, 7, 56, 57 and 23, in dichloromethane (3 mL) was added triethyl amine (97 μL, 0.70 mmol) followed by fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (TFFH) (138 mg, 0.5 mmol). The reaction mixture was stirred for 18 h. The reaction mixture was

concentrated and the residue was purified by flash chromatography (40 g silica gel; 0-40% ethyl acetate, hexane gradient over 14 min., 40 mL/min) to provide (R)-4-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzoyl fluoride (127 mg, 56% yield). LCMS: RT = 2.39 min [M+H] 644 (Chromolith Performance 18e 4.6 x 100 mm column, 10-90% methanol, water with 0.1% trifluoroacetic acid gradient over 2 min, 5 mL/min)



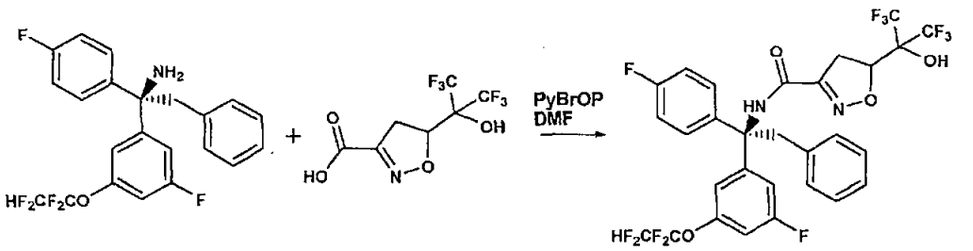

**[00437]** To a suspension of (R)-4-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzoyl fluoride (20 mg, 0.03 mmol) in acetonitrile (1 mL) was added ammonia (7 M in methanol, 20 μL, 0.14 mmol). The reaction mixture was stirred for 24 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (4 g silica gel; 0-100% ethyl acetate, hexane gradient over 14 min., 18 mL/min) to provide (R)-N-(1-(4-carbamoylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 320, 13 mg, 65% yield). LCMS: RT = 1.81 min [M+H] 631 (Chromolith Performance 18e 4.6 x 100 mm column, 50-90% methanol, water with 0.1% trifluoroacetic acid gradient over 2 min, 5 mL/min). $^1$H NMR (400 MHz, $CDCl_3$) ppm 7.86 (1 H, d, $J$=4.83 Hz), 7.77 (1 H, dt, $J$=8.35, 2.20 Hz), 7.71 (2 H, d, $J$=8.35 Hz), 7.14 - 7.25 (3 H, m), 7.08 (3 H, t, $J$=7.47 Hz), 6.85 - 6.90 (3 H, m), 6.71 (1 H, s), 6.63 (2 H, d, $J$=7.03 Hz), 6.05 (1 H, s), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 5.70 (1 H, s), 3.86 (2 H, dd, $J$=37.4, 13.2 Hz).

## EXAMPLE 321



**N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazole-3-carboxamide**

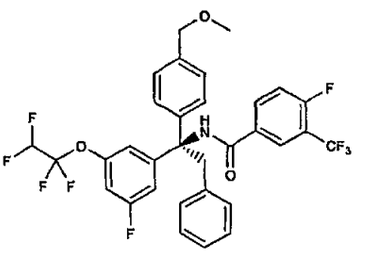
### Procedure 137



**[00438]** (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine was prepared by the methods described in Procedure 3, 4, 5 and 6. 5-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazole-3-carboxylic acid was prepared as described in Journal of Medicinal Chemistry, 2006, 49, 14, 4055. To a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (60 mg, 0.14 mmol), in anhydrous DMF (1 mL) was added N-methylmorpholine (26 mg, 0.28 mmol), PyBrOP (73 mg, 0.14 mmol) and 5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazole-3-carboxylic acid (40 mg, 0.14 mmol). The resulting solution was stirred at rt for 16 h. The resulting solution was diluted with MeOH (0.5 mL) and purified by preparative HPLC (YMC Sunfire 30 x 100 mm column, eluting with 10-90% MeOH/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm). (N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazole-3-carboxamide (Example 321, 3 mg, 3% yield) was isolated as a colorless oil at a retention time of

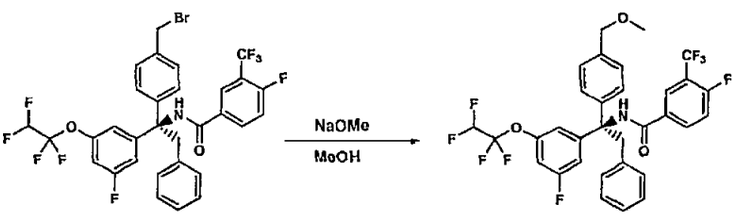
11.29 min. LCMS: RT = 2.18 min [M+H] 689.45 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 4.14 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400 MHz $^1H$ ($CDCl_3$) Diastereomeric ratio is 1:1; 7.28 – 6.86 ppm, 24 H, m; 6.64 ppm, 1 H, m; 6.61 ppm, 1 H, m; 5.88 ppm, 2 H, t, J=60.0 Hz; 5.16 ppm, 2 H, t, J=16.0 Hz; 3.94 ppm, 1 H, d, J=12.0 Hz; 3.88 ppm, 1 H, d, J=12.0 Hz; 3.75 ppm, 1 H, d, J=12.0 Hz; 3.68 ppm, 1 H, d, J=12.0 Hz; 3.61 ppm, 2 H, m; 3.40 ppm, 1 H, dm, J=12.0 Hz; 3.33 ppm, 1 H, dm, J=12.0 Hz.

**EXAMPLE 322**



**(R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-(methoxymethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

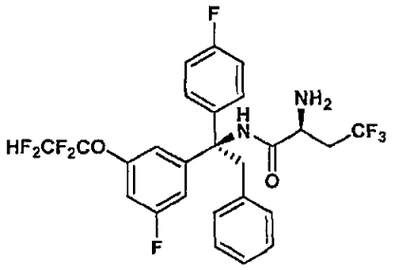
**Procedure 138**




**[00439]** (R)-N-(1-(4-(bromomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (prepared as described in Procedure 3, 4, 5, 6, 7, 56, 57, 100 and 32, 24 mg, 0.035 mmol) was dissolved in 0.5 mL of methanol. To this solution was added sodium methoxide (25% by wt, 0.5 mL) and the reaction mixture was stirred for 40 min. The reaction was quenched with 1.0 M HCl and extracted with ethyl acetate. The organic

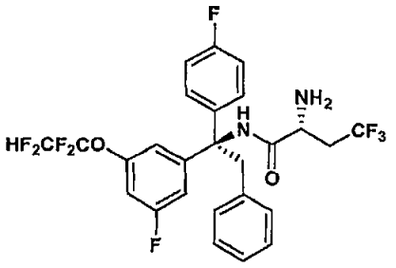
layer was dried over magnesium sulfate, filtered and concentrated. The resulting oil was purified by flash chromatography (4 g silica gel column, 0-100% EtOAc/hexane gradient over 11 min., flow rate 18 mL/min) to provide (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-(methoxymethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 321) as a white solid (15 mg, 67% yield). LC/MS: RT = 1.62 min [M+H] 642 (Chromolith Performance 18e 4.6 x 100 mm column, 50-90% acetonitrile, water with 0.1% trifluoroacetic acid gradient over 2 min, 5 mL/min); $^1$H NMR (400 MHz, *CDCl$_3$*) ppm 7.91 (1 H, d, *J*=7.15 Hz), 7.77 - 7.87 (1 H, m), 7.08 - 7.44 (7 H, m), 6.97 - 7.05 (2 H, m), 6.92 (1 H, d, *J*=8.79 Hz), 6.66 - 6.75 (3 H, m), 5.87 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 4.47 (2 H, s), 4.09 (1 H, d, *J*=13.2 Hz), 3.81 (1 H, d, *J*=13.2 Hz), 3.42 (3 H, s).

**EXAMPLE 323A**



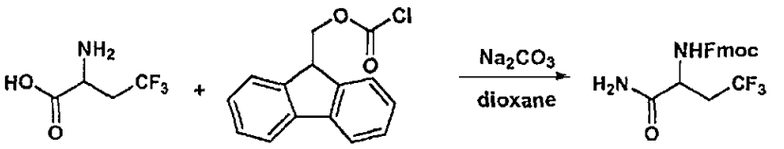

**(S)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide**

**EXAMPLE 323B**



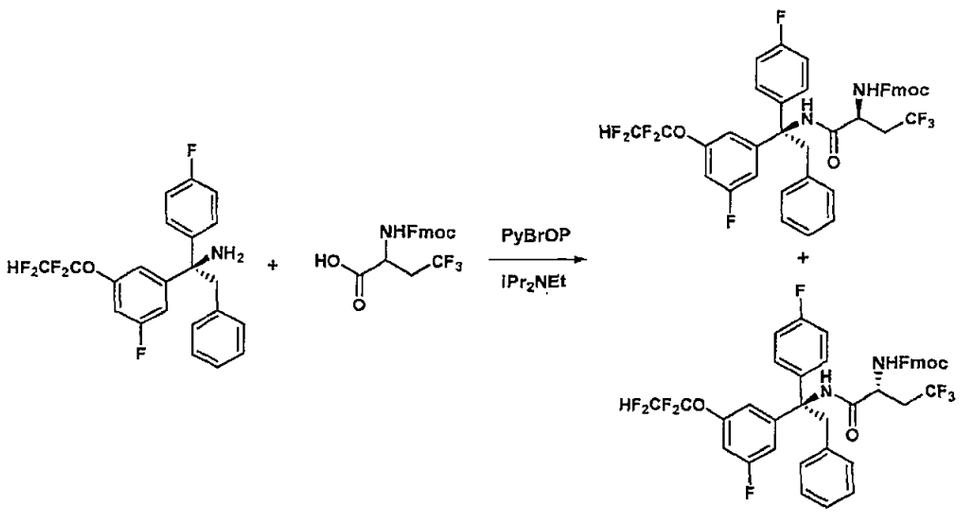

**(R)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide**

**Procedure 139**




**[00440]** To a solution of 2-amino-4,4,4-trifluorobutanoic acid (239.0 mg, 1.52 mmol) ) in dioxane (6 mL) was added 10% $Na_2CO_3$, followed by (9 H-fluoren-9-yl)methyl carbonochloridate (394.0 mg, 1.52 mmol). The reaction mixture was stirred at 0 °C for 1 h, then at rt for 1 h. The reaction mixture was poured into a mixture of ether and water. The aqueous layer was treated with concentrated HCl, then extracted with 3 x EtOAc. The organic layers were combined and dried over $MgSO_4$ and concentrated. The residue was purified by ISCO chromatography (10 g column, eluting with 0-30% EtOAc/hexane containing 0.1% AcOH) to yield (9 H-fluoren-9-yl)methyl 1-amino-4,4,4-trifluoro-1-oxobutan-2-ylcarbamate as a white solid (260.0 mg, yield 45%). LCMS: RT = 3.06 min [M+H] 380.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

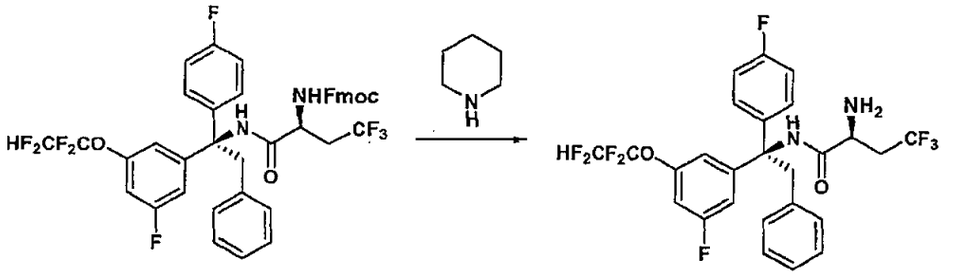
**Procedure 140**




**[00441]** To a solution of (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (31 mg, 0.07 mmol), prepared as described in Procedure 3, 4, 5 and 6, in DCM (1 mL) was added (9 H-fluoren-9-yl)methyl 1-

amino-4,4,4-trifluoro-1-oxobutan-2-ylcarbamate (31 mg, 0.08 mmol), followed by PyBrOP and $iPr_2NEt$. The reaction mixture was stirred at rt for 72 h and concentrated. The residue was purified by preparative HPLC (Axia column, 30 x 100 mm, 60-100% MeOH/$H_2O$ with 0.1% TFA over 12 min, flow rate 40 mL/min, monitoring at 220 nm) to yield (9H-fluoren-9-yl)methyl 4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-1-oxobutan-2-ylcarbamate as white solid (20 mg, 38% yield). LCMS: RT = 4.5 min [M+H] 787.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). This diastereomer mixture was separated by Chiralpak AD column eluting with 10% MeOH/EtOH(1:1)/90% heptane with flow rate 20 mL/min. (9H-fluoren-9-yl)methyl (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-1-oxobutan-2-ylcarbamate was eluted at a retention time of 8.26 min and isolated as a white solid (10 mg). (9H-fluoren-9-yl)methyl (R)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-1-oxobutan-2-ylcarbamate was eluted at a retention time of 12.97 min and isolated as a white solid (10 mg). The stereochemistry of (9H-fluoren-9-yl)methyl (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-1-oxobutan-2-ylcarbamate and (9H-fluoren-9-yl)methyl (R)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-1-oxobutan-2-ylcarbamate was assigned arbitrarily.

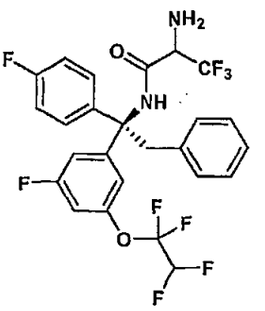
**Procedure 141**




**[00442]** To a solution of (9H-fluoren-9-yl)methyl (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-

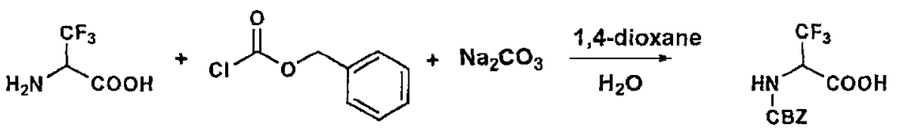
1-oxobutan-2-ylcarbamate (10 mg, 0.01 mmol) in DCM (0.5 mL) was added piperidine (20 mg, 0.1 mmol). The reaction mixture was stirred at rt for 1.5 h and concentrated. The residue was purified by preparative HPLC (Axia column, 30 x 100 mm, 30-100% MeOH/$H_2O$ with 0.1% TFA over 12 min, flow rate 40 mL/min, monitoring at 220 nm) to yield (S)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 323A) as a white solid (6 mg, 82% yield). LCMS: RT = 3.1 min [M+H] 565.22 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (1 H, s), 7.17 - 7.22 (1 H, m), 7.12 (2 H, t, *J*=7.33 Hz), 7.03 - 7.08 (2 H, m), 6.96 - 7.02 (2 H, m), 6.88 (3 H, s), 6.59 (2 H, d, *J*=7.07 Hz), 5.85 (1 H, t, *J*=2.53 Hz), 4.09 (1 H, s), 3.91 (1 H, d, *J*=13.14 Hz), 3.71 (1 H, d, *J*=13.39 Hz), 2.66 (2 H, m). (R)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 323B) was prepared in the same method here and isolated as a white solid (6 mg, 82% yield). LCMS: RT = 3.1 min [M+H] 565.22 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (1 H, s), 7.19 (1 H, t, *J*=7.33 Hz), 7.08 - 7.15 (4 H, m), 6.93 - 7.00 (2 H, m), 6.84 - 6.92 (2 H, m), 6.81 (1 H, s), 6.58 (2 H, d, *J*=7.07 Hz), 5.84 (1 H, t, *J*=2.65 Hz), 4.26 (1 H, d, *J*=5.56 Hz), 3.76 - 3.86 (2 H, m), 2.53 (1 H, d, *J*=10.61 Hz), 2.43 - 2.49 (1 H, m). The stereochemistry of (S)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 323A) and (R)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 323B) was assigned arbitrarily.

**EXAMPLE 324**

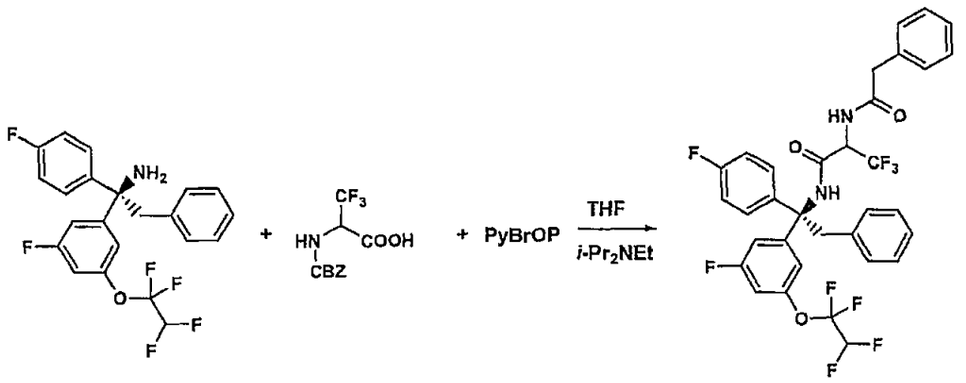


**2-amino-3,3,3-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide**

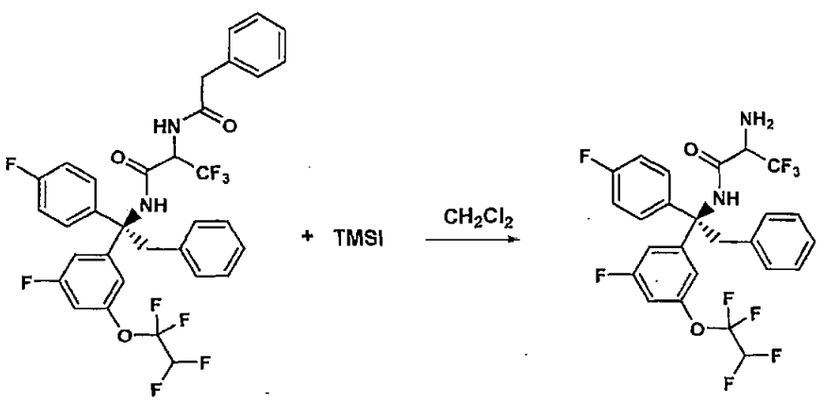
**Procedure 142**



**[00443]** At 0 °C to a solution of 2-amino-3,3,3-difluoropropanoic acid (143 mg, 0.1 mmol) in 1,4-dioxane (1.3 mL) was added 10% aqueous $Na_2CO_3$ (2.6 mL), followed by dropwise addition of benzyl carbonochloridate (170 mg, 0.1 mmol) in 1,4-dioxane (2.6 mL). The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm up rt and stirred at rt for 72 h. The reaction mixture was concentrated and the residue was purified by prep HPLC (Phenomenex Luna AXIA 5 μ 21.2 x 100 mm, 10% - 90% ACN/$H_2O$ containing 0.1% TFA, flow rate 20 mL/min, gradient time 10 min) to yield 2-(benzyloxycarbonylamino)-3,3,3-trifluoropropanoic acid as a white solid (108 mg, 76% yield). HPLC: RT = 2.64 min [M+Na] 300.1 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.12 - 7.22, m, 5 H; 4.96, s, 2 H; 4.92 – 4.99, m, 1 H.



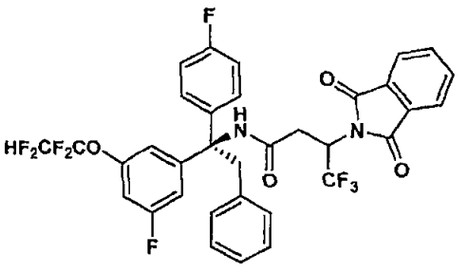

**[00444]** Following Procedure 140, benzyl 1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-3-oxopropan-2-ylcarbamate was prepared as yellow solid (13 mg, 25% yield). HPLC: RT = 4.15 min [M+H] 685.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.26 - 7.51, m, 6 H; 7.18 – 7.23, m, 1 H; 6.97 – 7.15, m, 7 H; 6.84 - 6.93, m, 3 H; 6.58 – 6.61, m, 2 H; 5.71 – 5.98, t, $J$ = 34, 1 H; 5.73, m, 1 H; 5.07 – 5.11, m, 2 H; 4.87, m, 1 H; 3.81 – 3.90, m, 1 H; 3.69 – 3.73, m, 1 H.




**[00445]** To a solution of benzyl 1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-3-oxopropan-2-ylcarbamate (10 mg, 0.014 mmol) in $CH_2Cl_2$ (0.5 mL) was added TMSI (18 mg, 0.094 mmol). The reaction mixture was sealed and stirred at rt for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by

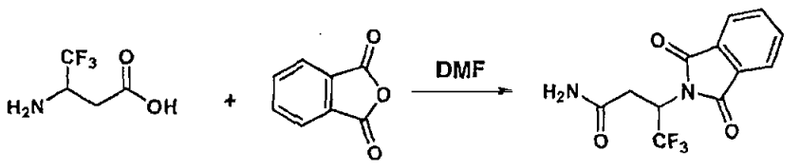
prep HPLC (Phenomenex Luna AXIA 5 μ 21.2 x 100 mm, 10% - 90% ACN/$H_2O$ containing 0.1% TFA, flow rate 20 mL/min, gradient time 10 min) to yield 2-amino-3,3,3-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide (Example 324) as a white solid (5 mg, 65% yield). HPLC: RT = 1.90 min [M+H] 551.5 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 - 7.85, m, 1 H; 7.19 – 7.23, m, 1 H; 7.11 – 7.17, m, 2 H; 7.07 – 7.11, m, 1 H; 6.98 – 7.03, m, 3 H; 6.89 – 6.93, m, 2 H; 6.80 – 6.86, m, 1 H; 6.61 – 6.64, m, 2 H; 5.73 – 5.99, t, $J$ = 52, 1 H; 4.00 – 4.03, $J$ = 12, d, 1 H; 3.98, m, 1 H; 3.63 – 3.67, d, $J$ = 12, 1 H;

**EXAMPLE 325**



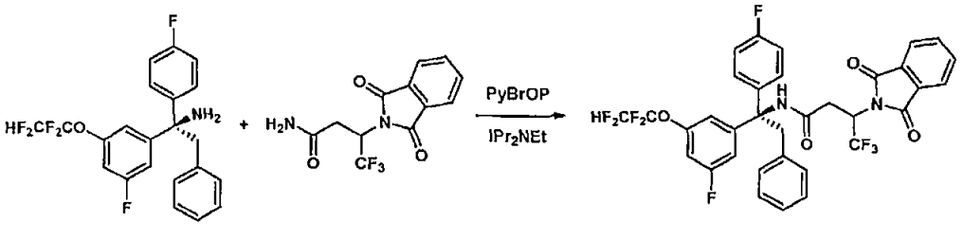
**3-(1,3-dioxoisoindolin-2-yl)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide**

**Procedure 143**



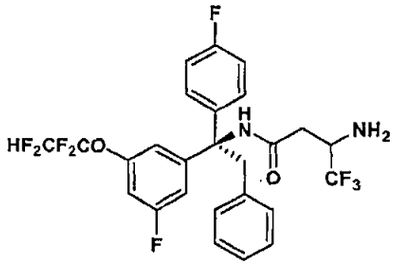
**[00446]** A solution of 3-amino-4,4,4-trifluorobutanoic acid (628 mg, 4 mmol) and isobenzofuran-1,3-dione (592 mg, 4 mmol) in DMF (5 mL) was heated to 140 °C under microwave irradiation for 15 min. The reaction mixture was purified by preparative HPLC (Axia luna column, 30 x 75 mm, 10-100% ACN/$H_2O$ with 0.1% TFA over 10 min, flow rate 40 mL/min, monitoring at 220 nm) to yield 3-(1,3-dioxoisoindolin-2-yl)-4,4,4-trifluorobutanamide (620 mg, 54% yield). LCMS: RT =

1.54 min [M+H] 288.2 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).



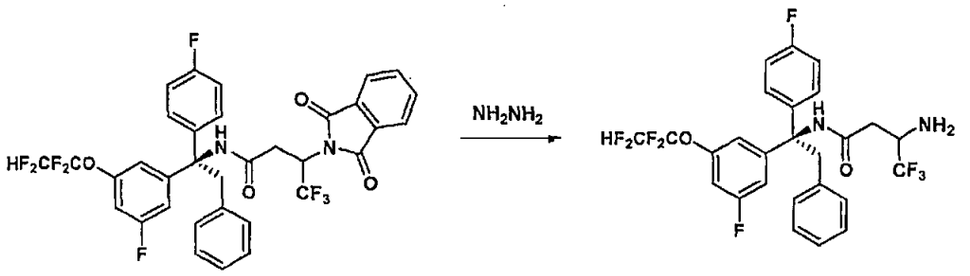

**[00447]** 3-(1,3-Dioxoisoindolin-2-yl)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 325) was prepared as white solid (12 mg, 27% yield) as described in Procedure 140. LCMS: RT = 3.62 min [M+H] 695.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.76 - 7.88 (4 H, m), 7.15 - 7.01 (3 H, m), 6.91 - 6.97 (2 H, m), 6.80 - 6.86 (2 H, m), 6.61 - 6.72 (3 H, m), 6.54 (2 H, dd, *J*=13.26, 7.71 Hz), 6.21 (1 H, d, *J*=4.55 Hz), 5.84 (1 H, t, *J*=2.78 Hz), 5.25 (1 H, m), 3.87 (1 H, d, *J*=13.14 Hz), 3.71 (1 H, ddd, *J*=15.66, 11.49, 4.42 Hz), 3.62 - 3.55 (1 H, m), 2.85 - 2.95 (1 H, m).

## EXAMPLE 326



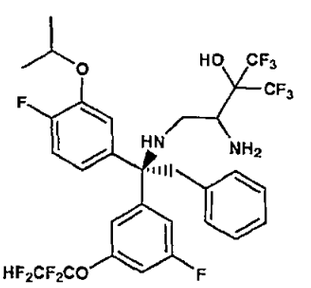

**3-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide**

**Procedure 144**




**[00448]** To a solution of 3-(1,3-dioxoisoindolin-2-yl)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 325, 30 mg, 0.04 mmol) in MeOH (1 mL) was added hydrazine (0.03 mL, 1 mmol) and the reaction mixture was heated at 50 °C for 4 h. The reaction mixture was purified by preparative HPLC (Axia luna column, 30 x 75 mm, 10-100% ACN/$H_2O$ with 0.1% TFA over 10 min, flow rate 40 mL/min, monitoring at 220 nm) to yield 3-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 326) as white solid (7 mg, 24% yield). LCMS: RT = 3.62 min [M+H] 565.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 (1 H, d, *J*=17.94 Hz), 7.13 - 7.24 (3 H, m), 6.96 - 7.11 (4 H, m), 6.82 - 6.92 (3 H, m), 6.62 (2 H, d, *J*=7.83 Hz), 5.86 (1 H, t, *J*=1.77 Hz), 3.88 (1 H, t, *J*=12.63 Hz), 3.75 - 3.84 (1 H, m), 3.70 (1 H, d, *J*=13.14 Hz), 2.82 - 2.93 (1 H, m), 2.77 (1 H, m).

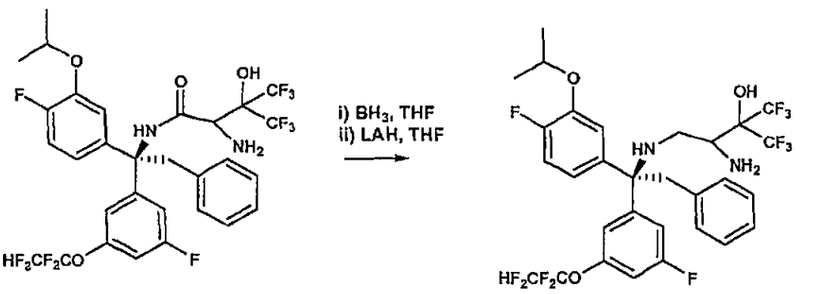
**EXAMPLE 327**




**3-amino-1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-**

**(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)-2-(trifluoromethyl)butan-2-ol**

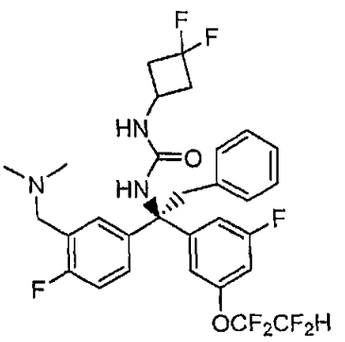
**Procedure 145**




**[00449]** To a solution of 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl)butanamide, prepared as described in Example 293, (20 mg, 0.028 mmol) in THF (0.5 mL) was added borane (0.2 mL, 1.0 M solution in THF). After hydrogen evolution ceased, the solution was heated in a sealed microwave vial under microwave irradiation at 100 °C for 5 min. The solvents were removed under a stream of nitrogen then THF (0.5 mL) was added to the residue followed by $BF_3{\cdot}Et_2O$ (30 mg, 0.21 mmol) and LAH (0.2 mL, 1.0 M solution in THF). After evolution of hydrogen gas had ceased, the sealed microwave vial was heated at 100 °C for 10 min. The solvents were removed under a stream of nitrogen and the residue dissolved in $NH_4OH$ (ca. 10 mL). LiCl (10%, ca. 10 mL) was added and the aqueous extracted with DCM (3 x 10 mL). The combined organic portions were concentrated under reduced pressure and purified by preparative TLC (25 x 25 mm, silica gel 1 mm elution with hexane:EtOAc 4:1). 3-Amino-1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)-2-(trifluoromethyl)butan-2-ol (Example 327, 5 mg, 20% yield) was isolated as a colorless oil at $R_f$ of 0.5. LCMS: RT = 3.88 min [M+H] 693.1 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.88 min, Purity 91% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.15 ppm, 3 H, m; 7.05 ppm, 1 H, m; 6.86 ppm, 2H,

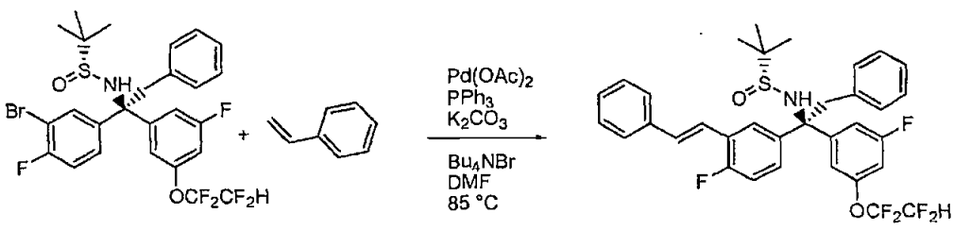
d, J=8.0Hz; 6.83 ppm, 3 H, m; 6.61 ppm, 2H, d, J=8.0Hz; 5.87 ppm, 1H, t,t, J=52.0Hz and J=4.0Hz; 4.41 ppm, 1H, sept, J=8.0Hz; 3.57 ppm, 1H, d, J=12.0Hz; 3.48 ppm, 1H, d, J=12.0Hz; 2.99 ppm, 2H, m; 2.53 ppm, 1H, brt; 1.27 ppm, 3H, d, J=8.0Hz; 1.25 ppm, 3H, d, J=8.0Hz.

**EXAMPLE 328**



**(R)-1-(3,3-difluorocyclobutyl)-3-(1-(3-((dimethylamino)methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea**

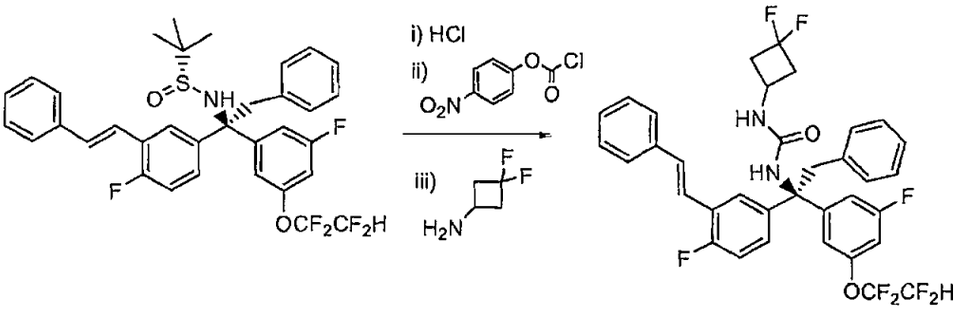
**Procedure 146**




**[00450]** Following Procedure 3, 62, 5 and 6, N-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was prepared and the diastereomer mixture was separated by chiral preparative HPLC (Chiralpak AD column, 5 x 50 cm isocratic elution with 60% IPA/heptane, 50 mL/min, monitoring at 254 nm) to yield (R)-N-((S)-1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a white foam (3.92 g, 33% yield) with a retention time of 40 min.

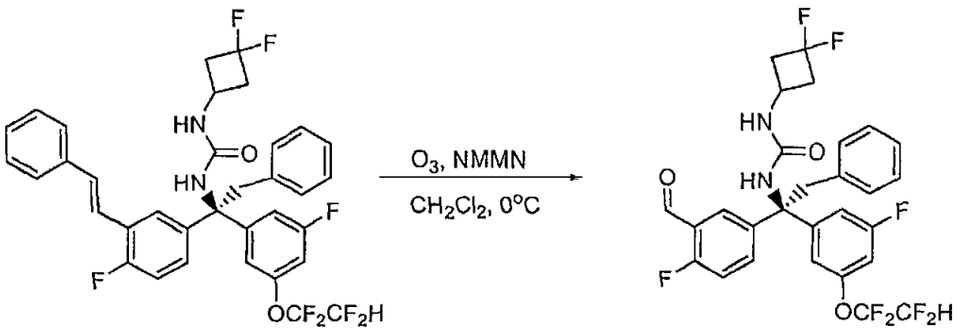
**[00451]** To a suspension of $Pd(OAc)_2$ (9 mg, 0.04 mmol) and $PPh_3$ (2 mg, 0.008 mmol) in DMF was added $Bu_4NBr$ (265 mg, 0.8 mmol), (R)-N-((S)-1-(3-bromo-4-

fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide, prepared as described in Procedure 62, (500 mg, 0.8 mmol), styrene (137 mg, 1.3 mmol) and $K_2CO_3$ (136 mg, 1.0 mmol). The reaction mixture was degassed and backfilled with argon several times. The reaction mixture was heated at 85 °C for 16 h. The reaction mixture was then poured into sat. $NH_4Cl$ and the aqueous phase was extracted with EtOAc. The combined organic portions were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by ISCO chromatography (12 g column, 0-30% EtOAc/hexane) to yield (R)-N-((R)-1-(4-fluoro-3-styrylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (119 mg, 23% yield). LCMS: RT = 4.62 min [M+H] 632 (Phenomenex Luna C18, 50 x 4.6 mm, 10%-90% $H_2O$/ACN with 0.1% TFA, 4 min gradient, flow rate 4 mL/min, monitoring at 220 nm).



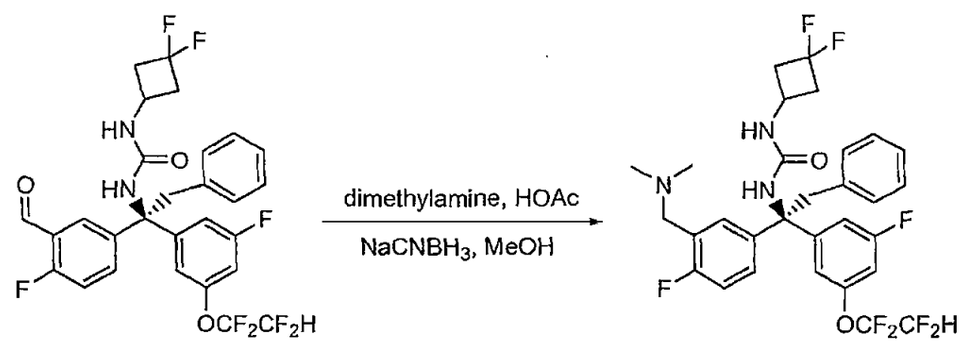

**[00452]** Using the methods described in Procedure 6 and 12, (R,E)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-styrylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea was prepared as a clear oil (170 mg, 57% yield). LCMS: RT = 4.19 min [M+H] 661 (Phenomenex Luna C18, 50 x 4.6 mm, 10%-90% $H_2O$/ACN with 0.1% TFA, 4 min gradient, flow rate 4 mL/min, monitoring at 220 nm).

**Procedure 147**




**[00453]** To a solution of (R,E)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-styrylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea (509 mg, 0.8 mmol) in DCM (10 ml) at 0 °C was added 4-methylmorpholine N-oxide (104 mg, 0.8 mmol). Ozone was bubbled through the resulting yellow solution for 10 min. The reaction solvent was removed and the residue was purified by ISCO chromatography (12 g column, 0-30% EtOAc/hexane) to yield (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-formylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea as a colorless oil (106 mg, 23 % yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 10.22 (s, 1 H), 8.06 (m, 1 H), 7.67 (dd, *J*=6.19, 2.65 Hz, 1 H), 7.16 (m, 4 H), 6.85 (m, 3 H), 6.69 (m, 3 H), 5.85 (m, 1 H), 5.40 (d, *J*=6.57 Hz, 1 H), 4.00 (m, 1 H), 2.90 (m, 2 H).

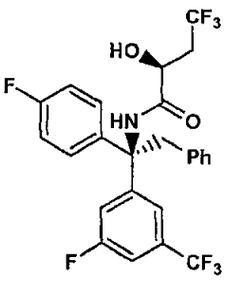
**Procedure 148**




**[00454]** To a solution of (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-formylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea (20 mg, 0.03 mmol) in MeOH (2 mL) was added $NHMe_2$ (0.009 mL) and a drop of acetic acid. The reaction mixture was stirred at rt for 30 min, followed by addition of

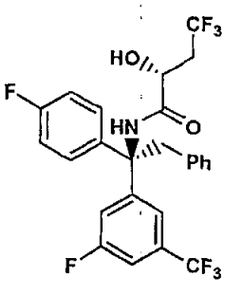
$NaCNBH_3$ (2 mg, 0.03 mmol). The reaction mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure and the residue was partitioned between sat. $NaHCO_3$ and EtOAc. The organic phase was concentrated and purified by prep HPLC (Phemomenex Luna 5u C18 Axia column, 21 x 100 mm, 10%-90% $H_2O$/ACN with 0.1% TFA/, monitoring at 220 nm) to yield (R)-1-(3,3-difluorocyclobutyl)-3-(1-(3-((dimethylamino)methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea (Example 328, 8 mg, 44% yield). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (d, *J*=2.27 Hz, 1 H), 7.09 (m, 7 H), 6.88 (d, *J*=8.84 Hz, 1 H), 6.63 (d, *J*=7.07 Hz, 2 H), 6.51 (br. s., 1 H), 5.88 (m, 1 H), 4.34 (d, *J*=12.63 Hz, 1 H), 4.10 (m, 2 H), 3.87 (m, 1 H), 3.31 (d, *J*=12.63 Hz, 2 H), 2.92 (m, 3 H), 2.74 (d, *J*=2.78 Hz, 3 H), 2.70 (d, *J*=3.28 Hz, 3 H), 2.46 (m, 2 H).

**EXAMPLE 329A**



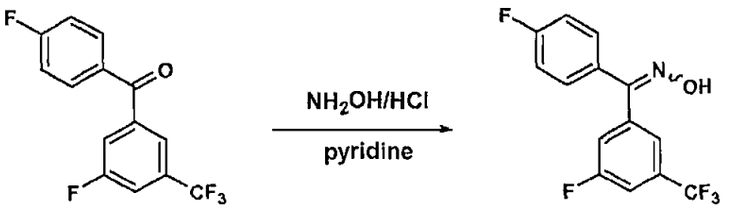

**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide**

**EXAMPLE 329B**



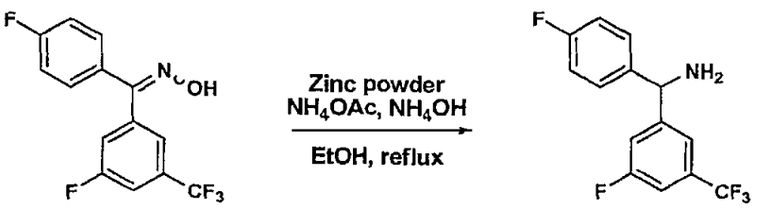

**(R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide**

**Procedure 149**




**[00455]** To a solution of (3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methanone, prepared as described in Procedure 4, (860 mg, 3.0 mmol) in pyridine (6 mL) was added hydroxylamine hydrochloride (830 mg, 12.0 mmol) and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (50 mL), washed with 1 N HCl (2 x 20 mL), water (20 mL) and sat. NaCl (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield (3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methanone oxime (912 mg, 100 % yield) as a white solid. TLC (30% EtOAc/hexane) shows two spots, the cis and trans isomers of (3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methanone oxime, that were not separated. LCMS: RT = 1.59 min [M+H] 302.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

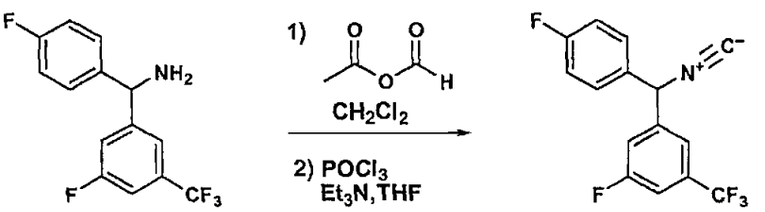
**Procedure 150**




**[00456]** To a suspension of (3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methanone oxime (904 mg, 3.0 mmol) in EtOH (3 mL) and conc. $NH_4OH$ (15 mL) was added ammonium acetate (120 mg, 1.6 mmol) followed by zinc powder (1.05 g, 16.2 mmol) and the reaction mixture was heated at reflux for 2 h. The reaction mixture was allowed to cool to rt then filtered. The filtered solid was washed with 10 N NaOH (15 mL) and EtOAc (15 mL). The combined filtrate was extracted with EtOAc (2 x 30 mL). The combined organic fractions were washed

with sat. NaCl (2 x 10 mL) then dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield (3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methanamine (804 mg, 93% yield) as a clear, colorless oil. LCMS: RT = 0.96 min [M-$NH_2$] 271.0 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 1.68 (bs, 2 H), 5.25 (s, 1 H), 7.03 (t, *J*=8.57 Hz, 2 H), 7.19 (d, *J*=7.91 Hz, 1 H), 7.29 - 7.35 (m, 3 H), 7.48 (s, 1 H).

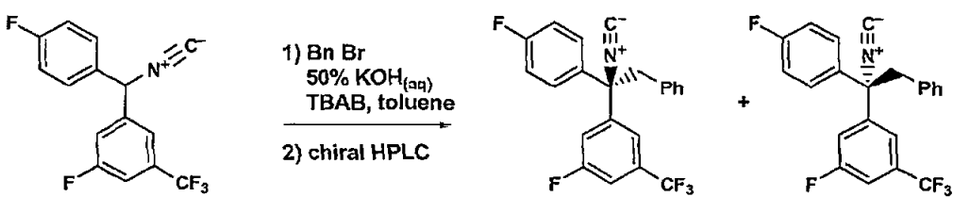
**Procedure 151**




**[00457]** To a solution of (3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methanamine (315 mg, 1.1 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was added acetic formic anhydride (314 uL, formed by heating a 2:1 *v/v* ratio of acetic anhydride and formic acid at 60 °C for 2 h). The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified on a 40 g column of silica gel, eluting with 0 to 100% EtOAc/hexane, to give N-((3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methyl)formamide (327 mg, 94% yield) as a clear, viscous oil. LCMS: RT = 1.37 min [M+H] 316.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 6.13 (bs, 1 H), 6.34 (d, *J*=7.47 Hz, 1 H), 7.05 - 7.20 (m, 5 H), 7.27 - 7.34 (m, 2 H), 8.35 (s, 1 H). To a solution of N-((3-fluoro-5-(trifluoromethyl)phenyl)(4-fluorophenyl)methyl)formamide (327 mg, 1.04 mmol) in THF (5 mL) at 0 °C was added $Et_3N$ (0.79 mL, 5.7 mmol) followed by phosphorous oxychloride (0.125, 1.35 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with ice-water (25 mL) and extracted with

$Et_2O$ (3 x 20 mL). The combined organic layers were washed with sat. NaCl (20 mL), dried over anhydrous $Na_2SO_4$, the filtered through basic alumina. The filtrate was concentrated to give 1-fluoro-3-((4-fluorophenyl)(isocyano)methyl)-5-(trifluoromethyl)benzene (268 mg, 93% yield) as a pale brown oil. LCMS: RT = 1.71 min [M-NC] 271.0 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); IR $\nu_{max}$ $cm^{-1}$ neat: 2139 (N=C); NMR: 500MHz $^1H$ ($CDCl_3$) δ ppm 5.94 (s, 1 H), 7.12 (t, *J*=8.52 Hz, 2 H), 7.25 - 7.29 (m, 1 H), 7.30 - 7.35 (m, 3 H), 7.41 (s, 1 H).

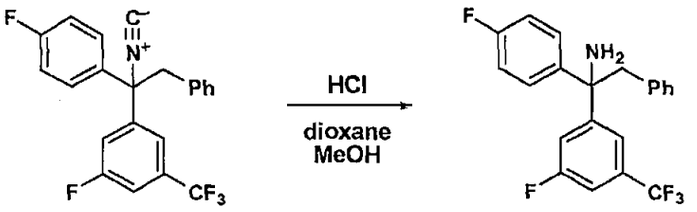
**Procedure 152**




**[00458]** To a solution of 1-fluoro-3-((4-fluorophenyl)(isocyano)methyl)-5-(trifluoromethyl)benzene (234 mg, 0.79 mmol) in toluene (8 mL) was added tetrabutylammonium bromide (75 mg, 0.23 mmol) and benzyl bromide (0.185 mL, 1.56 mmol) followed by 50% KOH(aq) (2.5 mL). The reaction mixture was vigorously stirred for 3 minutes. The reaction mixture was transferred to a separatory funnel and washed with $H_2O$ (2.5 mL). The organic fraction was dried over $Na_2SO_4$, filtered through a pad of basic alumina and concentrated under reduced pressure. The residue was purified by chiral prep HPLC (Chiralcel OD-H column, 20 x 250 mm isocratic elution with isopropyl alcohol (10%) and heptane, 20 mL/min, monitoring at 254 nm) to give (R)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene (RT = 6.2 minutes, 128 mg, 42% yield) and (S)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene (RT = 7.8 minutes, 128 mg, 42% yield) as clear colorless oils. LCMS: RT = 1.94 min [M-NC] 361.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 3.61 (d, *J*=13.18 Hz, 1 H), 3.67 (d, *J*=13.18 Hz, 1 H), 6.83 (d, *J*=7.47 Hz, 2 H), 7.08 (t, *J*=8.57 Hz, 2 H), 7.17 - 7.34 (m, 8 H).

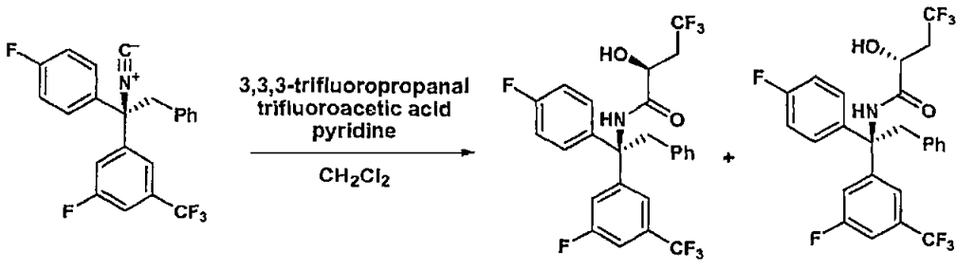
[00459] The reaction could be run in 16% ee of the (R) isomer by substituting *N*-benzylcinchoninium chloride in place of tetrabutylammonium bromide and running the reaction at 0 °C for 1 h.

**Procedure 153**




[00460] To a solution of 1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene (20 mg, 0.052 mmol) in MeOH (0.4 mL) was added 4 N HCl in dioxane (0.3 mL) and the reaction mixture was stirred for 3 minutes. The reaction solvent was evaporated under a stream of nitrogen. The residue was diluted with 1 N NaOH (5 mL) and the aqueous portion was extracted with $Et_2O$ (3 x 5 mL). The combined organic fractions were washed with sat. NaCl (5 mL), dried over $Na_2SO_4$, filtered and evaporated under vacuum to yield 1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethanamine (19 mg, 97% yield) as a clear glass.

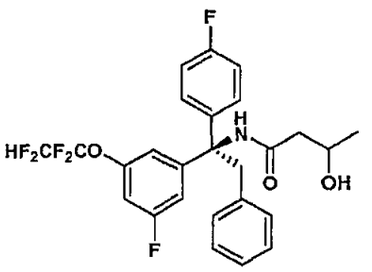
**Procedure 154**




[00461] To a solution of (R)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene (22 mg, 0.057 mmol) in $CH_2Cl_2$ (0.10 mL) was added 3,3,3-trifluoropropanal (0.010 mL, 0.11 mmol) and pyridine (0.018 mL, 0.23 mmol) followed by trifluoroacetic acid (0.009 mL, 0.11 mmol). The reaction mixture was heated at 40 °C for 4 h. Additional 3,3,3-trifluoropropanal (0.010 mL, 0.11 mmol) was added and heating at 40 °C for was continued for 2 h. The reaction

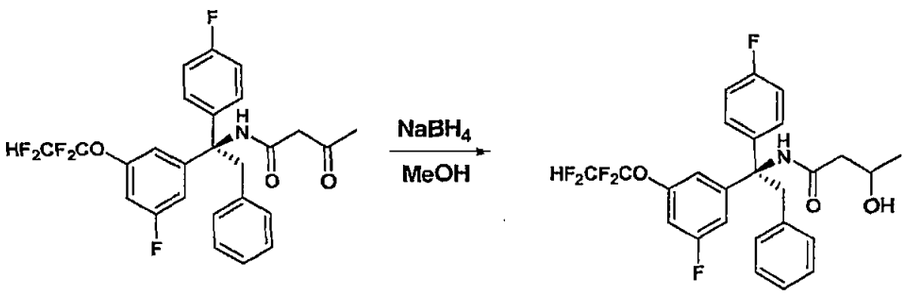
mixture was allowed to cool to room temperature and the solvent was removed under a stream of nitrogen. The residue was purified by prep TLC plate, eluting with 40% $Et_2O$/hexane, to yield (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 329A, 11 mg, 36% yield) and (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 329B, 11 mg, 36% yield) as clear colorless oils. (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 329A): LCMS: RT = 1.81 min [M+H] 518.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.24 - 2.36 (m, 1 H) 2.81 - 2.91 (m, 2 H), 3.74 (d, *J*=13.18 Hz, 1 H), 3.99 (d, *J*=13.18 Hz, 1 H), 4.43 (dd, *J*=10.11, 3.52 Hz, 1 H), 6.60 (d, *J*=7.47 Hz, 2 H), 6.99 - 7.07 (m, 4 H), 7.12 - 7.28 (m, 6 H), 7.70 (s, 1 H). (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 329B): LCMS: RT = 1.82 min [M+H] 518.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.23 - 2.35 (m, 1 H), 2.77 - 2.88 (m, 2 H), 3.73 (d, *J*=12.75 Hz, 1 H), 3.99 (d, *J*=12.74 Hz, 1 H), 4.45 (dd, *J*=8.35, 3.95 Hz, 1 H), 6.61 (d, *J*=7.47 Hz, 2 H), 6.98 - 7.04 (m, 4 H), 7.16 - 7.28 (m, 6 H), 7.69 (s, 1 H). The stereochemistry of (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 329A) and (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 329B) was assigned arbitrarily.

## EXAMPLE 330



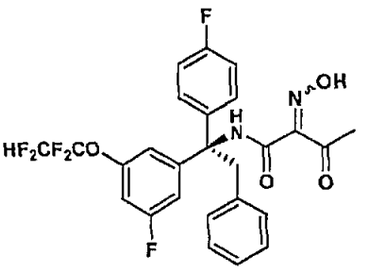
**N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxybutanamide**

### Procedure 155



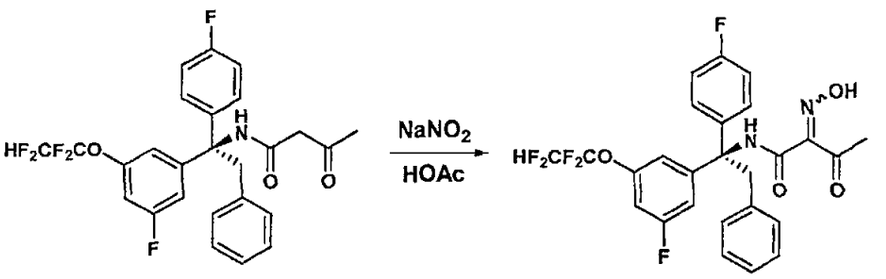
**[00462]** To a solution of (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-oxobutanamide (Example 251, 51 mg, 0.1 mmol), in MeOH (1 mL) was added $NaBH_4$(10 mL, 0.26 mmol). The reaction mixture was stirred at rt for 1 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (Axia luna column, 30 x 100 mm, 40-100% MeOH/$H_2O$ with 0.1% TFA over 10 min, flow rate 40 mL/min, monitoring at 220 nm) to yield N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxybutanamide (Example 330) as a pale yellow oil (28 mg, 55% yield). LCMS: RT = 2.66 min [M+H] 512.2 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.13 - 7.23 (3 H, m), 7.02 - 7.08 (2 H, m, *J*=4.96, 4.56, 4.56, 2.43, 2.43 Hz), 6.96 - 7.02 (2 H, m), 6.85 - 6.93 (4 H, m), 6.67 (2 H, d, *J*=7.07 Hz), 5.87 (1 H, t, *J*=2.78 Hz), 4.10 - 4.20 (1 H, m), 3.95 (1 H, dd, *J*=12.76, 10.74 Hz), 3.73 (1 H, dd, *J*=12.76, 10.74 Hz), 2.32 - 2.38 (2 H, m), 1.22 (3 H, d, *J*=6.32 Hz).

## EXAMPLE 331



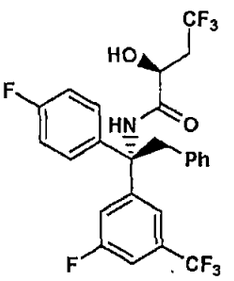
**(R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-(hydroxyimino)-3-oxobutanamide**

### Procedure 156



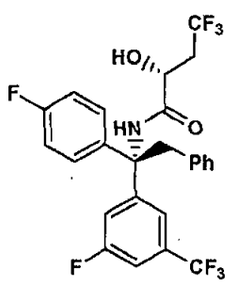
**[00463]** To a solution of (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-oxobutanamide (Example 251, 62 mg, 0.12 mmol), in acetic acid (0.5 mL) was added dropwise a solution of $NaNO_2$ (25 mg, 0.36 mmol) in $H_2O$ (0.5 mL). The reaction mixture was stirred at rt for 10 min and diluted with $H_2O$ (10 mL). The aqueous portion was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-(hydroxyimino)-3-oxobutanamide (Example 331) as a yellow solid (65 mg, 100% yield). LCMS: RT = 1.99 min [M+H] 539.4 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 10.07 (1 H, s), 7.15 - 7.21 (2 H, m), 7.07 - 7.14 (7 H, m), 7.00 - 7.05 (4 H, m), 6.84 - 6.96 (6 H, m), 6.55 - 6.60 (2 H, m), 5.88 (1 H, t, *J*=2.78 Hz), 3.91 (1 H, d, *J*=13.14 Hz), 3.72 - 3.80 (1 H, m), 2.52 (3 H, s).

**EXAMPLE 332A**



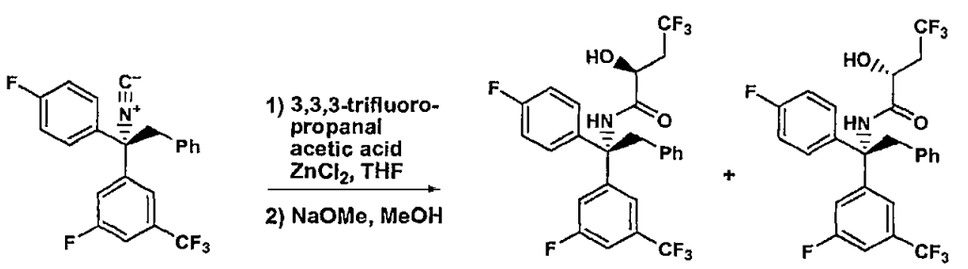
**(S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide**

**EXAMPLE 332B**



**(R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide**

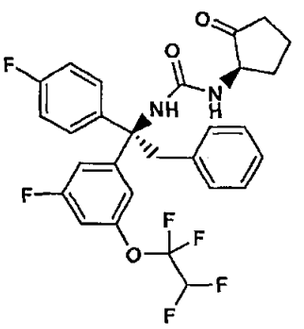
**Procedure 157**




**[00464]** To a solution of (S)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene prepared as described in Procedure 149, 150, 151 and 152 (23 mg, 0.060 mmol) in THF (0.25 mL) was added 3,3,3-trifluoropropanal (0.006 mL, 0.071 mmol) and acetic acid (0.004 mL, 0.071 mmol)

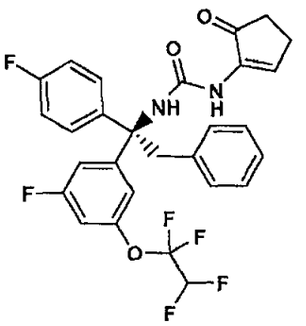
followed by a 0.5M solution of zinc chloride in THF (0.142 mL, 0.071 mmol). The reaction mixture was heated at 55 °C for 16 h. The reaction mixture was allowed to cool to room temperature then a solution of 25% NaOMe in MeOH (25 uL) was added and the reaction mixture was heated at 40 °C for 18 h. The reaction mixture was allowed to cool to room temperature then a drop of acetic acid was added and the solvent was removed under a stream of nitrogen. The residue was purified by prep TLC plate, eluting with 25% EtOAc/hexanes, to yield (S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 332A, 7 mg, 22% yield) and (R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 332B, 6 mg, 18% yield) as clear colorless oils. (S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 332A): LCMS: RT = 1.82 min [M+H] 518.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.23 - 2.35 (m, 1 H) 2.77 - 2.88 (m, 2 H) 3.73 (d, *J*=12.75 Hz, 1 H) 3.99 (d, *J*=12.74 Hz, 1 H) 4.45 (dd, *J*=8.57, 4.17 Hz, 1 H) 6.61 (d, *J*=7.47 Hz, 2 H) 6.98 - 7.04 (m, 4 H) 7.16 - 7.28 (m, 6 H) 7.69 (s, 1 H). (R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 332B): LCMS: RT = 1.81 min [M+H] 518.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.23 - 2.34 (m, 1 H) 2.77 - 2.88 (m, 2 H) 3.73 (d, *J*=12.75 Hz, 1 H) 3.99 (d, *J*=12.74 Hz, 1 H) 4.44 - 4.47 (m, 1 H) 6.61 (d, *J*=7.47 Hz, 2 H) 6.98 - 7.07 (m, 4 H) 7.14 - 7.28 (m, 6 H) 7.69 (s, 1 H). The stereochemistry of (S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 332A) and (R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxybutanamide (Example 332B) was assigned arbitrarily.

**EXAMPLE 333**



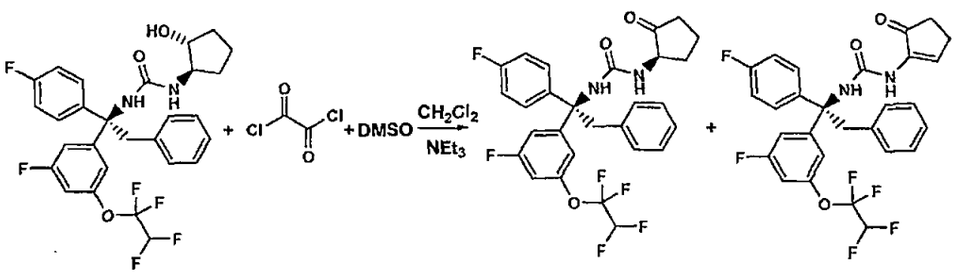
**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((R)-2-oxocyclopentyl)urea**

**EXAMPLE 334**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(5-oxocyclopent-1-enyl)urea**

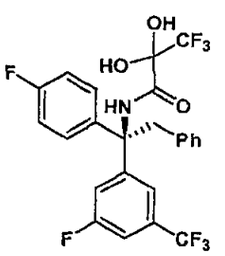
**Procedure 158**



**[00465]** To a solution of oxalyl chloride (2 M in $CH_2Cl_2$, 150 uL) at -78 °C was added DMSO (47 mg, 0.60 mmol) dropwise. The reaction mixture was stirred at -78 °C for 15 min, then 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-

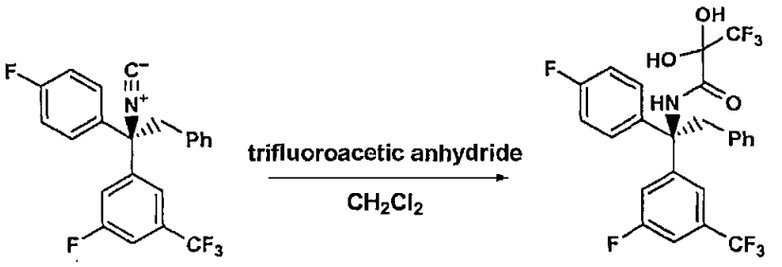
fluorophenyl)-2-phenylethyl)-3-((1R,2R)-2-hydroxycyclopentyl)urea (Example 246, 113 mg, 0.20 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and purified by ISCO flash chromatography with EtOAc and hexane as eluting solvent to yield (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(5-oxocyclopent-1-enyl)urea (Example 333) as a white solid (15 mg, 14% yield) and 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((R)-2-oxocyclopentyl)urea (Example 334) as a white solid (66 mg, 60% yield). (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(5-oxocyclopent-1-enyl)urea: HPLC: RT = 3.99 min [M+H] 551.09 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 - 1.37 (m, 1 H), 1.36 - 1.58 (m, 1 H), 1.68 - 1.84 (m, 1 H), 1.84 - 2.00 (m, 2 H), 2.12 - 2.30 (m, 3 H), 2.48 - 2.73 (m, 1 H), 3.58 - 4.05 (m, 3 H), 5.35 - 5.52 (m, 1 H), 5.64 - 6.03 (m, 2 H), 6.62 - 6.78 (m, 2 H), 6.78 - 7.02 (m, 5 H), 7.04 - 7.23 (m, 5 H). 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((R)-2-oxocyclopentyl)urea: HPLC: RT = 4.09 min [M+H] 549.1 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 1.84 – 1.94 (m, 2 H), 2.43 – 2.62 (m, 2 H) 3.92 (dd, 2 H) 5.82 (t, 1 H) 6.62 – 6.78 (m, 2 H) 6.79 – 6.88 (m, 1 H) 6.90 – 7.01 (m, 5 H), 7.01 – 7.15 (m, 3 H), 7.14 – 7.25 (m, 2 H), 7.62 – 7.74 (m, 1 H), 8.09 – 8.25 (m, 1 H).

**EXAMPLE 335**



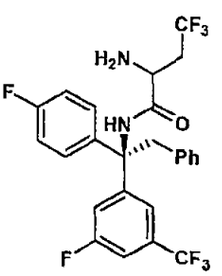
**(R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,2-dihydroxypropanamide**

**Procedure 159**



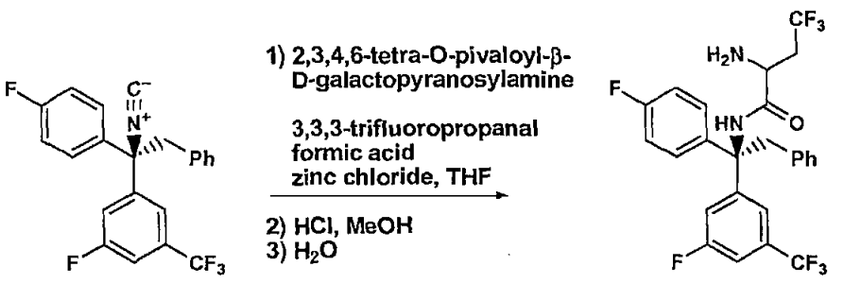

**[00466]** To a solution of (R)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene (26 mg, 0.067 mmol) prepared as described in Procedure 4, 149, 150, 151 and 152, in $CH_2Cl_2$ (0.7 mL) at -78 °C was added trifluoroacetic anhydride (0.06 mL, 0.42 mmol) and the reaction mixture was allowed to warm to -40 °C over 6 h. The reaction mixture was quenched by the addition of $H_2O$ (5 mL) then allowed to warm to room temperature. The mixture was extracted with $CH_2Cl_2$ (3 x 5 mL) then dried over $Na_2SO_4$, filtered and volatiles removed under vacuum. The residue was purified using silica gel (4 g), eluting with 0 to 100% $Et_2O$/hexane, to give (R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,2-dihydroxypropanamide (Example 335, 11 mg, 32%) as a clear colorless glass. LCMS: RT = 1.69 min [M-H] 518.0 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% $NH_4Ac$; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) δ ppm 3.71 (d, *J*=13.18 Hz, 1 H) 3.92 (d, *J*=13.18 Hz, 1 H) 6.61 (d, *J*=7.47 Hz, 2 H) 6.98 - 7.06 (m, 4 H) 7.12 - 7.30 (m, 7 H).

**EXAMPLE 336**



**2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide**

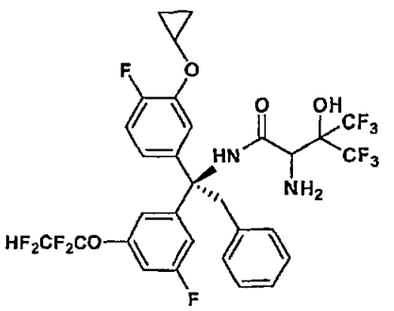
**Procedure 160**




[00467] To a solution of (R)-1-fluoro-3-(1-(4-fluorophenyl)-1-isocyano-2-phenylethyl)-5-(trifluoromethyl)benzene (35 mg, 0.09 mmol) prepared as described in Procedure 4, 149, 150, 151 and 152, in THF (0.7 mL) was added 3,3,3-trifluoropropanal (0.008 mL, 0.095 mmol), 2, 3, 4, 6-O-pivaloyl-β-D-galactopyranosylamine (49 mg, 0.095 mmol) and formic acid (0.004 mL, 0.10 mmol). The reaction mixture was cooled to - 20 °C then a 0.5 M solution of zinc chloride in THF (0.19 mL, 0.095 mmol) was added and the reaction mixture was stirred at 0 °C for 16 h. Additional 3,3,3-trifluoropropanal (0.016 mL, 0.19 mmol), 2, 3, 4, 6-O-pivaloyl-β-D-galactopyranosylamine (98 mg, 0.19 mmol), formic acid (0.008 mL, 0.20 mmol) and zinc chloride solution (0.38 mL, 0.19 mmol) were added and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The volatiles were removed under vacuum and the residue was dissolved in $CH_2Cl_2$ (5 mL) and washed with sat. $NaHCO_3$ (2 x 10 mL) and $H_2O$ (10 mL) then dried over $MgSO_4$, filtered and volatiles removed under vacuum. The flask containing the residue was cooled in an ice bath then sat. HCl in methanol (2 mL) was added and the reaction mixture was stirred for 0.5 h at 0 °C then rt for 1.5 h. $H_2O$ (0.5 mL) and MeOH (1.5 mL) were added and the reaction mixture was stirred for 24 h. Most of MeOH was removed under a stream of nitrogen then the reaction mixture was diluted with 1 N NaOH (5 mL) and extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic fractions were washed with $H_2O$ (5 mL), dried over $Na_2SO_4$, filtered and volatiles removed under vacuum. The residue was purified by prep HPLC (RT = 6.2 min using Axia Luna 5μ C18 30 x 100 mm column with flow rate of 40 mL/min over

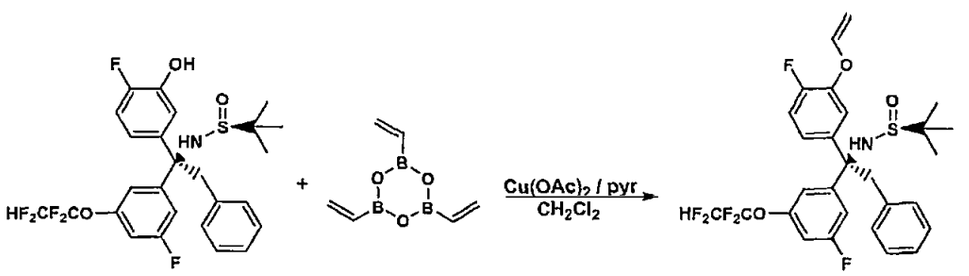
10 min period. 20 to 100% solvent B. Solvent A = 10/90/0.1% ACN/$H_2O$/TFA. Solvent B = 90/10/0.1%) to give the trifluoroacetic acid salt of 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 336, 9 mg, 15% yield) as a clear colorless glass. LCMS: RT = 1.34 min [M+H] 517.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% acetonitrile/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CD_3Cl$) δ ppm 2.59 - 2.70 (m, 1 H), 2.72 - 2.84 (m, 1 H), 3.93 - 4.03 (m, 2 H), 4.34 (dd, *J*=9.01, 3.73 Hz, 1 H), 6.68 - 6.72 (m, 2 H), 7.02 - 7.09 (m, 2 H), 7.11 - 7.22 (m, 3 H), 7.25 - 7.40 (m, 5 H).

**EXAMPLE 337**



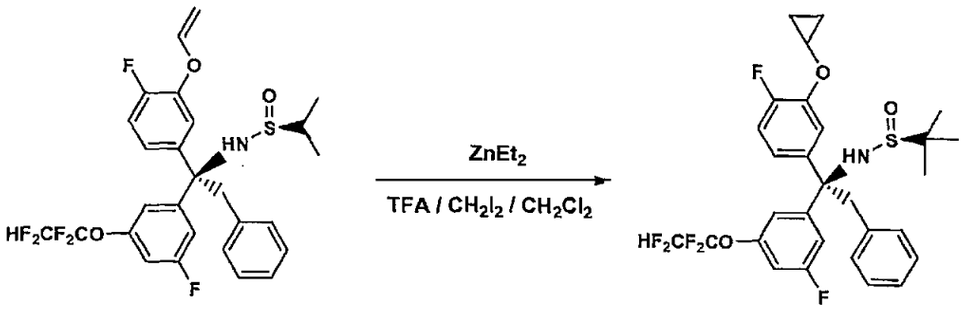
**2-amino-N-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl)butanamide**

**Procedure 161**



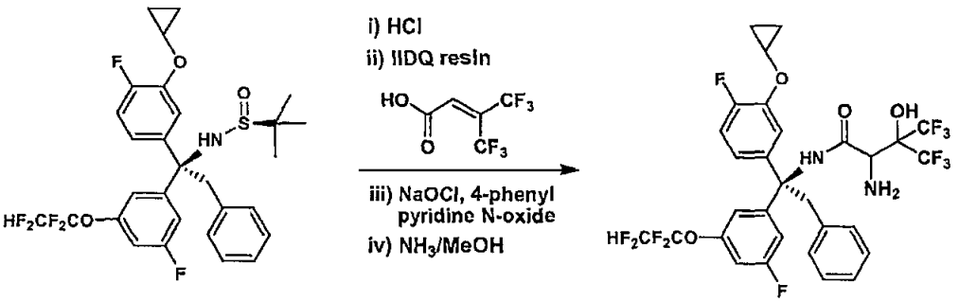
**[00468]** To a solution of (S)-N-((R)-1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide, prepared as described in Procedure 109, 110, 111, 112, 113, 114, (0.545 g , 1 mmol)

in $CH_2Cl_2$ (10 mL) was added $Cu(OAc)_2$ (0.182 g, 1 mmol), followed by pyridine (0.79 g, 10 mmol) and 2,4,6-trivinyl-1,3,5,2,4,6-trioxatriborinane (0.159 g, 0.66 mmol). The reaction mixture was stirred overnight under ambient air and filtered through a plug of celite and neutral alumina. The solid was washed with ethyl acetate and the filtrate was concentrated under reduced pressure to yield (S)-N-((R)-1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as an off-white foam (0.495 g, 87% yield). LCMS: RT = 3.653 min [M+H] 572.2 (Phenomenex Luna C18 5 μ column, eluting with 10-90% aqueous acetonitrile containing 0.1% trifluoroacetic acid over a 4 minute gradient, monitoring at 220 nM). $^1H$ NMR ($CDCl_3$) ppm 7.2-7.1 (m, 5 H), 7.02 (d, J=6.2 Hz, 1 H), 6.89 ( d, J=6.2 Hz, 2 H), 6.82 (d, J=8.8 Hz, 1H), 6.68 (br, 2 H), 6.54 (dd, J=6.2 Hz, 13.6Hz, 1 H), 5.84 (t, J=52.7 Hz, 1 H), 4.62 (dd, J=2.2 Hz, 13.6 Hz, 1 H), 4.40 (dd, J=2.2Hz, 5.7 Hz, 1 H), 4.21 (s, 1 H), 3.95 (d, J=12.8 Hz, 1H), 3.55 (d, J=12.7 Hz, 1 H), 1.19 (s, 9 H).



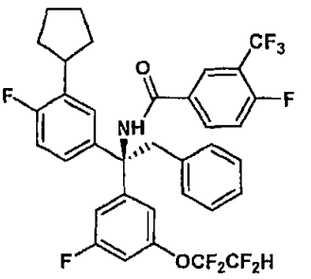

**[00469]** To an oven-dried 3-necked 25 mL RB flask under nitrogen was added $CH_2Cl_2$ (3.5 mL) and 1 M diethylzinc solution in hexane (3.43 mL, 3.43 mmol). The flask was cooled in an ice-bath and a solution of trifluoroacetic acid (0.391 g, 3.43 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise via syringe. After stirring for 15 min, a solution of diiodomethane (0.918 g, 3.43 mmol) in $CH_2Cl_2$ (1 mL) was added. The reaction mixture was stirred at rt for 15 min, followed by addition of (S)-N-((R)-1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (0.495 g, 0.87 mmol) in $CH_2Cl_2$ (1 mL). The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction mixture was diluted with $CH_2Cl_2$ and washed successively with sat. sodium

bicarbonate, water, sat. NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by ISCO using a gradient of 5-70% EtOAc/hexane as eluent to yield (S)-N-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a white foam (0.347 g, 71% yield). HPLC: RT = 3.668 min [M+H] 586.3 (Phenomenex Luna C18 5μ column, eluting with 10-90% aqueous acetonitrile containing 0.1% trifluoroacetic acid over a 4 minute gradient, monitoring at 220 nm). $^1$H NMR ($CDCl_3$) ppm 7.2-7.05 (m, 6 H), 6.91 (d, J=6.6 Hz, 2H), 6.83 (d, J=8.4 Hz, 1 H), 6.71 (m, 2 H), 5.84 (t, J=53.1 Hz, 1 H), 4.21 (s, 1 H), 3.99 (d, J=12.3 Hz, 1 H), 3.62 (m, 1 H), 3.56 (d, J=12.8 Hz, 1 H), 1.22 ( s, 9 H), 0.72-0.65 (m, 4 H).



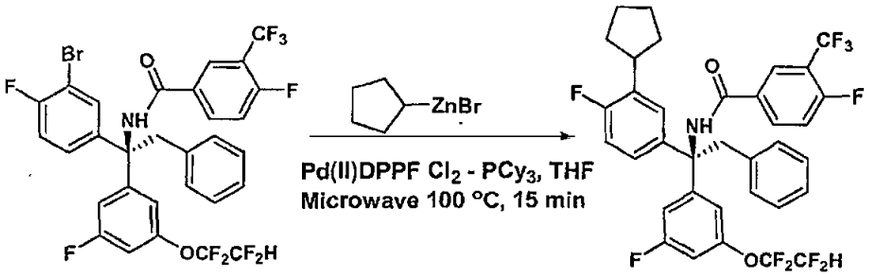

**[00470]** Following Procedure 6, 90, 91 and 92, 2-amino-N-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl)butanamide (Example 337) was prepared. HPLC: RT = 3.466 min [M+H] 705.3 (Phenomenex Luna C18 5 μ column, eluting with 10-90% aqueous acetonitrile containing 0.1% trifluoroacetic acid over a 4 minute gradient, monitoring at 220 nM). $^1$H NMR($CD_2Cl_2$) ppm 8.97 (s, 1 H), 7.14-6.5 (m, 11 H), 5.84 (t, J=53.1 Hz, 1 H), 3.79 (d, J=12.3Hz, 1 H), 3.67 (s, 1 H), 3.62 (d, J=13.1 Hz, 1 H), 3.52 (m, 1 H), 1.48 (br, 1 H), 0.55 (m, 4 H).

## EXAMPLE 338




**(R)-N-(1-(3-cyclopentyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

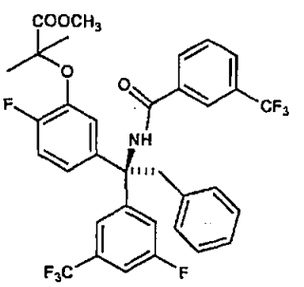
**Procedure 162**




**[00471]** To a solution of (S)-N-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide, prepared as described in Procedure 3, 62, 5, 6 and 7 in THF (0.1 M, 0.5 mL, 0.05 mmol) was added dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane (4 mg, 0.0054 mmol) and tricyclohexylphosphine (1.0 M in toluene, 0.05 mL, 0.05 mmol), followed by cyclopentyl zinc bromide (0.5 M in THF, 0.04 mL, 0.2 mmol). The reaction mixture was heated at 100 °C under microwave irradiation for 15 min. The reaction mixture was cooled and filtered through a plug of silica. The solid was washed with THF (2 mL) and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (1 mL) and purified by preparative HPLC (RT = 14.89 min, Sunfire Prep C18 OBD 19x100 mm eluting with 18-90% MeCN/$H_2O$ over 12 minutes and at 90% for 8 additional minutes containing 0.1% TFA; 20 mL/min, monitoring at 220 nm) to yield (R)-N-(1-(3-cyclopentyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-

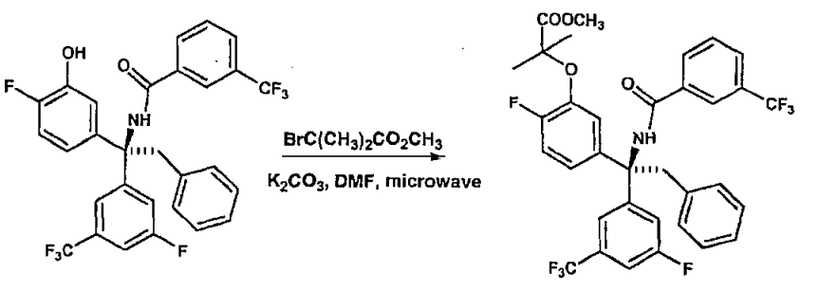
(trifluoromethyl)benzamide (Example 338) as a colorless gum (13 mg, 19% yield). LCMS: RT = 4.56 min [M+H] 684.3 (4 min Sunfire S5 C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1H$ NMR (500 MHz, $CD_3Cl$) δ ppm 7.90 (1 H, d, *J*=6.60 Hz), 7.84 (1 H, dd, *J*=8.25, 4.40 Hz), 7.28 (1 H, t, *J*=9.07 Hz), 7.23 (1 H, t, *J*=7.42 Hz), 7.16 (2 H, t, *J*=7.42 Hz), 7.01 - 7.05 (2 H, m), 6.92 - 6.96 (2 H, m), 6.86 (1 H, dd, *J*=6.60, 2.75 Hz), 6.79 - 6.82 (1 H, m), 6.69 (2 H, d, *J*=7.15 Hz), 6.65 (1 H, s), 5.75-5.98 (1 H, t), 4.12 (1 H, d, *J*=13.20 Hz), 3.66 (1 H, d, *J*=13.20 Hz), 3.14 - 3.21 (1 H, m), 1.94 - 2.03 (2 H, m), 1.62 - 1.72 (4 H, m), 1.43 - 1.48 (1 H, m), 1.36 - 1.42 (1 H, m).

**EXAMPLE 339**




**(*R*)-methyl 2-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)benzamido)ethyl)phenoxy)-2-methylpropanoate**

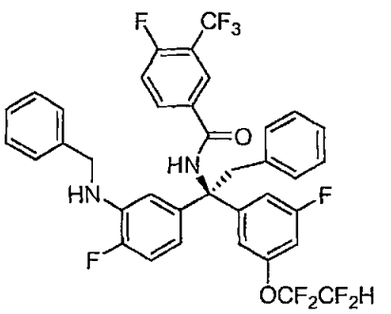
**Procedure 163**




**[00472]** A solution of (R)-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide benzamide, prepared as described in Example 264, (226 mg, 0.4 mmol), methyl 2-bromo-2-methylpropanoate (0.10 mL) and $K_2CO_3$ (326 mg, 2.36 mmol) in DMF (1 mL) was

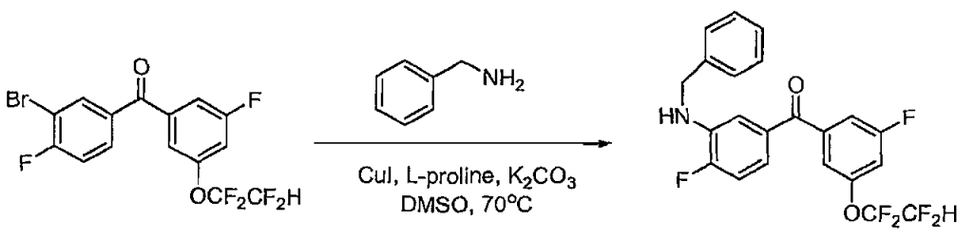
heated at 180 °C under microwave condition for 1200 seconds. The reaction mixture was allowed to cool, diluted with EtOAc and the organic layer was washed with $H_2O$ (2 x), saturated NaCl, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by ISCO flash chromatography (silica gel, hexanes/EtOAc) to give (R)-methyl 2-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl)benzamido)ethyl)phenoxy)-2-methylpropanoate (Example 273, 76 mg, yield: 29%). LCMS: RT = 2.26 min [M+H] 666.4 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**EXAMPLE 340**



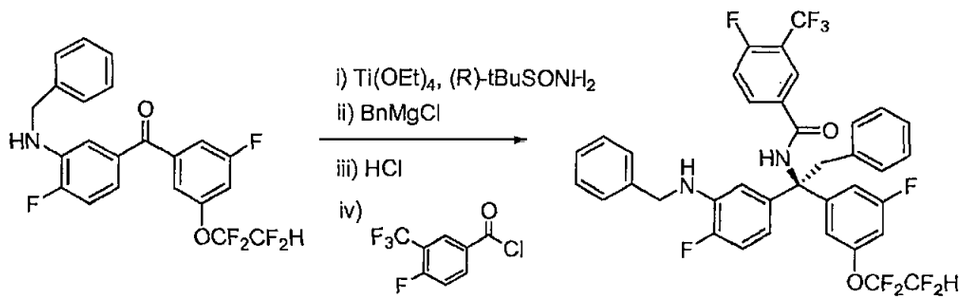

**(R)-N-(1-(3-(benzylamino)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

**Procedure 164**



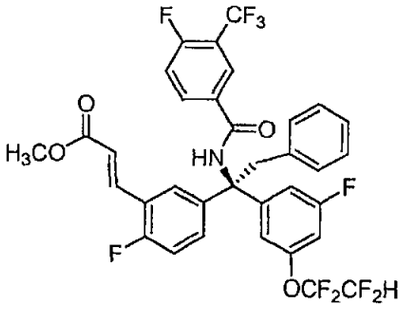

**[00473]** To a solution of (3-bromo-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)-phenyl)methanone, prepared as described in Procedure 62, (110 mg, 0.27 mol) in DMSO (2 mL) at rt was added benzylamine (43 μL, 0.4 mol), copper (I) iodide (5 mg, 0.03 mol), L-proline (23 mg, 0.05 mol), and potassium carbonate (55 mg, 0.4 mol). The reaction mixture was degassed and heated for 4 h at

70 °C. After cooling to rt, the reaction mixture was partitioned between water and EtOAc. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified via ISCO chromatography (4 g column, 0-30 % EtOAc/hexane) to yield (3-(benzylamino)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanonea as a clear, colorless oil (95 mg, 81% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, *J*=6.57, 2.02 Hz, 1 H), 7.79 (m, 1 H), 7.27 (m, 10 H), 6.95 (m, 3 H), 6.87 (dd, *J*=8.59, 2.53 Hz, 1 H), 6.73 (d, *J*=7.07 Hz, 2 H), 6.54 (m, 2 H), 5.87 (m, 1 H), 4.40 (s, 2 H), 3.75 (d, *J*=13.14 Hz, 1 H).



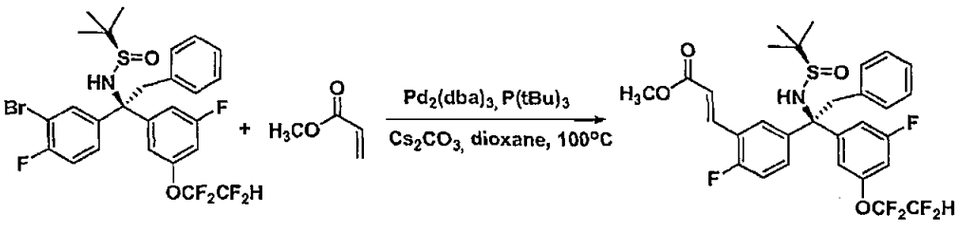

**[00474]** Using the methods described in Procedures 5, 6 and 7, (R)-N-(1-(3-(benzylamino)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 340) was prepared as a white solid (8 mg, 59% yield). $^1$H NMR (400 MHz, CDCl3) δ ppm 7.90 (dd, *J*=6.57, 2.02 Hz, 1 H), 7.79 (m, 1 H), 7.27 (m, 10 H), 6.95 (m, 3 H), 6.87 (dd, *J*=8.59, 2.53 Hz, 1 H), 6.73 (d, *J*=7.07 Hz, 2 H), 6.54 (m, 2 H), 5.87 (m, 1 H), 4.40 (s, 2 H), 3.75 (d, *J*=13.14 Hz, 1 H).

**EXAMPLE 341**

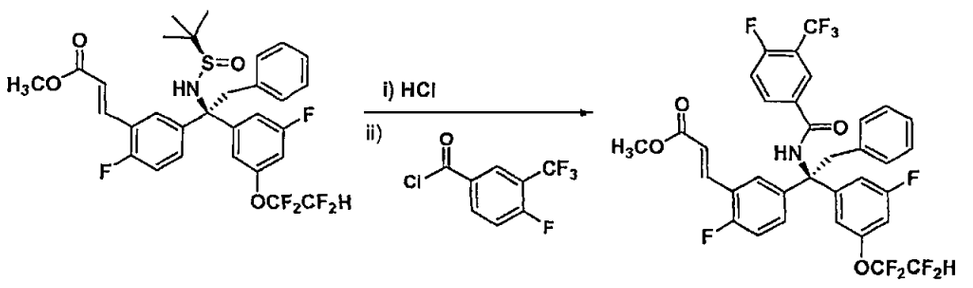


**(R,E)-methyl 3-(2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)phenyl)acrylate**

**Procedure 165**

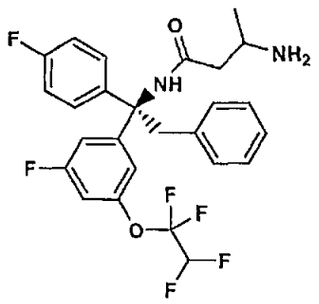



**[00475]** To a solution of (R)-N-((S)-1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)-phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide, prepared as described in Procedure 3, 62, 5 and 6, (500 mg, 0.82 mmol) in DMF (5 mL) at rt was added methyl acrylate (0.74 mL, 8.22 mmol), $Pd_2(dba)_3$ (75 mg, 0.082 mmol), tri-t-butyl phosphine (89 μL, 0.33 mmol), and cesium carbonate (536 mg, 1.64 mmol). The reaction mixture was degassed with argon and was heated at 100 °C for 4 h. The reaction mixture was poured into water and the aqueous phase extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by ISCO chromatography (4 g column, 0-40% EtOAc/hexane) to yield (E)-methyl 3-(5-((R)-1-((R)-1,1-dimethylethylsulfinamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-fluorophenyl)acrylate as a white foam (485 mg, 96% yield). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (d, *J*=16.42 Hz, 1 H), 7.59 (dd, *J*=6.69, 2.15 Hz, 1 H), 7.41 (m, 1 H), 7.16 (m, 4 H), 6.94 (dd, *J*=7.33, 1.77 Hz, 2 H), 6.86 (d, *J*=8.84 Hz, 1 H), 6.73 (t, *J*=4.93 Hz, 2 H), 6.53 (d, *J*=16.17 Hz, 1 H), 5.88 (m, 1 H), 4.29 (s, 1 H), 4.03 (d, *J*=12.38 Hz, 1 H), 3.79 (s, 3 H), 3.62 (d, *J*=12.38 Hz, 1 H), 1.24 (m, 9 H).



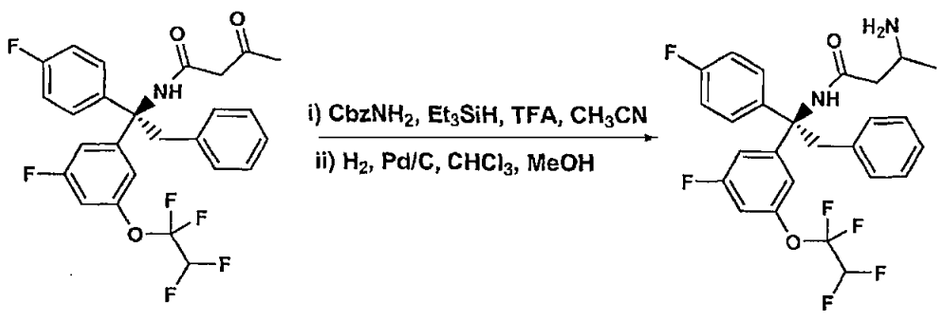
[00476] Using the methods described in Procedures 6 and 7, (R,E)-methyl 3-(2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)phenyl)acrylate (Example 341) was prepared as a white solid. LCMS: RT = 4.46 min [M+H+60] 781 (Phemonenex Luna C18, 50 x 4.6 mm, 4 min gradient, eluting with 105 -90% MeOH/$H_2O$ containing 0.1%TFA, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.92 (m, 1 H), 7.83 (m, 1 H), 7.69 (d, *J*=16.42 Hz, 1 H), 7.28 (m, 3 H), 7.18 (m, 2 H), 7.09 (t, *J*=9.35 Hz, 1 H), 6.94 (m, 3 H), 6.72 (m, 3 H), 6.51 (m, 1 H), 6.42 (d, *J*=16.42 Hz, 1 H), 6.42 (d, *J*=16.42 Hz, 1 H), ), 5.88 (m, 1 H), 3.95 (d, *J*=14.91 Hz, 1 H), 3.82 (m, 4 H).

**EXAMPLE 342**



**3-amino-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide**

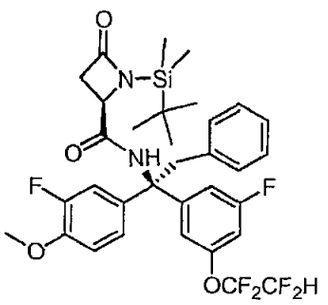
**Procedure 166**




[00477] To a solution of (R)-*N*-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-oxobutamide (Example 251, 27 mg, 0.053 mmol) in $CH_3CN$ (1 mL) was added Cbz-$NH_2$ (24 mg, 0.16 mmol), followed by triethylsilane (0.5 mL, 3 mmol), and TFA (0.4 mL, 5.3 mmol). The reaction mixture

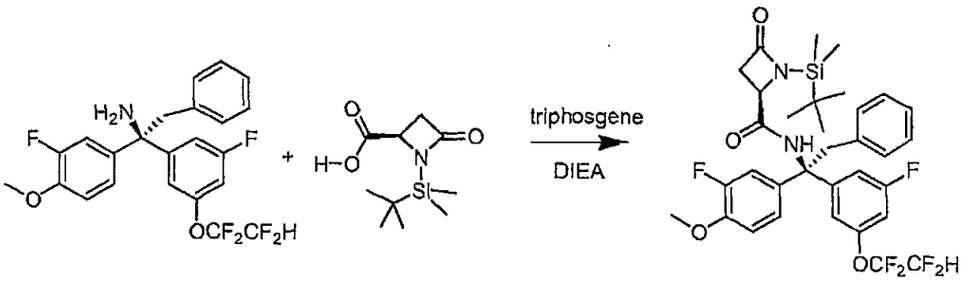
was stirred at rt for 3 days. The reaction mixture was concentrated and the residue was dissolved in a mixture of $CH_3OH$ (1 mL) and $CHCl_3$ (1 mL) and 10 wt% Pd/C (20 mg) was added. The reaction mixture was stirred under $H_2$ for 16 h and the solid was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by prep HPLC (Phenomenex Luna Axia, 5u 30 x 100, eluting with 10%-90% MeOH/$H_2O$ containing 0.1% TFA, gradient time 10 min, flow rate 40 ml/min, monitoring at 220 nm) to yield 3-amino-*N*-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide (Example 342, 5 mg, 19% yield). HPLC: RT = 3.28 min [M+H] 511.3 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.15 - 7.24, m, 3 H; 6.97 – 7.10, m, 4 H; 6.83 – 6.92, m, 3 H; 6.60 - 6.64, m, 3 H; 5.73 – 6.60, t, J = 54, 3.81 – 3.91, m, 1 H; 3.67 – 3.76, m, 1 H; 3.59, m, 1 H; 2.70, m, 2 H; 1.31, m, 3 H.

**EXAMPLE 343**



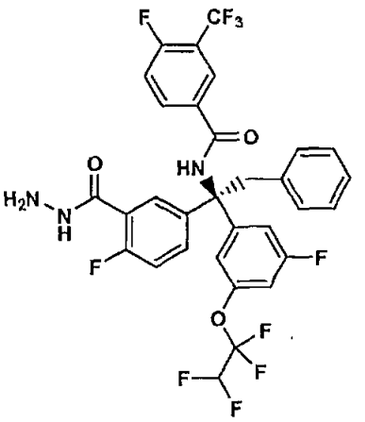

**(R)-1-(tert-Butyldimethylsilyl)-N-((R)-1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-oxoazetidine-2-carboxamide**

**Procedure 167**



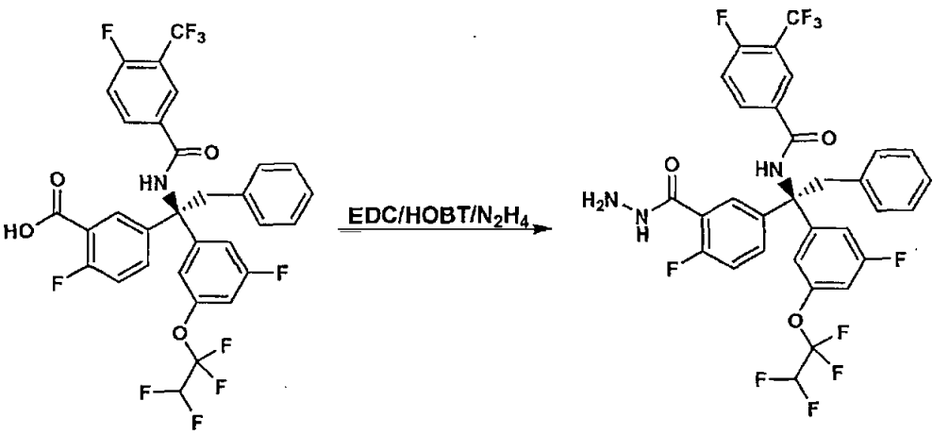

**[00478]** To a solution of (R)-1-(tert-butyldimethylsilyl)-4-oxoazetidine-2-carboxylic acid (126 mg, 0.55 mmol) in THF (1.5 mL) was added to a solution of triphosgene (54 mg, 0.18 mmol). The reaction mixture was stirred for 5 min at rt, followed by addition of 2,4,6- trimethylpyridine (203 µL, 1.54 mmol), a solution of (R)-1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine, prepared as described in Procedure 3, 62, 5 and 6, (50 mg, 0.11 mmol) in THF (0.6 mL), and *N,N*-diisopropylethylamine (268 µL, 1.54 mmol). The reaction mixture was stirred at room temperature for 40 min. Water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were washed with 2 N potassium carbonate and then sat. NaCl. The organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by ISCO Flash chromatography (Analogix column 4.2 g, eluting with hexane/EtOAc) to yield (R)-1-(tert-Butyldimethylsilyl)-N-((R)-1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-oxoazetidine-2-carboxamide (Example 343, 41 mg, 55 % yield). LCMS: RT = 4.18 min [M+H] 667.1 (Phenominex, Luna C18, 4.6 X 50 mm, 10%-90% MeOH/$H_2O$ containing 0.1% TFA, flow rate 4 mL/min, 4 min gradient, monitoring at 220 nm); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm -0.04 (s, 3 H), 0.24 (s, 3 H), 0.91 (s, 9 H), 2.79 (dd, *J*=15.4, 2.7 Hz, 1 H), 3.32 (dd, *J*=15.4, 6.6 Hz, 1 H), 3.79 - 3.85 (m, 1 H), 3.86 - 3.90 (m, 2 H), 3.91 (s, 3 H), 5.87 (none, 2 H), 6.59 (s, 1 H), 6.64 (d, *J*=7.1 Hz, 2 H), 6.75 (s, 1 H), 6.80 (d, *J*=9.3 Hz, 1 H), 6.87 - 6.94 (m, 4 H), 7.15 (t, *J*=7.4 Hz, 2 H), 7.20 (d, *J*=7.1 Hz, 1 H).

**EXAMPLE 344**



**((R)-4-fluoro-N-(1-(4-fluoro-3-(hydrazinecarbonyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

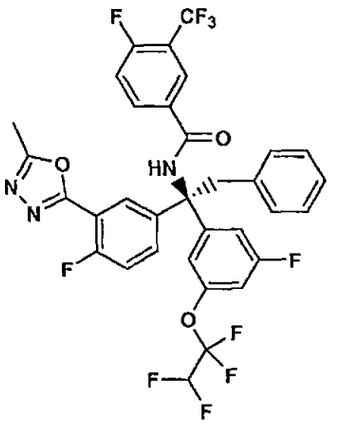
**Procedure 168**




**[00479]** To a solution of (R)-2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzoic acid, prepared as described in Procedures 3, 62, 5, 6, 7, 56, 57 and 23, (30 mg, 0.045 mmol) in dichloromethane (1 mL) was added hydroxybenzotriazole (8 mg, 0.058 mmol), followed by EDCI (11 mg, 0.058 mmol). The reaction mixture was stirred for 15 min at rt, then hydrazine hydrate was added (3 μL, 0.001 mmol) and the reaction mixture was stirred for an additional 15 min. The reaction mixture was loaded on an ISCO cartridge (4 g column) and eluted with 0 to 100% EtOAc in hexane to yield (R)-4-fluoro-N-(1-(4-fluoro-3-

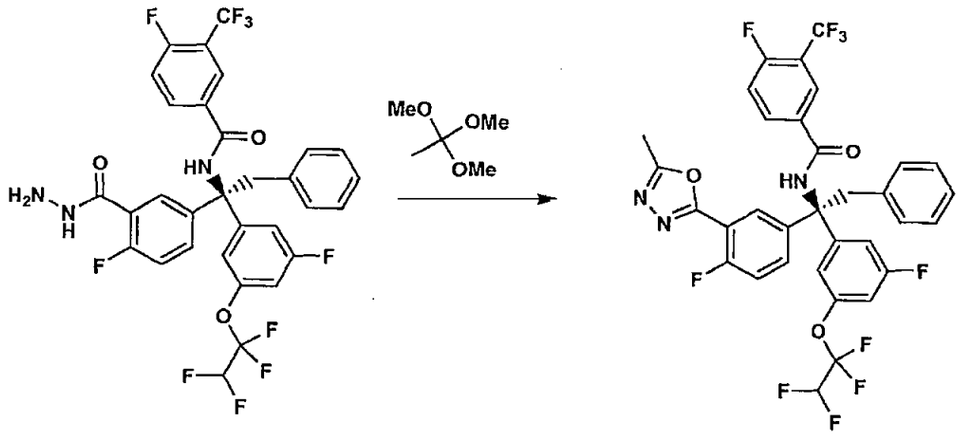
(hydrazinecarbonyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 344, 25 mg, 81% yield) as a white solid. LCMS: RT = 1.78 min [M+H] 674 (Chromolith Performance RP-18e column, 4.6 x 100 mm eluting with 10-90% ACN/$H_2O$ over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm).

**EXAMPLE 345**



**(R)-4-fluoro-N-(1-(4-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide**

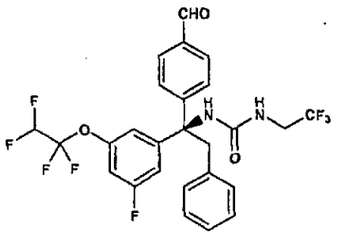
**Procedure 169**



**[00480]** A solution of (R)-4-fluoro-N-(1-(4-fluoro-3-(hydrazinecarbonyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-

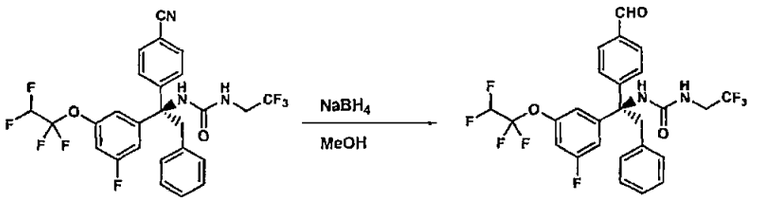
(trifluoromethyl)benzamide (Example 344, 35 mg, 0.052 mmol) in trimethyl orthoformate (1 mL) was heated at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by ISCO chromatography (4 g column, eluting with 0 to 100% EtOAc in hexane) to yield (R)-4-fluoro-N-(1-(4-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 345, 16 mg, 45% yield) as a white solid. LCMS RT = 2.06 min [M+H] 698 (Chromolith Performance RP-18e column, 4.6 X 100 mm eluting with 10-90% ACN/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**EXAMPLE 346**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-formylphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea**

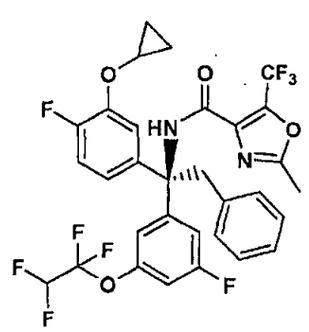
**Procedure 170**




**[00481]** To a solution of (R)-1-(1-(4-cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea, prepared as described in Procedure 3, 4, 5, 6, 25 and 56, (59 mg, 0.11 mmol) in methanol (2 mL) was added cobalt chloride hexahydrate (50 mg, 0.22 mmol), followed by sodium borohydride (40 mg, 1.1 mmol). The reaction mixture was stirred for 21 h at room temperature then quenched by addition of hydrochloric acid (1.0 M, 2 mL). The reaction mixture was extracted with ethyl acetate and the combined organic extracts

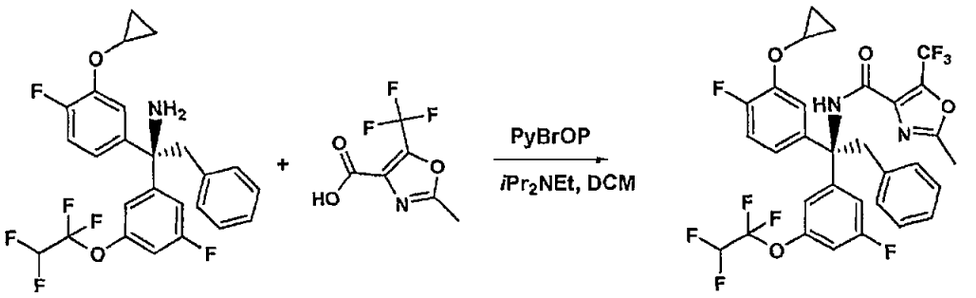
were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by ISCO flash chromatography (12 g silica gel, 0-100% ethyl acetate/hexane gradient over 11 min., flow rate 30 mL/min), then further purified by preparative HPLC (Phenomenex Onyx Monolithic 10 x 100 mm column; 10-90% acetonitrile/water with 0.1% trifluoroacetic acid gradient over 5 min., 25 mL/min) to yield (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-formylphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea (Example 346) as a white solid (2 mg, 3% yield). LCMS: RT = 1.07 min [M+H] 561 (Chromolith Performance 18e 4.6 x 100 mm column, 50-90% methanol/water with 0.1% trifluoroacetic acid gradient over 2 min, 5 mL/min); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 10.00 (1 H, s), 7.84 (2 H, d, *J*=8.24 Hz), 7.41 (2 H, d, *J*=8.79 Hz), 7.1 - 7.20 (5 H, m), 6.90 (3 H, m), 6.70 (2 H, d, *J*=7.15 Hz), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 5.16 (1 H, s), 4.88 (1 H, t, *J*=6.32 Hz), 3.79 (2 H, ddd, *J*=15.67, 9.07, 8.79 Hz).

**EXAMPLE 347**



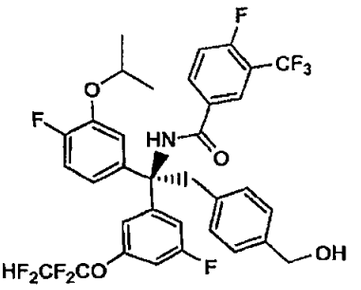

**(R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methyl-5-(trifluoromethyl)oxazole-4-carboxamide**

**Procedure 171**



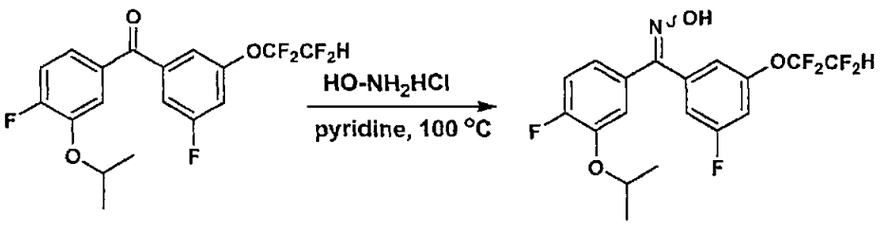

**[00482]** To a solution of (R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine, prepared as described in Procedure 109, 110, 111, 112, 113, 114, 161, (24 mg, 0.05 mmol) in $CH_2Cl_2$ (0.5 mL) was added 2-methyl-5-(trifluoromethyl)-oxazole-4-carboxylic acid (12 mg, 0.06 mmol), followed by PyBrOP (28 mg, 0.06 mmol) and $i$Pr$_2$NEt (9 mg, 0.065 mmol). The reaction mixture was stirred at rt for 72 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep HPLC (Phenomenex Luna 5 μ, 30 x 100 mm, eluting with 10% -90% MeOH/$H_2O$ containing 0.1% TFA, gradient time 10 min, flow rate 40 mL/min) to yield (R)-*N*-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methyl-5-(trifluoromethyl)oxazole-4-carboxamide (Example 347) as a white solid (23 mg, 70% yield). HPLC: RT = 2.18 min [M+H] 659.5 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.79, s, 1 H; 7.10 - 7.20, m, 3 H; 6.90 – 7.03, m, 5 H; 6.70, s, 1 H; 6.68, s, 1 H; 6.55 - 6.58, m, 1 H; 5.74 – 6.00, t, $J$ = 52; 4.15, 4.19, d, $J$ = 16, 1 H; 3.66 – 3.69, d, $J$ = 12, 1 H; 3.51 – 3.54, m, 1 H; 0.73 – 0.80, m, 1 H; 0.61 – 0.69, m, 2 H; 0.55 – 0.60, m, 1 H.

## EXAMPLE 348



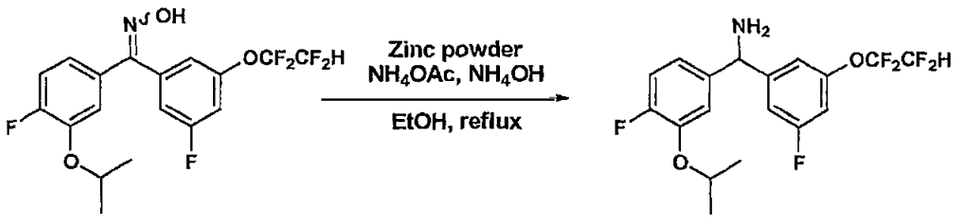
**(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl)phenyl)ethyl)-3-(trifluoromethyl)benzamide**

### Procedure 172



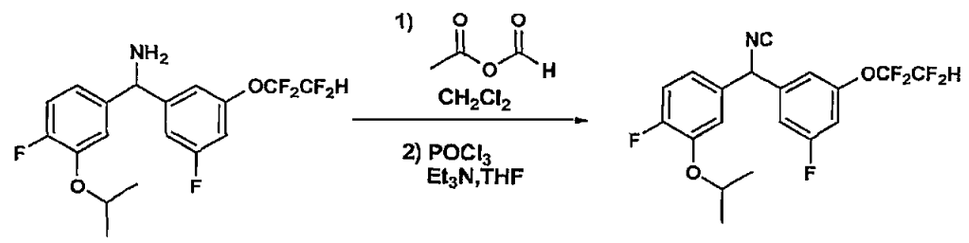

**[00483]** To a solution of (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone, prepared as described in Procedure 3, 4, 59 and 68, (207 mg, 0.53 mmol) in pyridine (1.5 mL) was added hydroxylamine hydrochloride (192 mg, 2.8 mmol) and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The organic portion was washed with 1 N HCl (2 x 20 mL), water (20 mL) and sat. NaCl (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by ISCO (40 g silica gel column, 0-30% EtOAc/hexane over 30 min) to yield (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone oxime (216 mg, 77 % yield) as a colorless oil. LCMS: RT = 2.13 min [M+H] 408.2 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**Procedure 173**




**[00484]** To a suspension of (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone oxime (3.5 g, 8.6 mmol) in EtOH (30 mL) and conc. $NH_4OH$ (50 mL) was added ammonium acetate (754 mg, 19.8 mmol), followed by zinc powder (3.2 g, 49.1 mmol) and the reaction mixture was heated at reflux for 3 h. The reaction mixture was allowed to cool to rt then filtered through celite. The solid was washed with 1 N NaOH (10 mL) and MeOH (10 mL). The combined filtrate was extracted concentrated and the residue was partitioned between EtOAc and water. The organic layer was separated and washed with 1 N NaOH (15 mL), sat. NaCl (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanamine (2.8 g, 83% yield) as a light yellow oil. LCMS: RT = 1.76 min [M-$NH_2$] 377.1 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 6.97 - 7.09 (4 H, m), 6.81 - 6.89 (2 H, m), 5.76-6.03 (1 H, m), 5.14 (1 H, s), 4.52 (1 H, ddd, *J*=11.97, 6.15, 6.04 Hz), 1.73 (2 H, bs), 1.29 - 1.36 ( 6 H, m).

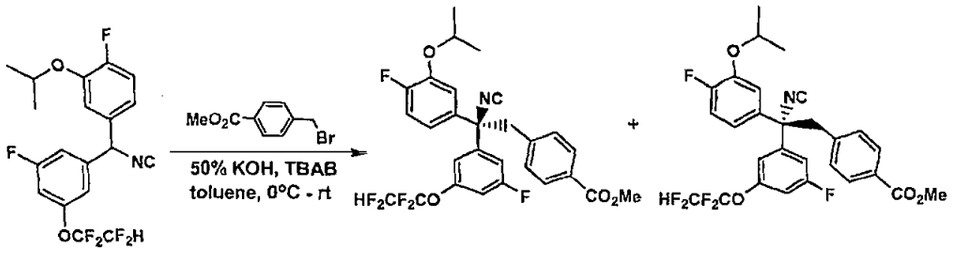
**Procedure 174**



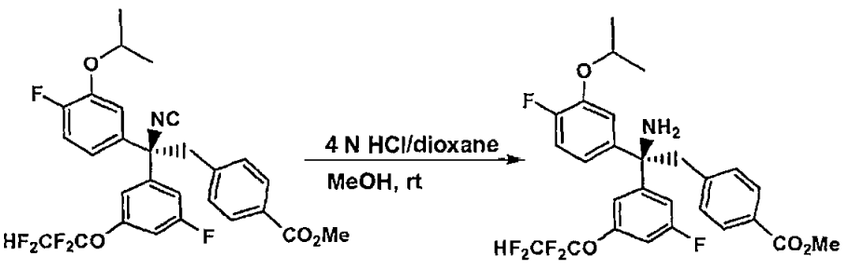

**[00485]** To a solution of (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanamine (2.8 g, 7.1 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C was added acetic formic anhydride (2.8 mL, formed by heating a 2:1 *v/v* ratio of

acetic anhydride and formic acid at 60 °C for 2 h). The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by ISCO (120 g silica gel column, 0 to 60% EtOAc/hexane over 60 min gradient) to give N-((4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl)formamide (2.56 g, 85% yield) as a colorless oil. LCMS: RT = 1.99 min [M+H] 422.0 (Phenomenex Luna C18 4.6 x 30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm). To a solution of N-((4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl)formamide (225 mg, 0.53 mmol) in THF (2 mL) at 0 °C was added $Et_3N$ (0.4 mL, 2.9 mmol) followed by phosphorous oxychloride (74 µL, 0.80 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was diluted with ice water (15 mL) and extracted with $Et_2O$ (3 x 15 mL). The combined organic layers were washed with sat. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by ISCO (12 g silica gel column, 0-50% EtOAc/hexane over 30 min) to yield 1-fluoro-4-((3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)(isocyano)methyl)-2-isopropoxybenzene (143 mg, 67% yield) as a pale yellow oil. LCMS: RT = 2.13 min [M-NC] 377 (Phenomenex Luna C18 4.6x30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.%TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.07 - 7.13 (1 H, m), 6.91 - 7.03 (4 H, m), 6.84-6.86 (1 H, m), 5.78-6.04 (1 H, m), 5.82 (1 H, s), 4.54 (1 H, ddd, *J*=11.97, 6.15, 6.04 Hz), 1.35 (6 H, t, *J*=5.05 Hz).

**Procedure 175**

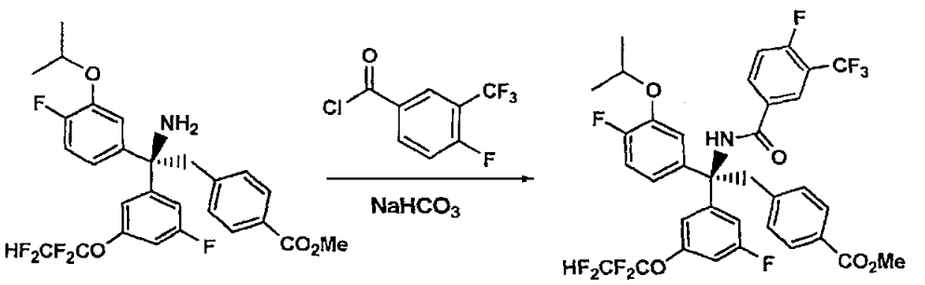


**Procedure 176**




**[00488]** To a solution of (R)-methyl 4-(2-(4-fluoro-3-isopropoxyphenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-isocyanoethyl)benzoate (120 mg, 0.22 mmol) in MeOH (2 mL) was added 4 N HCl in dioxane (0.5 mL) and the reaction mixture was stirred for 3 minutes. The reaction solvent was evaporated under a stream of nitrogen. The residue was diluted with EtOAc (15 mL), washed with saturated sodium bicarbonate solution (10 mL) and sat. NaCl, dried over $MgSO_4$, filtered and evaporated to yield (R)-methyl 4-(2-amino-2-(4-fluoro-3-isopropoxyphenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)benzoate (103 mg, 86% yield) as a clear glass. LCMS: RT = 1.87 min [M-$NH_2$] 525.1 (Phenomenex Luna C18 4.6x30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.%TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm).

**Procedure 177**

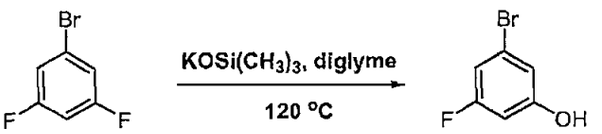



**[00489]** To a solution of (R)-methyl 4-(2-amino-2-(4-fluoro-3-isopropoxyphenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)benzoate (50 mg, 0.09 mmol) in THF (2 mL) was added sodium bicarbonate (30 mg, 0.36 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by ISCO (4 g silica gel column, 0-50% EtOAc/hexane over 30 min) to yield (R)-methyl 4-(2-(4-

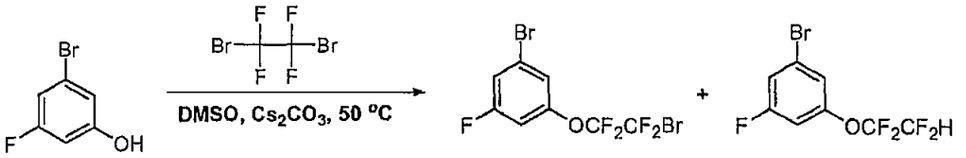
LCMS: RT = 2.17 min [M+H] 704.1 (Phenomenex Luna C18 4.6x30mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.1% TFA, 2 min gradient, flow rate 5 mL/min, wavelength 220 nm); HPLC: RT = 4.0 min (Phenomenex Luna C18 4.6 X 50 mm column, eluting with 10-90% MeOH/$H_2O$ containing 0.2% PPA, flow rate 4 mL/min, wavelength 220 nm); $^1$H NMR (400 MHz,$CDCl_3$) δ ppm 7.91 (1 H, d, *J*=6.59 Hz), 7.85-7.87 (1 H, m) 7.26 - 7.31 (1 H, m), 7.16 (2 H, d, *J*=7.91 Hz), 6.93-7.05 (4 H, m), 6.68 - 6.73 (3 H, m), 6.60 - 6.66 (2 H, m), 5.75-6.01 (1 H, m), 4.64 (3 H, s), 4.35 (1 H, m), 4.06 (1 H, d, *J*=13.2 Hz), 3.74 (1 H, d, *J*=13.2 Hz ), 1.29 (3 H, d, *J*=6.15 Hz), 1.26 (1 H, s), 1.23 (3 H, d, *J*=6.15 Hz).

**[00491]** Example 273 can also be prepared by alternate procedures as set forth below.

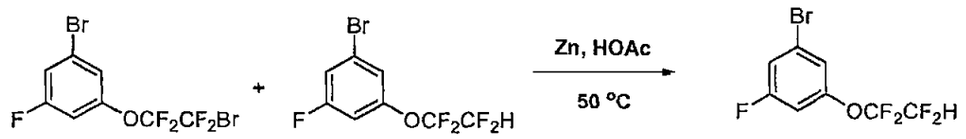
**Procedure 178**




**[00492]** To a $N_2$ flushed, 2 L four necked flask equipped with a mechanical stirrer, a condenser, a temperature controller and a $N_2$ inlet, was added potassium trimethylsilanolate (225.0 g, 1.75 mol, tech. purify 90%), 1-bromo-3,5-difluorobenzene (96.5 g, 0.5 mol) and diglyme (300 mL). The reaction mixture was heated to 120 °C under $N_2$ for 5 h. After cooling to rt, the heating mantle was replaced with an ice bath. The reaction mixture was acidified with a 3 N HCl solution (600 mL) while keeping the reaction temperature below 30 °C. Tertiary butyl methyl ether (1 L) was added and the resulting mixture was stirred below 20 °C for 30 min then transferred to a 5 L separatory funnel. The organic layer was separated and washed with water (3 X 500 mL), sat. NaCl (500 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude red solid (145.0 g). The crude material was then distillated at 52 – 55 °C / 0.1 mm Hg to yield 3-bromo-5-fluorophenol as a slightly yellow oil (88.0 g, 92% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, H), 6.47-6.52 (m, 1H), 6.77-6.83 (m, 2 H).

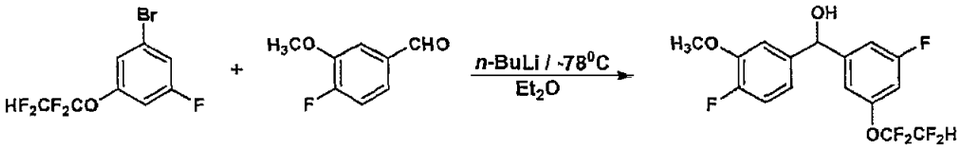



**[00493]** To a flame dried, 1 L, three necked round bottom flask equipped with a temperature controller, a mechanical stirrer, a condenser and a $N_2$ inlet was charged 3-bromo-5-fluorophenol (57.3 g, 300 mmol), 1,2-dibromo-1,1',2,2'-tetrafluoroethane (156.0 g, 600 mmol), dry DMSO (300 mL) and $Cs_2CO_3$ (146.6 g, 450 mmol) under $N_2$. The reaction mixture was heated to 50 °C for 5 h. After cooling to rt, water (300 mL) and hexane (300 mL) were added. The resulting mixture was stirred at rt for 30 min. The organic phase was separated and the aqueous layer was extracted with hexane (300 mL). The combined organic extracts were washed with water (500 mL), sat. NaCl (500 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1-bromo-3-(2-bromo-1,1,2,2-tetrafluoroethoxy)-5-fluorobenzene (104.2 g, 94% yield) containing 5% of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (5.2 g). 1-Bromo-3-(2-bromo-1,1,2,2-tetrafluoroethoxy)-5-fluorobenzene: $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.91-6.94 (m, 1H), 7.18-7.23 (m, 2 H).

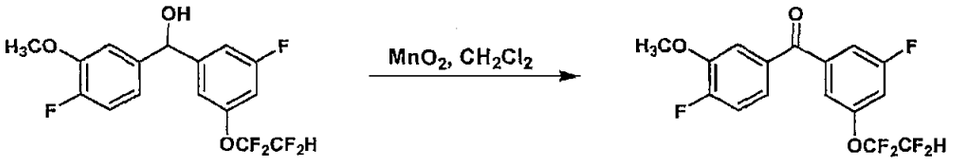



**[00494]** To a 1 L four necked round bottom flask equipped with a temperature controller, a mechanical stirrer, and a $N_2$ inlet, was added the crude mixture of 1-bromo-3-(2-bromo-1,1,2,2,-tetrafluoro-ethoxy)-5-fluorobenzene (104.0 g, 281 mmol) and 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (5.2 g, 18 mmol), acetic acid (300 mL). The reaction mixture was then heated to 50 °C. Zinc dust (91.9 g, 1.405 mol) was added portion wise. The reaction mixture was stirred at 50 °C for 1 h and allowed to cool to rt. Water (300 mL) and hexane (300 mL) were added. The resulting mixture was stirred at rt for 30 min. The organic phase was separated and the aqueous layer was extracted with hexane (2 x 300 mL). The combined organic extracts were washed with water (500 mL), sat. NaCl (500 mL), dried over MgSO4, filtered and concentrated *in vacuo* to yield 1-bromo-3-fluoro-5-(1,1,2,2-

tetrafluoroethoxy)benzene as a slightly yellow liquid (71 g, 87% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 5.87 (tt, J = 52.7 and 2.9 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 7.16-7.18 (m, 2 H). 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene may be distilled at 0.6 mm Hg, 47-48 °C (bath 77-100 °C) to a colorless oil.



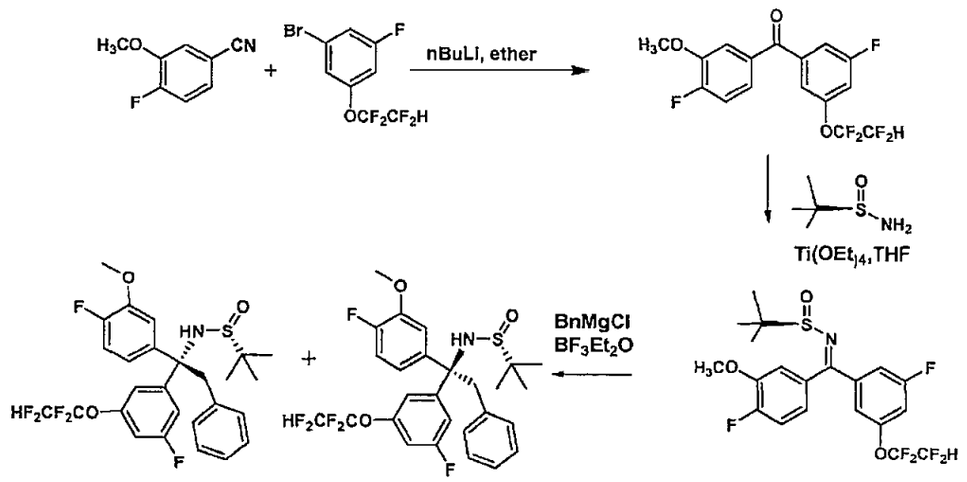

**[00495]** To a solution of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene, prepared as described in Procedure N, (1.00 g, 3.44 mmol) in diethyl ether in (10 mL) at -72 °C was added 2.5 M n-BuLi (1.37 mL, 3.44 mmol) dropwise. Upon completion of addition, the reaction mixture was stirred for 15 minutes at -72 °C, then 4-fluoro-3-methoxybenzaldehyde (0.53 g, 3.44 mmol ) was added while the reaction mixture temperature was maintained below -52 °C. The reaction mixture was stirred for 3 h at -72 °C. The reaction mixture was quenched by the addition of 1N HCl and the aqueous portion was extracted with EtOAc (2 x). The combined organic layers were washed with sat. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by ISCO using a gradient of 0-50% EtOAc/ hexane as eluent to yield (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol (0.83 g, 66% yield). HPLC: RT = 3.85 min (Phenomenex Luna C18 5µ column, eluting with 10-90% aqueous methanol containing 0.1% phosphoric acid over a 4 minute gradient, flow rate 4 mL/min, monitoring at 220 nm); $^1$H NMR ($CDCl_3$): 7.05 - 6.8 (m, 6 H), 5.87 (tt, J=2.8, 52.9Hz), 5.75 (s, 1 H), 3.85 (s, 3 H).




**[00496]** To a solution of (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanol (0.58 g, 1.57 mmol) in $CH_2Cl_2$ (5 mL) was added activated manganese dioxide (0.80 g, 7.86 mmol). The reaction mixture was stirred

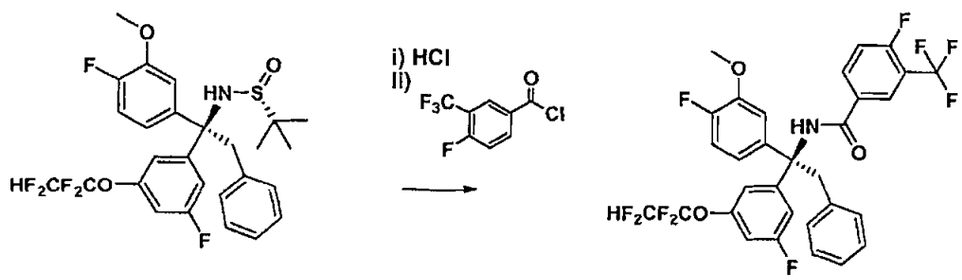
overnight at rt. Additional manganese dioxide (0.80 g, 7.86 mmol) was added and the reaction stirred at rt overnight. The reaction mixture was diluted with $CH_2Cl_2$ and filtered through celite and the solid was washed with $CH_2Cl_2$. The filtrate was concentrated under reduced pressure to yield (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone (0.56 g, 98% yield). HPLC: RT = 4.048 minutes (Phenomenex Luna C18 5μ column, eluting with 10-90% aqueous methanol containing 0.1% phosphoric acid over a 4 minute gradient, flow rate 4 mL/min, monitoring at 220 nm); LCMS: [M+H] 365.2 (Phenomenex Luna C18 5μ column, eluting with 10-90% aqueous methanol containing 0.1% TFA over a 2 minute gradient, flow rate 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, $CDCl_3$): 7.5-7.1 (m, 6 H), 5.92 (tt, J=2.2, 53.6Hz, 1 H), 3.93 (s, 3 H).

**[00497]** Alternatively, (4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone may be prepared by the methods described in Procedure 4 from 4-fluoro-3-methoxybenzonitrile in 68% yield.

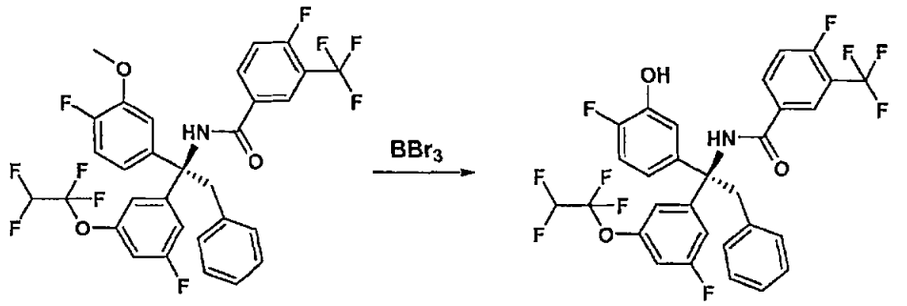



**[00498]** (R)-N-((4-fluoro-3-methoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide was prepared by the methods described in Procedures 5 yielding a 3:1 diastereomeric mixture of (R)-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide and (S)-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide in 90% yield. The diastereomers

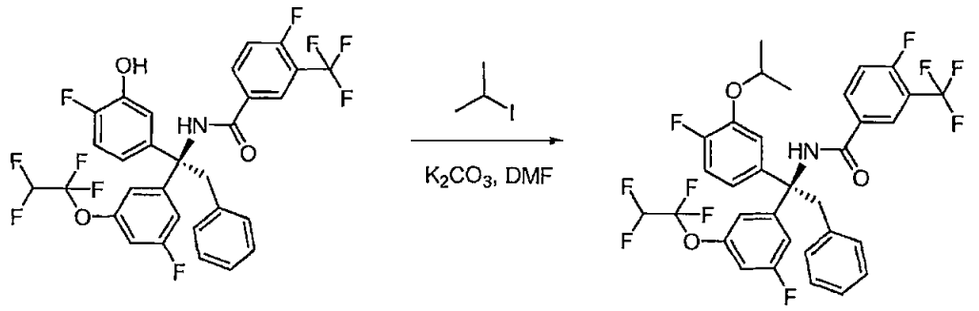
were separated by Chiralcel AD column chromatography elution with Heptane IPA (68% yield). Analytical data and yield for diastereomers in here. Isomer A: LCMS: [M+H] 560.2, retention time = 4.08 min (Phenomenex Luna C18 5µ column, eluting with 10-90% aqueous methanol containing 0.1% TFA over a 4 minute gradient, flow rate 5 mL/min, monitoring at 220 nm); $^1$H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.23 (s, 9 H), 3.63 (d, J = 12 Hz, 1H), 3.73 (s, 3 H), 3.89 (d, J = 12 Hz, 1H), 5.94 (tt, J = 53, 2.4 Hz, 1H), 6.67 – 6.74 (m, 2H), 6.96 – 7.03 (m, 3H), 7.36 - 7.14 (m, 6 H) ppm. Chiral HPLC: RT = 8.21 min (Chiral AD column 4.6 x 250 mm; 20% Isocratic; Solvent A = Heptane, Solvent B = 0.1% DEA in IPA). Isomer B: LCMS: RT = 4.022 min [M+H] 560.2 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (s, 9 H) 3.56 (d, *J*=12.09 Hz, 1 H) 3.77 (s, 3 H) 3.98 (d, *J*=12.64 Hz, 1 H) 4.20 (s, 1 H) 5.69 - 6.00 (m, 1 H) 6.67 - 6.74 (m, 2 H) 6.80 - 6.89 (m, 2 H) 6.91 (d, *J*=7.70 Hz, 2 H) 7.02 - 7.08 (m, 1 H) 7.10 (s, 1 H) 7.11 - 7.20 (m, 3 H). Chiral HPLC: RT = 10.34 min (Chiral AD column 4.6 x 250 mm; 20% Isocratic; Solvent A = Heptane, Solvent B = 0.1% DEA in IPA).




**[00499]** (R)-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was converted to (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide by the methods described in Procedure 6 and Procedure 7.




**[00500]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (2.8 g, 4.43 mmol), prepared as described in Procedure 5, 6 and 7 (44% yield), in $CH_2Cl_2$ (15 mL) was added $BBr_3$ (12 mL, 12 mmol). The resulting mixture was stirred at room temperature for 2 h and quenched by addition of ice. The reaction mixture was diluted with EtOAc and washed with sat. $NaHCO_3$, sat. NaCl, dried over $Na_2SO_4$, filtered and concentrated to afford (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264) as clear oil (2.9 g, 100 % yield). LCMS: RT = 4.176 min [M+H] 632.2 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm).

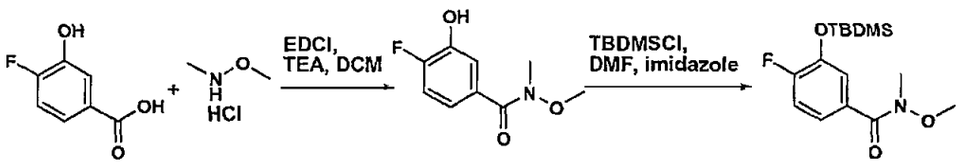



**[00501]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264, 2.70 g, 4.27 mmol) in DMF (6 mL) was added $K_2CO_3$ (1.47 g, 10.69 mmol), followed by isopropyl iodide (0.64 mL, 6.40 mmol). The reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered and the solid was washed with EtOAc. The filtrate was washed with $H_2O$,

sat. NaCl, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by ISCO silica gel column using 0 to 50% EtOAc in hexane as eluting solvents to yield (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 273) as white powder (2.4 g, 83% yield). LCMS: RT = 4.05 min [M+H] 674.1 (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). $^1H$ NMR (400 MHz, $CD_3OD$) δ ppm 7.95 - 8.00 (2 H, m), 7.42 - 7.47 (1 H, m), 7.19 (1 H, t, *J*=7.47 Hz), 7.12 (3 H, t, *J*=7.25 Hz), 6.99 - 7.07 (3 H, m), 6.71 - 6.81 (4 H, m), 6.14 - 6.41 (1 H, m), 4.26 - 4.32 (1 H, m, *J*=6.15, 6.15, 6.15, 6.15 Hz), 4.12 (1 H, d, *J*=13.18 Hz), 3.85 (1 H, d, *J*=12.74 Hz), 1.23 (3 H, d, *J*=6.15 Hz), 1.17 (3 H, d, *J*=6.15 Hz).

**[00502]** Alternatively, (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide may be prepared by the following Procedures:

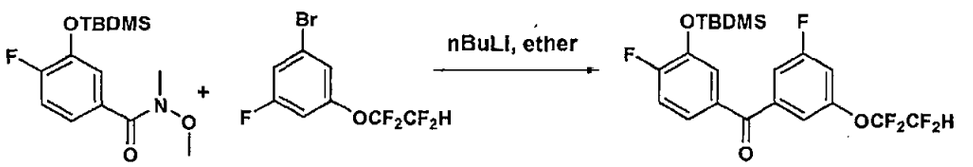
**Procedure 179**




**[00503]** To a solution of 4-fluoro-3-hydroxybenzoic acid (1.49 g, 9.55 mmol) in DCM (40 mL) was added TEA (1.2 mL, 8.61 mmol) followed by N,O-dimethylhydroxylamine hydrochloride (1.12 g, 11.5 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with DCM, washed with water twice, dried over $Na_2SO_4$, filtered and concentrated to yield 4-fluoro-3-hydroxy-N-methoxy-N-methylbenzamide as a colorless oil (1.90 g, 100% yield). LCMS: RT = 0.89 min [M+H] 200.10 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

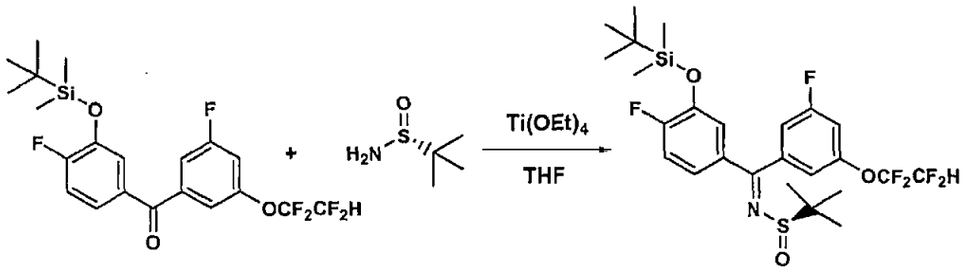
**[00504]** To a solution of 4-fluoro-3-hydroxy-N-methoxy-N-methylbenzamide (1.90 g, 9.55 mmol) in DMF (8 mL) was added imidazole (740 mg, 10.8 mmol) and

TBDMSCl (1.62 g, 10.8 mmol) at room temperature. The reaction mixture was stirred for 48 h and quenched with saturated $NaHCO_3$. The solution was extracted with ether (3 x) and the combined ether portions were washed with LiCl (10%), dried over $Na_2SO_4$, filtered and concentrated. The resulting colorless oil was purified by ISCO chromatography (120 g column) using hexanes/EtOAc (0-100% over 30 min) to give 3-(tert-butyldimethylsilyloxy)-4-fluoro-N-methoxy-N-methylbenzamide (RT = 10-12 minutes) as a colorless oil (2.00 g, 67% yield). LCMS: RT = 2.06 min [M+H] 314.22 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz $^1H$ ($CDCl_3$) 7.26 ppm, 2 H, m; 7.02 ppm, 1 H, m; 3.50 ppm, 3 H, s; 3.31 ppm, 3 H, s; 0.97 ppm, 9 H, s, 0.16 ppm, 6H, s.

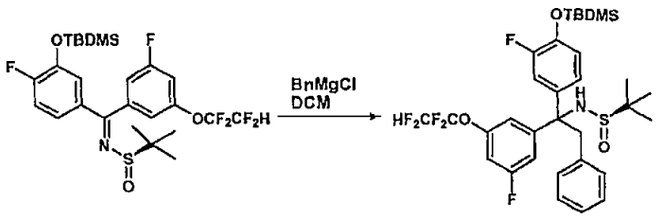



**[00505]** At -78 °C under argon, to a solution of 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (2.04 g, 7.01 mmol) in anhydrous ether (20 mL) was added nBuLi (3.5 mL, 2.0 M in cyclohexane, 7.0 mmol) dropwise and the reaction mixture was stirred for 1 h. 3-(Tert-butyldimethylsilyloxy)-4-fluoro-N-methoxy-N-methylbenzamide (2.00 g, 6.38 mmol) was added in one portion and the reaction mixture was stirred at -78 °C for 1.5 h. The pale yellow solution was poured into a 1 N HCl aqueous solution (30 mL) and ether (30 mL) was used to rinse the reaction flask. The aqueous phase was separated and extracted with diethyl ether (20 mL). The combined ether portions were dried over $Na_2SO_4$, filtered and concentrated. The resulting oil was purified by ISCO chromatography (120 g column) using hexanes/EtOAc (0-100% over 30 min) to give (3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone at a retention time of 7 min (2.11 g, 71% yield). LCMS: RT = 2.41 min [M+H] 465.19 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); NMR: 400MHz

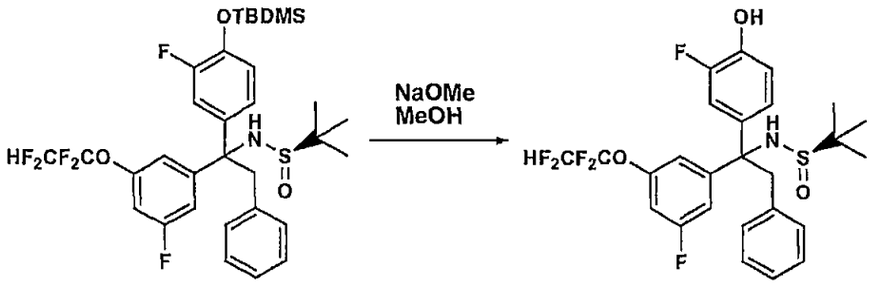
$^1$H ($CDCl_3$) 7.33 ppm, 3 H, m; 7.28 ppm, 1 H, m; 7.11 ppm, 2 H, m; 5.86 ppm, 1 H, t, J=53.39 Hz; 0.95 ppm, 9 H, s; 0.15 ppm, 6 H, s.



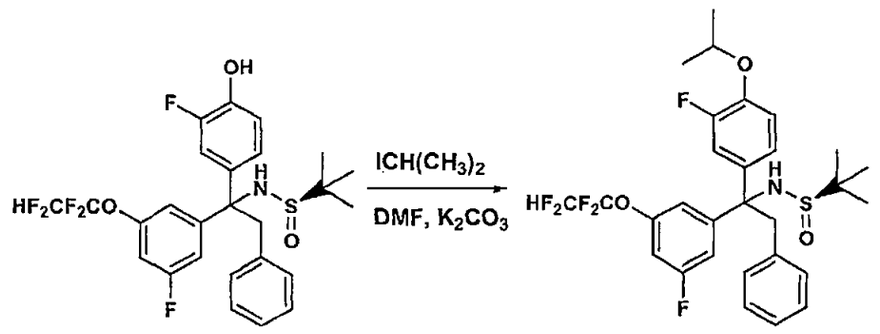

**[00506]** A round bottom flask was charged with (3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone (2.09 g, 4.50 mmol), (R)-2-methylpropane-2-sulfinamide (653 mg, 5.4 mmol), $Ti(OEt)_4$ (1.54 g, 6.76 mmol) and anhydrous THF (40 mL). The resulting solution was heated at 75 °C under argon for 14 h. The solvents were removed and the residue was diluted with ether (50 mL) and sat. NaCl (20 mL). The resulting mixture was filtered through a glass frit and the filtrate transferred to a separatory funnel. The organic portion was separated and the aqueous phase extracted with diethyl ether (2 x 20 mL). The combined organic portions were dried over $Na_2SO_4$, filtered and concentrated. The residue was dissolved in hexane:EtOAc and purified by ISCO chromatography (2 × 120 g column) using hexanes/EtOAc (0-100% over 30 min) to yield (R)-N-((3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide at a retention time of 14 min (2.05 g, 80% yield) LCMS: RT = 2.37 min [M+H] 568.24 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). NMR: 400MHz $^1$H ($CDCl_3$) 7.36 ppm, 1 H, m; 7.11 ppm, 5 H, m; 5.90 ppm, 1 H, t, *J*=52.73 Hz; 0.97 ppm, 9 H, s; 0.18 ppm, 6 H, s.




**[00507]** At -78 °C to a solution of (R)-N-((3-(tert-butyldimethylsilyloxy)-4-fluorophenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (1.0 g, 1.76 mmol) in DCM (50 mL) was added $BF_3 \cdot Et_2O$ (0.77 mL, 3.52 mmol) via syringe. After 5 min, BnMgCl solution (3.5 mL, 1.0 M solution in ether, 3.5 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. An additional portion of BnMgCl (3.5 mL, 1.0 M solution in ether, 3.5 mmol) was added dropwise and the reaction was stirred for an additional 1 h at -78 °C. The reaction mixture was poured into saturated NaCl (50 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The resulting oil was purified by ISCO chromatography (120 g column) using hexanes/EtOAc (0-100% over 30 min) to give an approximate 4:1 mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide and (S)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide at a retention time of 12 min (824 mg, 71% yield) LCMS: RT = 2.43 min [M+H] 660.39 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). The diastereomeric ratio of the product was determined to be 4:1 by Chiral HPLC analysis (Chiralcel® AD, 90:10 heptane :*i*-PrOH, 1 mL / min, 254 nm, RT (minor)= 4.43 min, PA=17%; RT (major) = 19.28 min, PA=71%) and the diastereomeric mixture was taken on directly to the next step, Procedure 112, or the diastereomers were separated as described in Procedure 114. NMR: 400MHz $^1H$ ($CDCl_3$) 7.30 ppm, 2 H, m; 7.06 ppm, 5 H, m; 6.85 ppm, 2 H, m; 6.76 ppm, 1 H, m; 6.62 ppm, 2 H, m; 5.79 ppm, 1 H, m; 4.13 ppm, 1H, s; 3.84 ppm, 1 H, m; 3.47 ppm, 1 H, m; 1.12 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6 H, d, *J*=4.39 Hz.

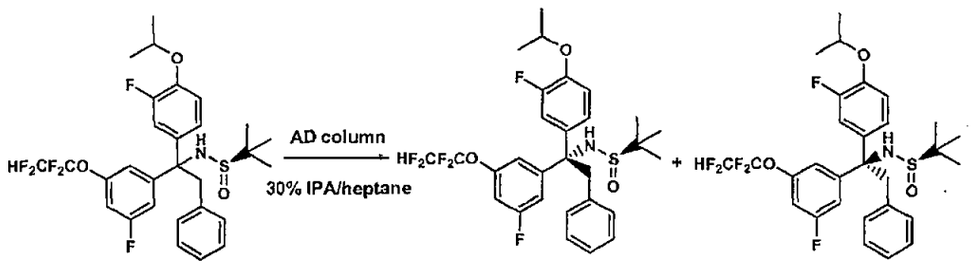



**[00508]** At room temperature a solution of NaOMe (5 mL, 0.5 M solution in MeOH) was added to the 4:1 diastereomeric mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (801 mg, 1.22 mmol). The reaction mixture was stirred for 15 minutes, MeOH was removed then the residue dissolved in EtOAc (50 mL) and transferred to a separation funnel. HCl (20 mL, 1.0 N solution) was added and the EtOAc layer was separated. The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to yield (R)-N-(1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a white foam (578 mg, 87% yield). LCMS: RT = 1.987 min [M+H] 546.35 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).




**[00509]** At rt to a solution of 4:1 diastereomeric mixture (R)-N-(1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (578 mg, 1.06 mmol) in DMF (10 mL) was added

$K_2CO_3$ (800 mg, 5.80 mmol) and the slurry was stirred vigorously. 2-Iodopropane (220 mg, 1.27 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with ether (50 mL), washed successively with 10% LiCl (2 × 20 mL) and water (20 mL). The organic portion was dried over $Na_2SO_4$, filtered and concentrated to yield (R)-N-(1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a pale orange foam (780 mg, 100% yield).

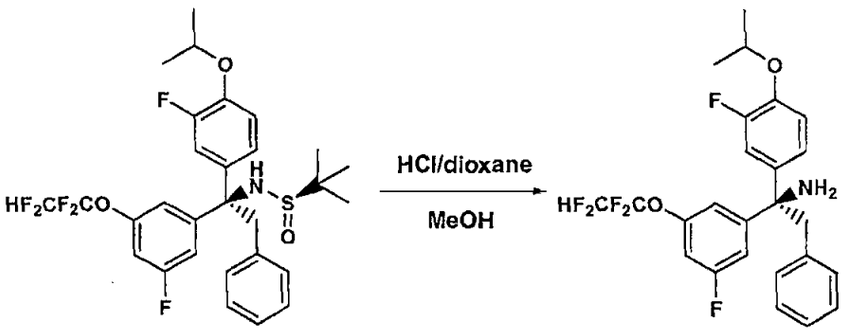



**[00510]** The 4:1 diastereomeric mixture of (R)-N-(1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (780 mg, 1.06 mmol crude) was separated by Chiral preparative HPLC chiralpak AD 20μ column, 5 × 50 cm, eluting with 30% IPA/Heptane with flow rate 50 mL/min.

**[00511]** (R)-N-((S)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 17 min and isolated as a colorless oil (101 mg, yield 16%). LCMS: RT = 2.128 min [M+H] 588.38 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); Chiral HPLC: RT = 4.35 min, ee 100% (Diacel Chiralpak AD 10μ column, 4.6 × 250 mm isocratic elution with IPA (20%) and heptane; 1 mL/min, monitoring at 254 nm).

**[00512]** (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 39 min and isolated and was isolated as a colorless oil (398 mg, yield 64%). LCMS: RT = 2.138 min [M+H] 588.38 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA;

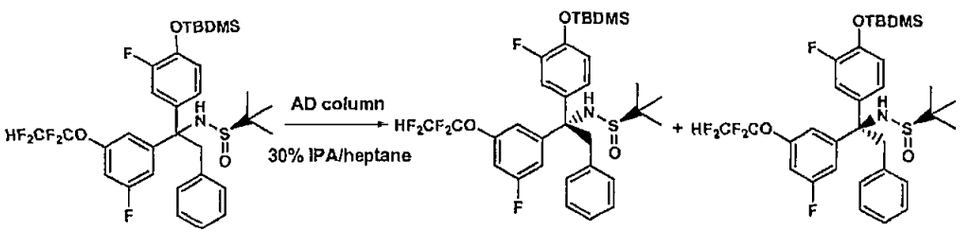
5 mL/min, monitoring at 220 nm); Chiral HPLC: RT = 9.98 min, ee 100% (Diacel Chiralpak AD 10 μ column, 4.6 × 250 mm isocratic elution with IPA (20%) and heptane; 1 mL/min, monitoring at 254 nm) NMR: 400MHz $^1$H ($CDCl_3$) 7.08 ppm, 5 H, m; 6.84 ppm, 2 H, d, *J*=7.47 Hz; 6.77 ppm, 2 H, d, *J*=7.47 Hz; 6.63 ppm, 2 H, m; 5.79 ppm, 1 H, t, *J*=52.95 Hz; 4.33 ppm, 1 H, m; 4.15 ppm, 1 H, s; 3.92 ppm, 1 H, d, *J*=12.30 Hz; 3.48 ppm, 1 H, d, *J*=12.30 Hz; 1.22 ppm, 3 H, d, *J*=6.15 Hz; 1.18 ppm, 3 H, d, *J*=5.71 Hz; 1.14 ppm, 9 H, s.




**[00513]** To a solution of (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (398 mg, 0.678 mmol) in MeOH (1.5 mL) was added HCl (1.5 mL, 4 M solution in dioxane) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with ether (50 mL) and the organic layer was washed with sat. $NaHCO_3$ (20 mL), dried over $Na_2SO_4$, filtered and concentrated to give (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine as a colorless oil (334 mg, 100% yield). LCMS: RT = 1.76 min [M-$NH_2$] 467.24 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.04 min, Purity 95% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1$H ($CDCl_3$) 7.15 ppm, 3 H, m; 6.99 ppm, 4 H, m; 6.89 ppm, 1 H, m; 6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=6.15 Hz; 5.87 ppm, 1 H, m; 4.42 ppm, 1 H, m; 3.47 ppm, 2 H, s; 1.27 ppm, 6 H, dd, *J*=7.91,6.15 Hz.

**[00514]** Alternatively, the diastereomeric mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-

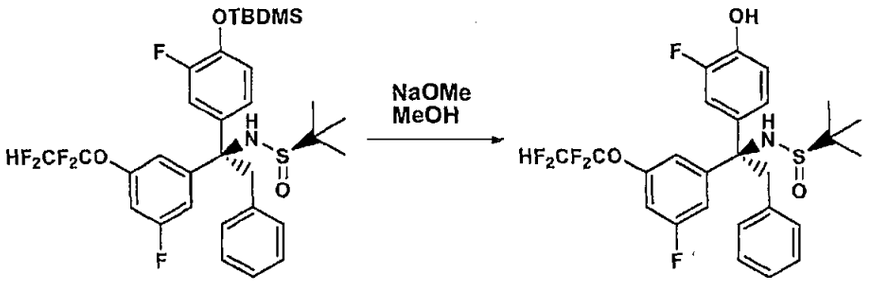
tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide can be separated as described in Procedure 114 and the individual diastereomers converted to (R) and (S)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine by the methods described in Procedure 113.



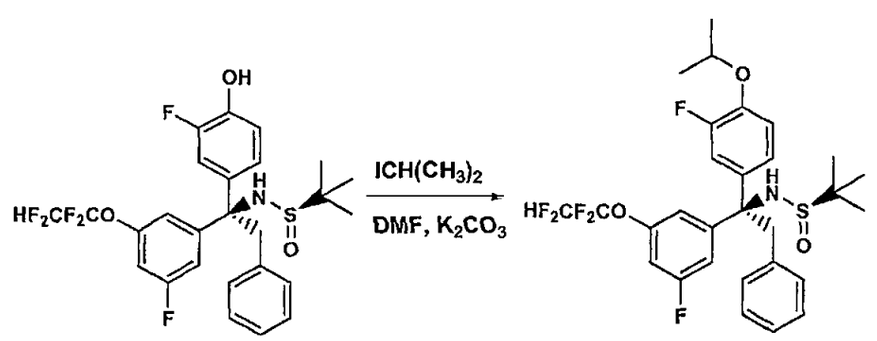

**[00515]** The diastereomer mixture of (R)-N-(1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (1.14 g, 1.73 mmol) was separated by Chiral preparative HPLC chiralpak AD 20μ column, 5 × 50 cm, eluting with 30% IPA/Heptane with flow rate 50 mL/min.

**[00516]** (R)-N-((S)-1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 19 min (114 mg, yield 10%). LCMS: RT = 2.45 min [M+H] 660.41 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm).

**[00517]** (R)-N-((R)-1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was eluted at a retention time of 36 min (634 mg, yield 56%). LCMS: RT = 2.41 min [M+H] 660.39 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); Chiral HPLC: RT = 8.54 min, ee 100% (Diacel Chiralpak AD 10μ column, 4.6 × 250 mm isocratic elution with IPA (20%) and heptane; 1 mL/min, monitoring at 254 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.03 ppm, 5 H, m; 6.84 ppm, 2 H, m; 6.74 ppm, 1 H, d, $J$=8.79 Hz; 6.66 ppm, 1 H, dd, $J$=8.13, 1.98 Hz; 6.61 ppm, 2 H, m; 5.76 ppm, 1 H, m; 4.12 ppm, 1 H, s; 3.90 ppm, 1 H, d, $J$=12.74 Hz; 3.46 ppm, 1 H, d, $J$=12.30 Hz; 1.11 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6 H, d, $J$=4.83 Hz.

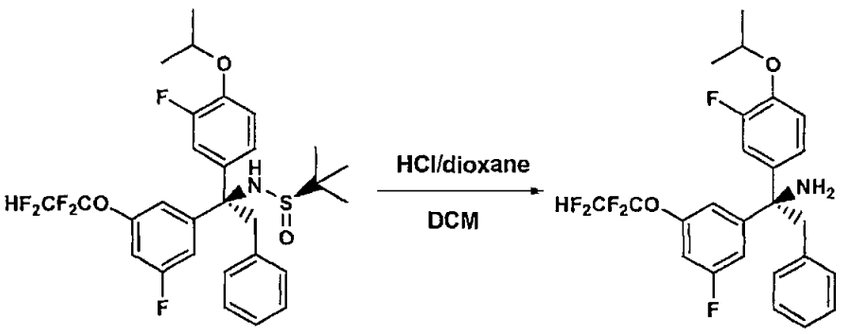



**[00518]** (R)-N-((R)-1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was prepared from (R)-N-((R)-1-(4-(tert-butyldimethylsilyloxy)-3-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as described in Procedure 112 in quantitative yield. LCMS: RT = 1.998 min [M+H] 546.28 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm). HPLC: RT = 3.83 min, Purity 98% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.61 ppm, 1 H, s; 7.40 ppm, 1 H, dd, *J*=8.13, 1.98 Hz; 7.13 ppm, 3 H, m; 6.99 ppm, 1 H, dd, *J*=10.33, 8.57 Hz; 6.84 ppm, 3 H, m; 6.68 ppm, 2 H, m; 6.61 ppm, 1 H, m; 5.85 ppm, 1 H, tt, *J*=52.95, 2.64 Hz; 4.30 ppm, 1 H, s; 4.02 ppm, 1 H, d, *J*=12.30 Hz; 3.50 ppm, 1 H, d, *J*=12.30 Hz; 1.24 ppm, 9 H, s.

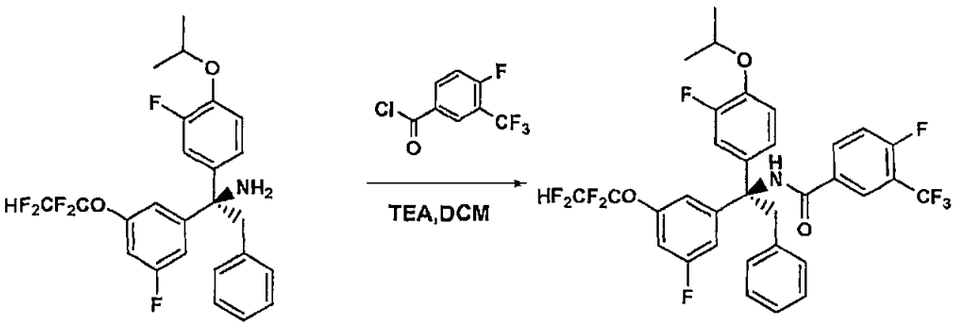



**[00519]** (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was prepared from (R)-N-(1-(3-fluoro-4-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-

tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as described in Procedure 6 in 78% yield. LCMS: RT = 2.17 min [M+H] 588.17 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm) HPLC: RT = 4.20 min, Purity 95% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.10 ppm, 2 H, m; 6.87 ppm, 4 H, m; 6.70 ppm, 2 H, m; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 4.31 ppm, 1 H, s; 3.98 ppm, 1 H, d, *J*=12.74 Hz; 3.56 ppm, 1 H, d, *J*=12.74 Hz; 1.30 ppm, 3 H, d, *J*=5.71 Hz; 1.25 ppm, 3 H, d, *J*=6.15 Hz; 1.22 ppm, 9 H, s.



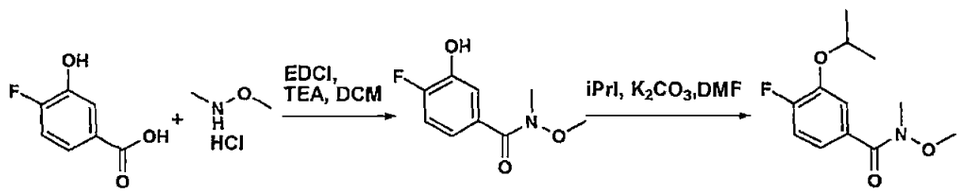

**[00520]** (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine was prepared from (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as described in Procedure 6 in 97% yield. LCMS: RT = 1.83 min [M-$NH_2$] 467.24 (Phenomenex Luna C18 column, 4.6 × 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 mL/min, monitoring at 220 nm); HPLC: RT = 3.17 min, Purity 100% (Phenomenex Luna C18 column, 4.6 × 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.2% PPA; 4 mL/min, monitoring at 220 nm) NMR: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.01 ppm, 3 H, m; 6.92 ppm, 2 H, m; 6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=7.03 Hz; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 3.49 ppm, 2 H, s; 1.25 ppm, 6 H, m.




**[00521]** (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide may be prepared from (R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine by the methods described in Procedure 7.

**[00522]** Alternatively, (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide may be prepared by the following procedures:

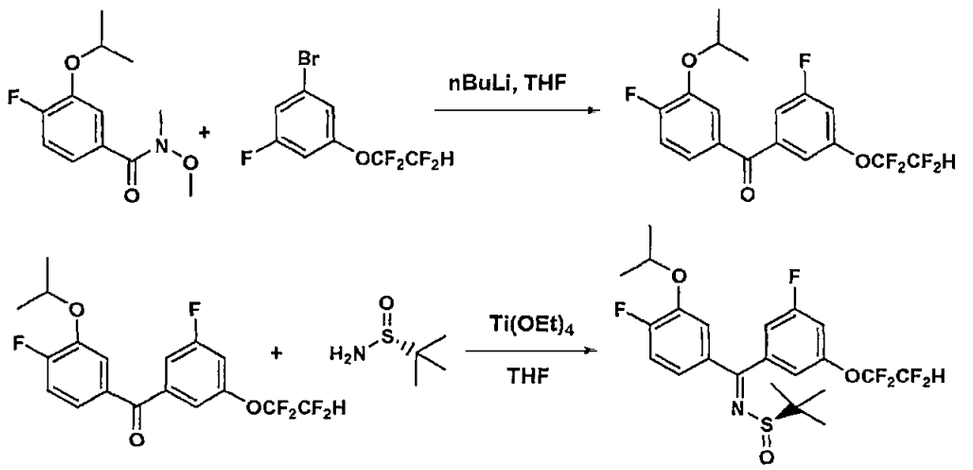
**Procedure 180**




**[00523]** To a 5 L four necked round bottom flask was added 3-hydroxy-4-fluorobenzoic acid (100 g, 0.64 mol) and $CH_2Cl_2$ (2.3 L). Triethylamine (107 mL, 0.768 mol) was then added to the suspension. The solution was cooled to –78 °C, and EDCI (184.2 g, 0.961 mol) was added portion wise followed by the addition of N,O-dimethylhydroxyamine hydrochloride (93.6 g, 0.96 mol). The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to 0 °C over a period of 2 h. The reaction mixture was transferred to a separatory funnel and washed water (2 X 1.2 L). The organic portion was dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to give 4-fluoro-3-hydroxy-N-methoxy-N-methylbenzamide as a white solid (94.4 g, 74%).

**[00524]** A 2 L round bottom flask equipped with a mechanical stirrer, a $N_2$ inlet, a condenser and a temperature controller, was charged 4-fluoro-3-hydroxy-N-methoxy-N-methylbenzamide (99.6 g, 0.5 mol), isopropyl iodide (110.5 g, 0.65 mol) and $Cs_2CO_3$ (195.5 g) and DMF (300 mL). The reaction mixture was heated at 50 °C for 3 h. Isopropyl iodide (17.0 g, 0.1 mol) was added and the reaction was heated at 50 °C for 12 h. The reaction mixture was allowed to cool to rt and water (1 L) and $CH_2Cl_2$ (500 mL) were added. The reaction mixture was stirred at rt for 0.5 h, and the organic phase was separated. The aqueous layer was extracted with CH2Cl2 (3 X 500 mL). The combined organic extracts were washed with water (2 X 1 L), brine (1 L), dried over MgSO4, filtered and concentrated *in vacuo* at 40 °C for 18 h to give 4-fluoro-3-isopropoxy-N-methoxy-N-methlbenzamide as an off-white solid (120.0 g, 100%).

**Procedure 181**

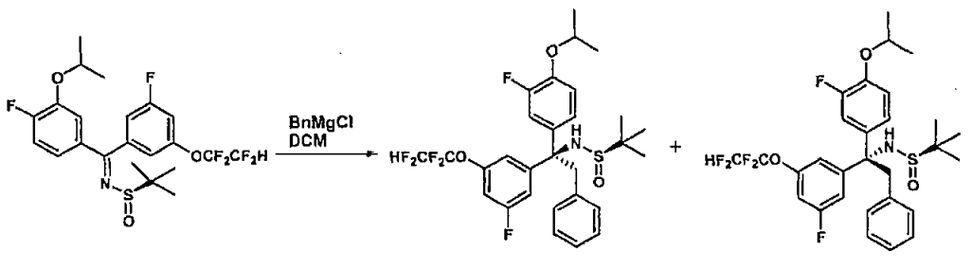



**[00525]** A 3-liter four neck round-bottomed flask (flame dried) was charged 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)benzene (72.88 g, 0.25 mol), 4-fluoro-3-isopropoxy-N-methoxy-N-methylbenzamide (60.39 g, 0.25 mol) and dry THF (700 mL) under $N_2$. The solution was cooled to -76°C, and a solution of n-BuLi in hexane (2.5M, 100 mL, 0.25 mol) was drop-wise maintaining the reaction mixture temperature below -70°C over a period of 40 min. The reaction mixture was stirred at -76°C for 1.5 h then quenched with 1N HCl (500 mL). The mixture was concentrated *in vacuo* to half the volume and was partitioned between EtOAc and $H_2O$ (v/v 1:0.3, 1L). The organic phase was separated and the aqueous layer was extracted with

EtOAc (500 mL). The combined organic extracts were washed with brine and then concentrated *in vacuo* to give a yellow oil which was purified by column chromatography using $CH_2Cl_2$ in hexanes (0% to 20%) to give (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone as a colorless oil contaminated with a by-product (49.0 g, 50%). LC-MS (10-90% MeOH in $H_2O$ with 0.1%TFA in a 2-min gradient) 393.2 (M+H), retention time = 2.15 min.

**[00526]** A solution of (4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methanone (49.0 g, 0.125 mol), (R)-(+)-2-methylpropane-2-sulfinamide (30.2 g, 0.25 mol), and $Ti(Oet)_4$ (51.9 mL, 0.25 mol) in dry THF was heated to reflux under $N_2$ for 20 h. After allowing to cool to rt, the reaction mixture was poured into ice water (800 mL) with stirring. The reaction flask was washed with small amount of EtOAc. The yellow suspension was then filtered through a Celite pad and the pad rinsed with EtOAc (ca. 500 mL). The filtrate was concentrated *in vacuo* to remove most of THF (<30°C). The remaining filtrate was partitioned between EtOAc and $H_2O$ (1:1, 1L). The organic phase was separated and washed with brine (1 L). After concentration *in vacuo*, the orange oily residue was dissolved in $CH_2Cl_2$ (ca. 100 mL). The solution was purified by silica gel flash column using EtOAc in Hexane (0-20%) to give (*R,Z/E*)-N-((4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (24.4 g). The mixed fractions were subjected to an additional silica gel flash column to give an additional 9.9g of (*R,Z/E*)-N-((4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide. The residual mixed fraction (ca. 9.7 g) was dissolved in EtOAc in hexane (25%, 80mL) and subjected to an additional silica gel flash chromatography column to give (*R,Z/E*)-N-((4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (6.90 g). Total yield: 41.2 g (67%). LC-MS (10-90% MeOH in $H_2O$ with 0.1%TFA in a 4-min gradient) 496.1 (M+H), retention time = 4.23 min.

**Procedure 182**




**[00527]** A flame dried 3L round bottom flask equipped with a mechanical stirrer, a thermometer, a $N_2$ inlet and a dropping funnel, was charged a solution of (*R,Z/E*)-N-((4-fluoro-3-isopropoxyphenyl)(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)methylene)-2-methylpropane-2-sulfinamide (40.5 g, 81.7 mol) in dry $CH_2Cl_2$ (1 L). The solution was cooled to -76°C and $BF_3{\cdot}Et_2O$ (12.3 mL, 90.0 mol, 1.2 eq) was added in one portion. The reaction mixture was stirred at -76°C for 15 min, and a solution of phenyl magnesium chloride (1.0 M in ether, 105.7 mL, 105.7 mol) was added dropwise below -70°C over a period of 1 h before the reaction mixture was quenched with brine (800 mL). The resulting solution was stirred for 10 min, then transferred a 2 L separatory funnel. The organic phase was separated and the aqueous layer was extracted with $CH_2Cl_2$ (500 mL). The combined organic phases were dried over $MgSO_4$. The solution was filtered and concentrated to ca. 100 mL. The residue was then purified by silica gel column chromatography using 0-20% of EtOAc in hexanes to give a yellow oil (48.5 g, 100%). LC-MS (10-90% MeOH in $H_2O$ with 0.1%TFA in a 4-min gradient) 588.3 (M+H), retention time = 4.36 min. Analytical chiral HPLC (AD column, 25% IPA in heptane with 0.01% DEA, isocratic), $t_{R1}$ = 4.16 min for (R)-N-((S)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide , $t_{R2}$ = 8.60 min for (*R*)-N-((*R*)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide. 48.5 g of the diastereomeric mixture compound (4/1 ratio) was separated by SFC on the Thar 350 system. A total of 33.5 g of (*R*)-N-((*R*)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (yield: 69.3 %) was obtained. Chiral preparative conditions are listed here.

**Sample Preparation:**

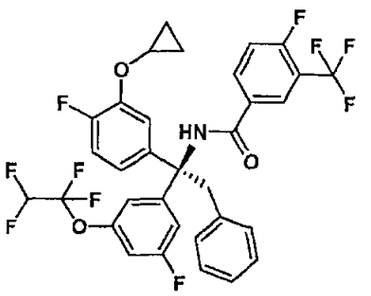
**[00528]** The sample is dissolved in IPA to a concentration of 110 mg/ml. at a concentration of 50 mg/ml. Sample readily dissolves.

**Preparative conditions on Thar SFC-350**

| | | |
|---|---|---|
| column | Chiralcel AD-H | 5x25 cm |
| mobile phase | 20% IPA in $CO_2$ | |
| pressure (bar) | 100 | |
| flow rate (ml/ min) | 240 | |
| solution concentration (mg/ml) | 110 | |
| injection amount (ml) | 10 | |
| Cycle time (min/inj) | 6.5 | |
| Temperature ($^0$C) | 35 | |
| throughput (g/ hr) | 10 | |
| Detector wavelength (nm) | 254 | |

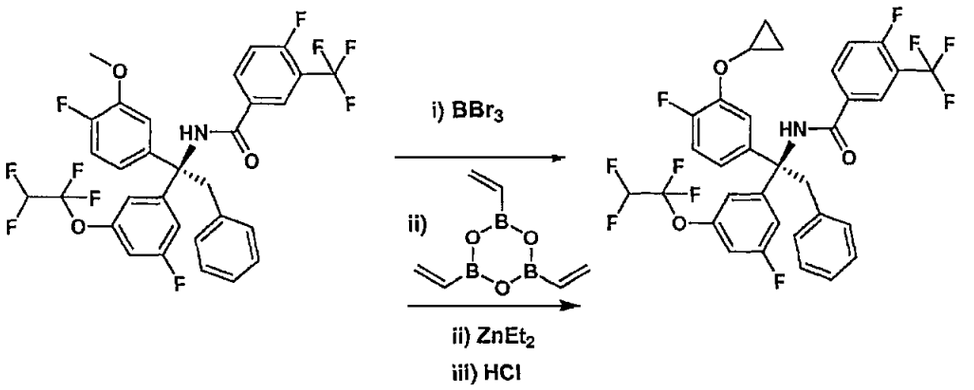
**[00529]** (R)-N-((R)-1-(3-fluoro-4-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was converted to (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5(1,1,2,2-tetrafluoro ethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide as described in 114.

**EXAMPLE 349A**



**(R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide**

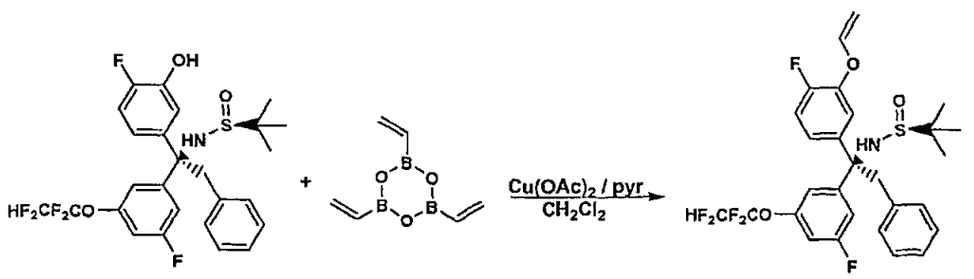
**Procedure 183**




**[00530]** (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 273) was converted to (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide as described in Procedure 59. (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide was subsequently converted to (R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide by the methods described in Procedure 161.

**[00531]** Alternatively, (R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide may be prepared by the following Procedures:

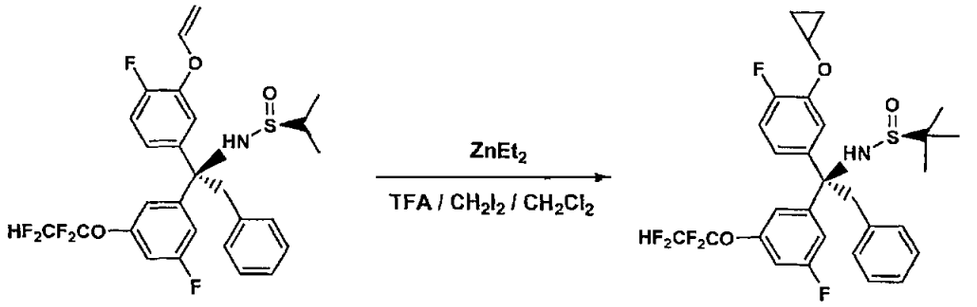
**Procedure 184**




**[00532]** To a solution of (S)-N-((R)-1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide

prepared as described in Procedure 3, 4, 5, 6 and 59 (0.545 g , 1 mmol) in $CH_2Cl_2$ (10 mL) was added $Cu(OAc)_2$ ( 0.182 g, 1 mmol), followed by pyridine (0.79 g, 10 mmol) and 2,4,6-trivinyl-1,3,5,2,4,6-trioxatriborinane (0.159 g, 0.66 mmol). The reaction mixture was stirred overnight under ambient air and filtered through a plug of celite and neutral alumina. The solid was washed with ethyl acetate and the filtrate was concentrated under reduced pressure to yield (S)-N-((R)-1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as an off-white foam (0.495 g, 87% yield). LCMS: RT = 3.653 min [M+H] 572.2 (Phenomenex Luna C18 5 μ column, eluting with 10-90% aqueous acetonitrile containing 0.1% trifluoroacetic acid over a 4 minute gradient, monitoring at 220 nM). $^1$H NMR ($CDCl_3$) ppm 7.2-7.1 (m, 5 H) , 7.02 (d, J=6.2 Hz, 1 H), 6.89 ( d, J=6.2 Hz, 2 H), 6.82 (d, J=8.8 Hz, 1H), 6.68 (br, 2 H), 6.54 (dd, J=6.2 Hz, 13.6Hz, 1 H), 5.84 (t, J=52.7 Hz, 1 H), 4.62 (dd, J=2.2 Hz, 13.6 Hz, 1 H), 4.40 (dd, J=2.2Hz, 5.7 Hz, 1 H), 4.21 (s, 1 H), 3.95 (d, J=12.8 Hz, 1H), 3.55 (d, J=12.7 Hz, 1 H), 1.19 (s, 9 H).

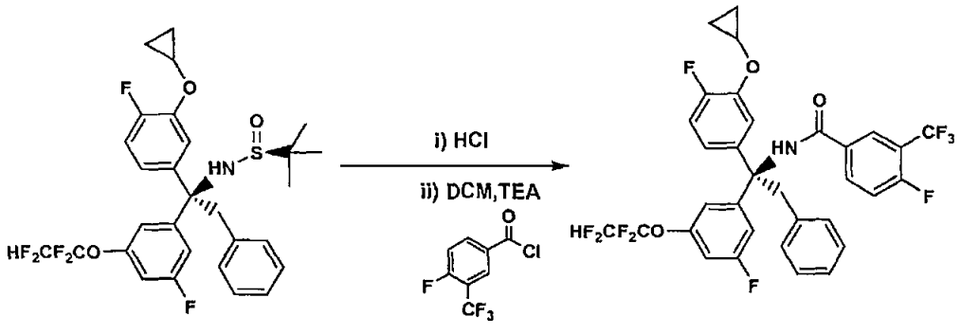
**Procedure 185**




**[00533]** To an oven-dried 3-necked 25 mL RB flask under nitrogen was added $CH_2Cl_2$ (3.5 mL) and 1 M diethylzinc solution in hexane (3.43 mL, 3.43 mmol). The flask was cooled in an ice-bath and a solution of trifluoroacetic acid (0.391 g, 3.43 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise via syringe. After stirring for 15 min, a solution of diiodomethane (0.918 g, 3.43 mmol) in $CH_2Cl_2$ (1 mL) was added. The reaction mixture was stirred at rt for 15 min, followed by addition of (S)-N-((R)-1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (0.495 g, 0.87 mmol) in $CH_2Cl_2$ (1 mL).

The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction mixture was diluted with $CH_2Cl_2$ and washed successively with sat. sodium bicarbonate, water, sat. NaCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by ISCO using a gradient of 5-70% EtOAc/hexane as eluent to yield (S)-N-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide as a white foam (0.347 g, 71% yield). HPLC: RT = 3.668 min [M+H] 586.3 (Phenomenex Luna C18 5μ column, eluting with 10-90% aqueous acetonitrile containing 0.1% trifluoroacetic acid over a 4 minute gradient, monitoring at 220 nm). $^1H$ NMR ($CDCl_3$) ppm 7.2-7.05 (m, 6 H), 6.91 (d, J=6.6 Hz, 2H), 6.83 (d, J=8.4 Hz, 1 H), 6.71 (m, 2 H), 5.84 (t, J=53.1 Hz, 1 H), 4.21 (s, 1 H), 3.99 (d, J=12.3 Hz, 1 H), 3.62 (m, 1 H), 3.56 (d, J=12.8 Hz, 1 H), 1.22 ( s, 9 H), 0.72-0.65 (m, 4 H).

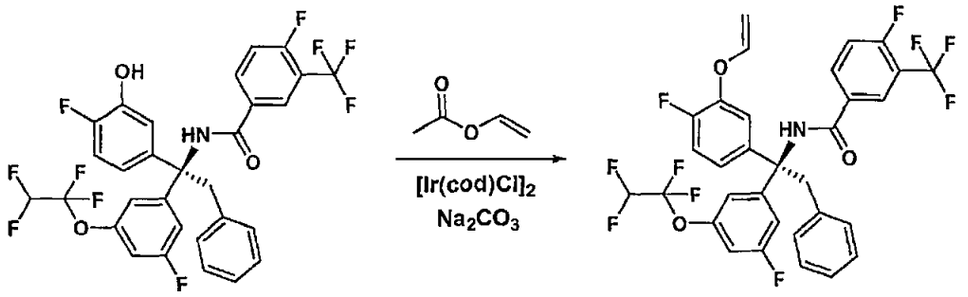
**Procedure 186**




**[00534]** (S)-N-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide was converted to (R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide by the methods described in Procedures 6 and 7.

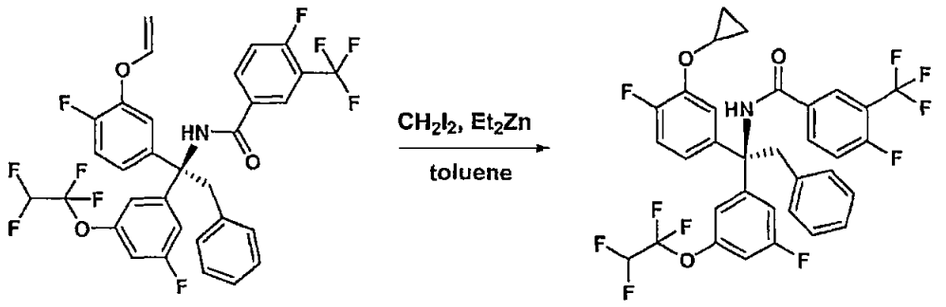
**[00535]** Alternatively, R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide may be prepared from (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide by the following methods:

**Procedure 187**




**[00536]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (Example 264, 100 mg, 0.158 mmol) in toluene (0.2 ml) was added $Na_2CO_3$ (25 mg, 0.235 mmol) and catalytic amount of $[Ir(cod)Cl]_2$ (2 mg), followed by vinyl acetate (68 mg, 0.79 mmol). The reaction mixture was stirred at 100 °C for 16 h. The resulting mixture was filtered and the solid was washed with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with 1 N NaOH, $H_2O$ and the organic portion dried over $Na_2SO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column using 0 to 60% EtOAc in hexane to afford (R)-4-fluoro-N-(1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide eluting out at 20% EtOAc in hexane as colorless oil (80 mg, 77%). LCMS: RT = 2.237 min [M+H] 658.3 (2 min Phenomenex Luna C18 column, 4.6 X 30 mm eluting with 10-90% MeOH/$H_2O$ over 2 minutes containing 0.1% TFA; 5 Ml/min, monitoring at 220 nm. NMR: 400MHz $^1H$ ($CD_3OD$) ppm 3.87 (d, *J*=12.74 Hz, 1 H), 4.05 – 4.15 (m, 1 H), 4.35 (dd, *J*=5.93, 1.98 Hz, 1 H), 4.55 (dd, *J*=13.84, 1.98 Hz, 1 H), 6.12 – 6.41 (m, 1 H), 6.48 (dd, *J*=13.62, 6.15 Hz, 1 H), 6.72 (d, *J*=7.03 Hz, 2 H), 6.87 – 7.24 (m, 9 H), 7.37 – 7.51 (m, 1 H), 7.88 – 8.04 (m, 2 H).

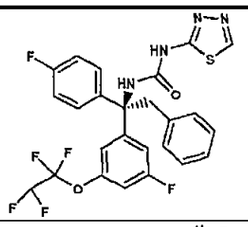
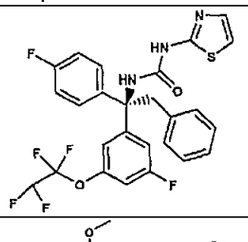
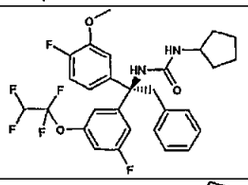
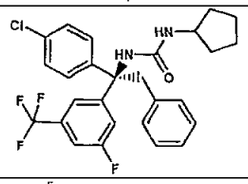
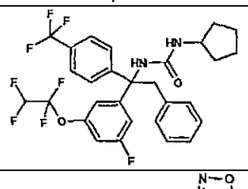
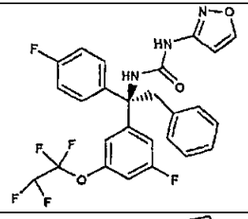
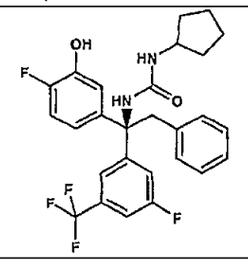
**Procedure 188**

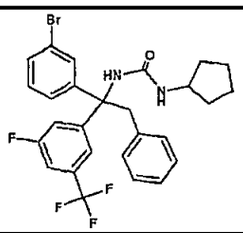
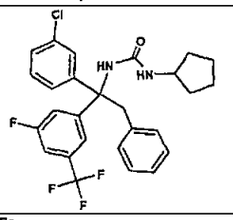
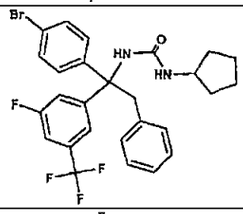
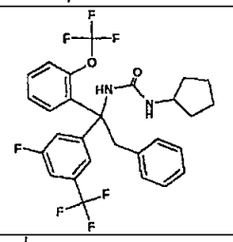
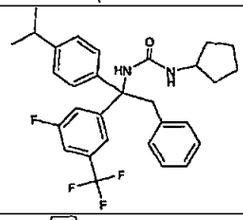
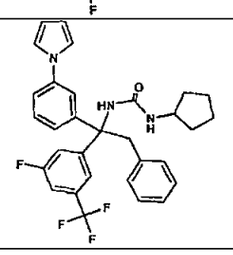


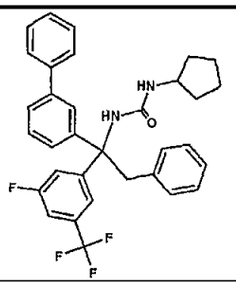
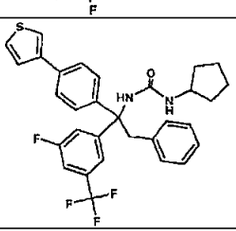
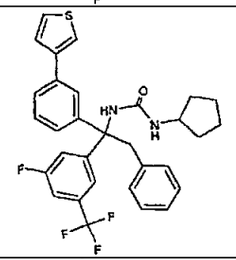
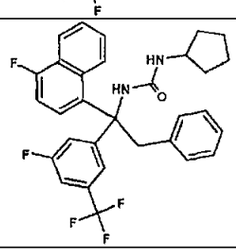
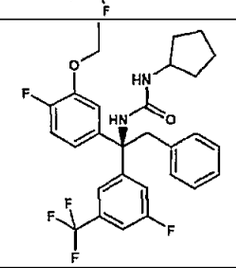

**[00537]** To a solution of (R)-4-fluoro-N-(1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide (66 mg, 0.10 mmol) in 0.5 ml toluene was added $Et_2Zn$ (1 N, 0.2 ml, 0.2 mmol), followed by $CH_2I_2$ (16 ml, 0.2 mmol). The reaction mixture was stirred at 120 °C for 3 h. The reaction mixture was quenched by addition of 1 N HCl and the aqueous layer was extracted with $CH_2Cl_2$. The organic layer was washed with sat. $NaHCO_3$ and concentrated under reduced pressure. The resulting residue was purified by ISCO silica gel column using 0 to 50% to EtOAc in hexane as eluting solvents and Prep HPLC (phenomenex AXIA Luna 75X30 mm, 5u column eluting with 10-90% ACN/$H_2O$ over 10 minutes containing 0.1% TFA; 40 mL/min, monitoring at 220 nm) to afford (R)-N-(1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide (Example 305) as white lyophillate (36 mg, 52% yield). LCMS: RT = 4.268 min [M+H] 672.3 (4 min Phenomenex Luna C18 column, 4.6 X 50 mm eluting with 10-90% MeOH/$H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. NMR: 400MHz $^1H$ ($CDCl_3$) ppm 0.45 - 0.73 (m, 4 H), 3.51 - 3.59 (m, 1 H), 3.76 (d, J=13.18 Hz, 1 H), 4.22 (d, J=12.74 Hz, 1 H), 6.13 - 6.44 (m, 1 H), 6.66 - 6.76 (m, 3 H), 6.97 - 7.08 (m, 3 H), 7.10 - 7.23 (m, 5 H), 7.42 - 7.50 (m, 1 H), 7.95 - 8.03 (m, 2 H).

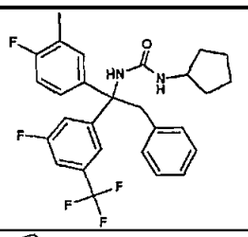
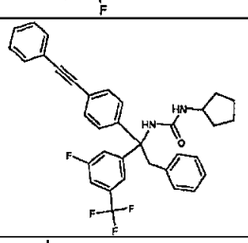
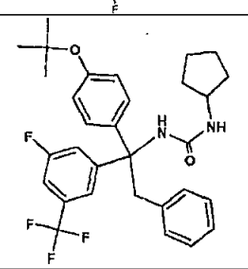
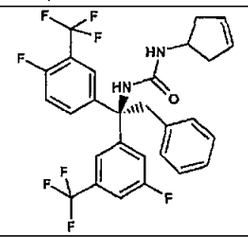
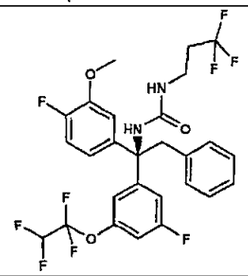
**TABLE 9**

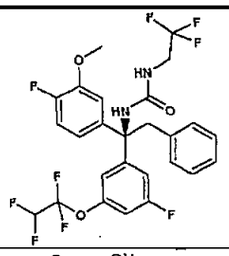
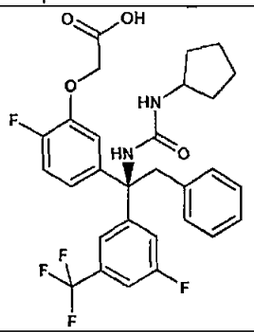
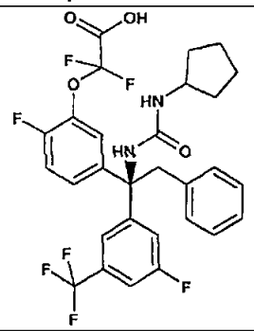
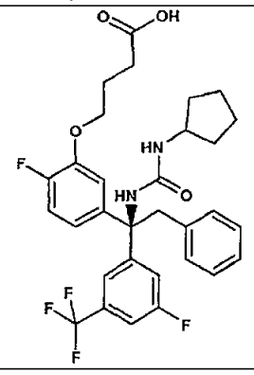
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
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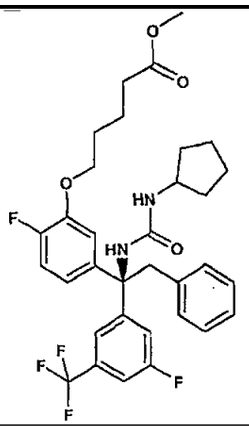
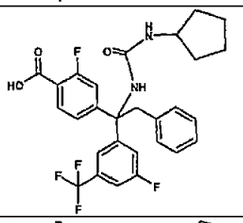
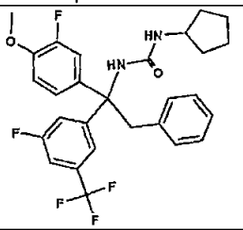
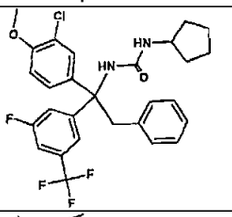
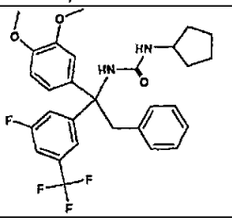
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| 349B |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1,3,4-thiadiazol-2-yl)urea | 4.02 LC (1) 553.27 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 350 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(thiazol-2-yl)urea | 4.12 LC (1) 552.28 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 351 |  | (R)-1-cyclopentyl-3-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.524 LC (1) 567.01 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 352 |  | (R)-1-(1-(4-chlorophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 3.803 LC (1) 505.37 $[M+H]^+$ | Procedures 4, 5, 6 and 2 |
| 353 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethyl) urea | 3.845 LC (1) 587.11 $[M+H]^+$ | Procedures 3, 1, 2 and 23 |
| 354 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(isoxazol-3-yl)urea | 4.11 LC (1) 536.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 355 |  | (R)-1-cyclopentyl-3-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 3.176 LC (1) 505.22 $[M+H]^+$ | Procedures 4, 5, 6, 2 and 59 |

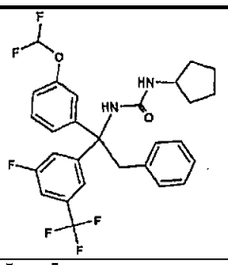
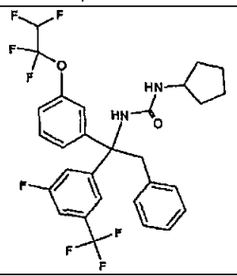
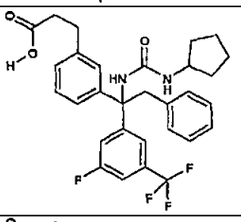
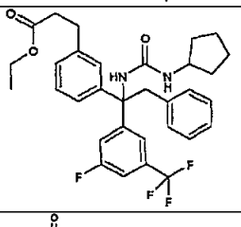
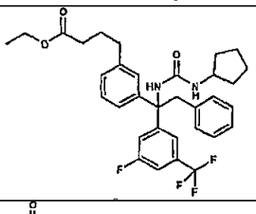
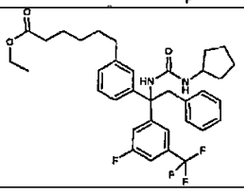
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 356 |  | 1-(1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.25 LC (4) 549.21 $[M+H]^+$ | Procedures 1 and 2 |
| 357 |  | 1-(1-(3-chlorophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.23 LC (4) 505.26 $[M+H]^+$ | Procedures 1 and 2 |
| 358 |  | 1-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.29 LC (4) 549.16 $[M+H]^+$ | Procedures 1 and 2 |
| 359 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(2-(trifluoromethoxy) phenyl)ethyl)urea | 4.21 LC (4) 555.21 $[M+H]^+$ | Procedures 1 and 2 |
| 360 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-isopropylphenyl)-2-phenylethyl)urea | 4.40 LC (4) 513.32 $[M+H]^+$ | Procedures 1 and 2 |
| 361 |  | 1-(1-(3-(1H-pyrrol-1-yl)phenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.26 LC (4) 536.28 $[M+H]^+$ | Procedures 1 and 2 |

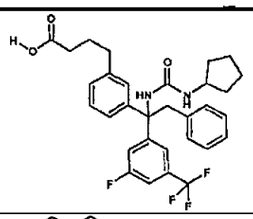
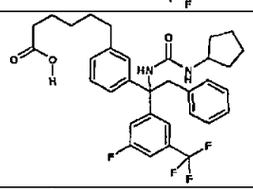
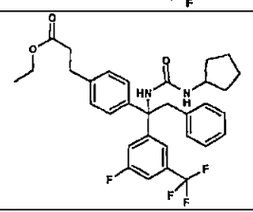
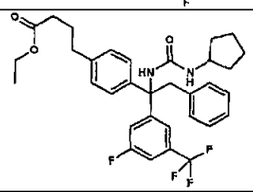
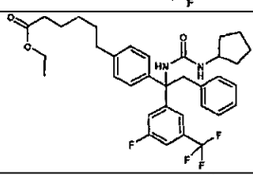
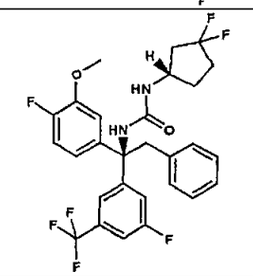
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 362 |  | 1-cyclopentyl-3-(1-(biphenyl-3-yl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.40 LC (4) 547.28 $[M+H]^+$ | Procedures 1 and 2 |
| 363 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(4-(thiophen-3-yl)phenyl)ethyl) urea | 4.33 LC (4) 553.23 $[M+H]^+$ | Procedures 1 and 2 |
| 364 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(thiophen-3-yl)phenyl)ethyl)urea | 4.33 LC (4) 553.26 $[M+H]^+$ | Procedures 1 and 2 |
| 365 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluoronaphthalen-1-yl)-2-phenylethyl)urea | 4.29 LC (4) 539.27 $[M+H]^+$ | Procedures 1 and 2 |
| 366 |  | (R)-1-cyclopentyl-3-(1-(3-ethoxy-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)urea | 3.683 LC (1) 533.36 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59 and 68 |

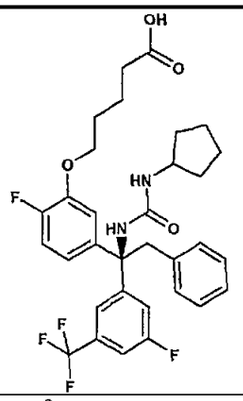
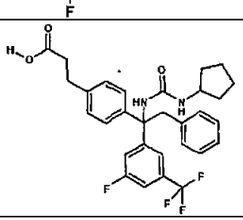
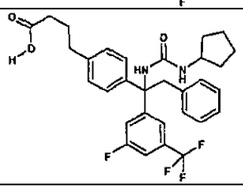
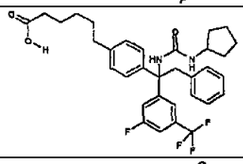
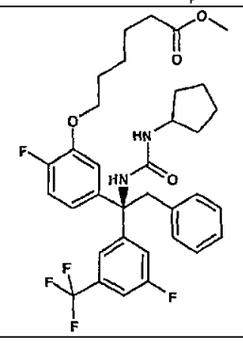
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 367 |  | 1-cyclopentyl-3-(1-(4-fluoro-3-methylphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.23 LC (4) 503.31 $[M+H]^+$ | Procedures 1 and 2 |
| 368 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(4-(2-phenylethynyl) phenyl)ethyl)urea | 4.49 LC (4) 571.28 $[M+H]^+$ | Procedures 1 and 2 |
| 369 |  | 1-(1-(4-tert-butoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.29 LC (4) 543.34 $[M+H]^+$ | Procedures 1 and 2 |
| 370 |  | (R)-1-(cyclopent-3-enyl)-3-(1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.24 LC (1) 555.23 $[M+H]^+$ | Procedures 4, 5, 6 and 10 |
| 371 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.39 LC (1) 595.63 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |

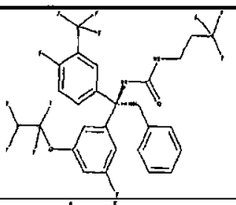
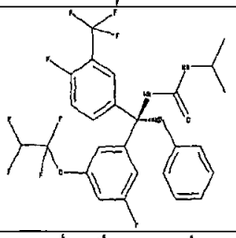
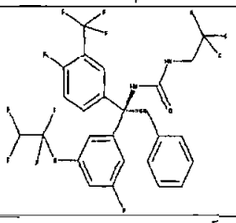
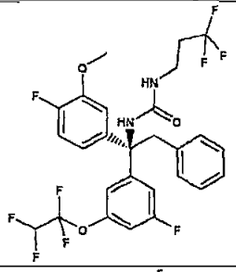
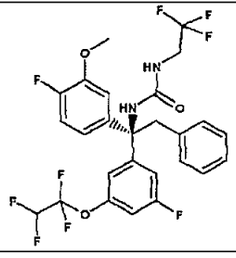
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 372 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.391 LC (1) 581.15 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 373 |  | (R)-2-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) acetic acid | 3.210 LC (1) 563.29 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59, 68 and 23 |
| 374 |  | (R)-2-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy)-2,2-difluoroacetic acid | 3.131 LC (1) 599.27 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59, 68 and 23 |
| 375 |  | (R)-4-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) butanoic acid | 3.068 LC (1) 591.31 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59, 68 and 23 |

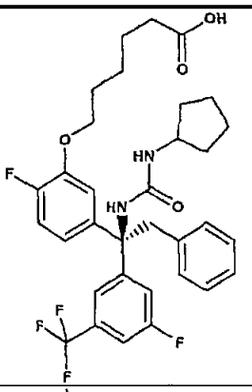
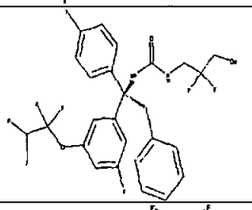
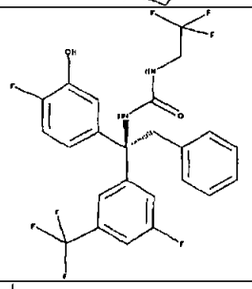
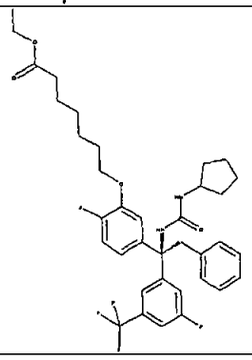
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 376 |  | (R)-methyl 5-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) pentanoate | 3.715 LC (1) 619.33 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59 and 68 |
| 377 |  | 4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-2-fluorobenzoic acid | 3.46 LC (5) 533.24 $[M+H]^+$ | Procedures 1 and 2 |
| 378 |  | 1-cyclopentyl-3-(1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 4.08 LC (4) 519.22 $[M+H]^+$ | Procedures 1 and 2 |
| 379 |  | 1-(1-(3-chloro-4-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.15 LC (4) 535.20 $[M+H]^+$ | Procedures 1 and 2 |
| 380 |  | 1-cyclopentyl-3-(1-(3,4-dimethoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 3.99 LC (4) 531.27 $[M+H]^+$ | Procedures 1 and 2 |

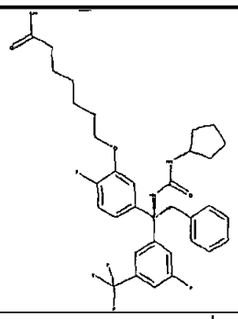
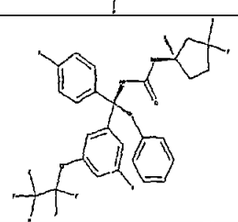
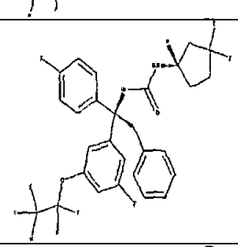
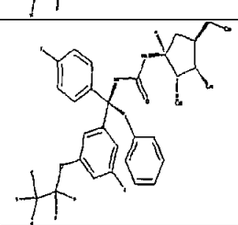
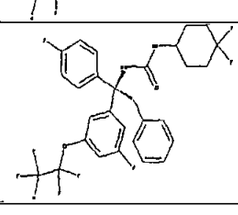
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 381 |  | 1-cyclopentyl-3-(1-(3-(difluoromethoxy)phenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)urea | 4.10 LC (4) 537.20 $[M+H]^+$ | Procedures 1 and 2 |
| 382 |  | 1-cyclopentyl-3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl) urea | 4.15 LC (4) 587.17 $[M+H]^+$ | Procedures 1 and 2 |
| 383 |  | 3-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl) propanoic acid | 4.251 LC (4) 554.2 $[M+H]^+$ | Procedures 1, 2, 24 and 23 |
| 384 |  | ethyl 3-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl) phenyl)propanoate | 4.285 LC (4) 571.3 $[M+H]^+$ | Procedures 1, 2 and 24 |
| 385 |  | ethyl 4-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl)butanoate | 4.376 LC (4) 585.3 $[M+H]^+$ | Procedures 1, 2 and 24 |
| 386 |  | ethyl 6-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl) phenyl)hexanoate | 4.536 LC (4) 613.4 $[M+H]^+$ | Procedures 1, 2 and 24 |

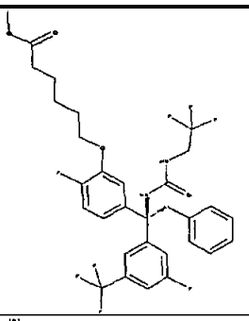
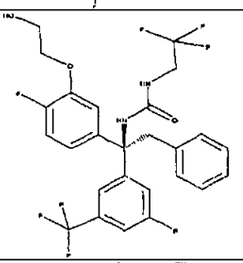
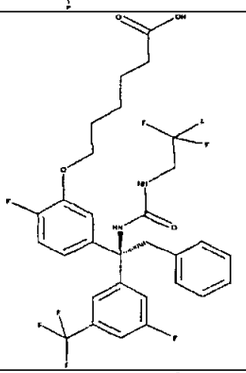
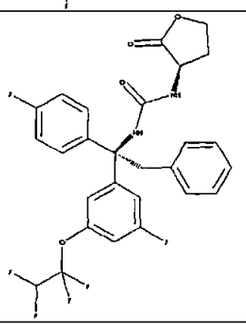
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 387 |  | 4-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl) butanoic acid | 4.135 LC (4) 557.3 $[M+H]^+$ | Procedures 1, 2, 24 and 23 |
| 388 |  | 6-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl) hexanoic acid | 4.288 LC (4) 585.3 $[M+H]^+$ | Procedures 1, 2, 24 and 23 |
| 389 |  | ethyl 3-(4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl)propanoate | 4.286 LC (4) 571.3 $[M+H]^+$ | Procedures 1, 2 and 24 |
| 390 |  | ethyl 4-(4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl) phenyl)butanoate | 4.391 LC (4) 585.3 $[M+H]^+$ | Procedures 1, 2 and 24 |
| 391 |  | ethyl 6-(4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)phenyl)hexanoate | 4.54 LC (4) 613.3 $[M+H]^+$ | Procedures 1, 2 and 24 |
| 392 |  | 1-((S)-3,3-difluorocyclopentyl)-3-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)urea | 3.456 LC (1) 555.27 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |

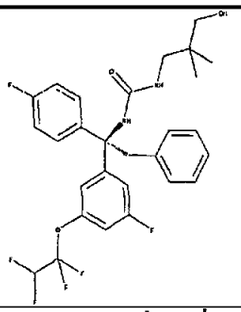
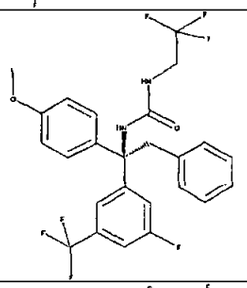
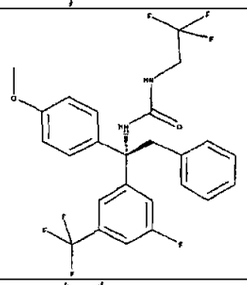
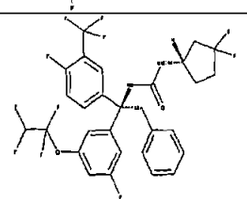
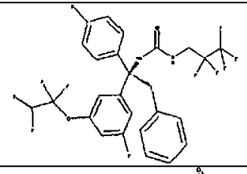
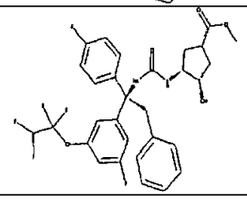
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 393 |  | (R)-5-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) pentanoic acid | 3.265 LC (1) 605.15 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59, 68 and 23 |
| 394 |  | 3-(4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl) propanoic acid | 4.045 LC (4) 543.3 $[M+H]^+$ | Procedures 1, 2, 24 and 23 |
| 395 |  | 4-(4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl) butanoic acid | 4.098 LC (4) 557.2 $[M+H]^+$ | Procedures 1, 2, 24 and 23 |
| 396 |  | 6-(4-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)phenyl) hexanoic acid | 4.275 LC (4) 585.2 $[M+H]^+$ | Procedures 1, 24 and 23 |
| 397 |  | (R)-methyl 6-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) hexanoate | 3.818 LC (1) 633.45 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59, 68 and 23 |

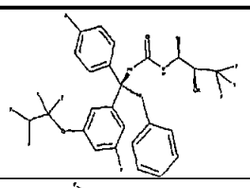
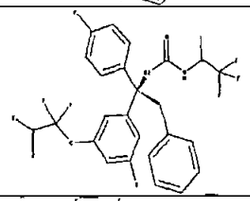
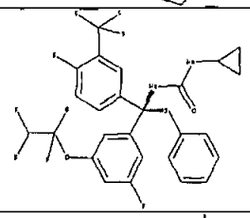
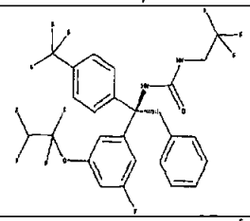
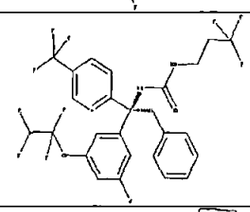
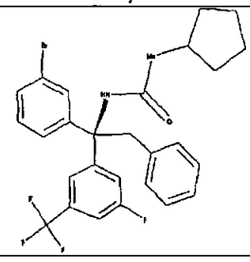
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 398 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.653 LC (1) 633.14 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 399 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-isopropylurea | 3.59 LC (1) 579.03 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 400 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.06 LC (1) 619.64 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 401 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.39 LC (1) 595.63 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 402 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.4 LC (1) 581.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |

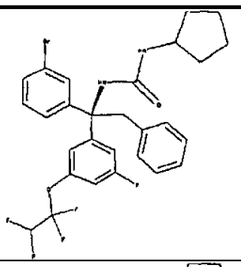
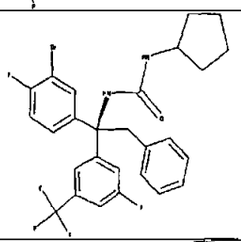
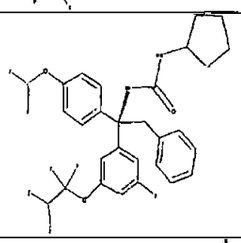
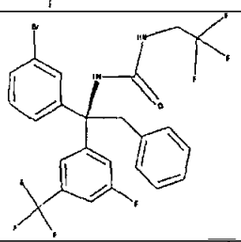
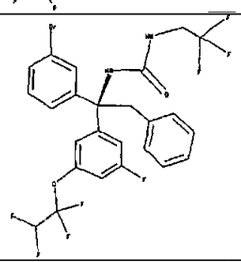
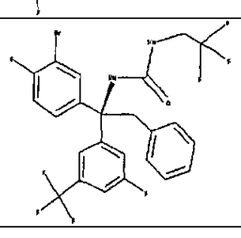
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 403 |  | (R)-6-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) hexanoic acid | 3.37 LC (1) 619.39 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59, 68 and 23 |
| 404 |  | (R)-1-(2,2-difluoro-3-hydroxypropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.82 LC (1) 563.16 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 405 |  | (R)-1-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.07 LC (1) 519.14 $[M+H]^+$ | Procedures 4, 5, 6, 10 and 59 |
| 406 |  | (R)-ethyl 7-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) heptanoate | 4.09 LC (1) 661.37 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59 and 68 |

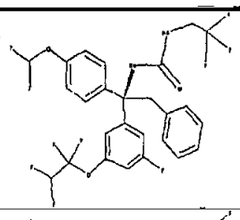
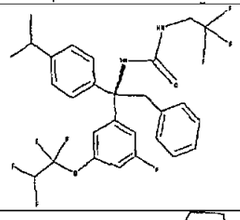
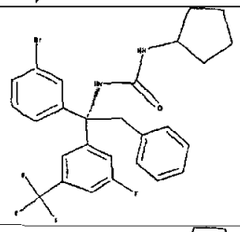
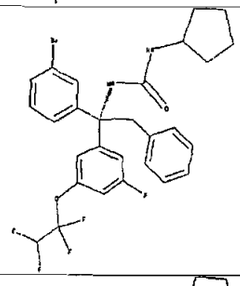
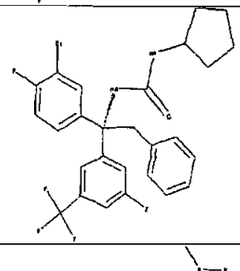
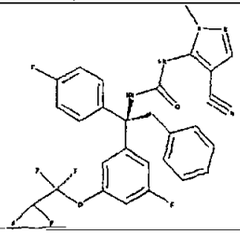
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 407 |  | (R)-7-(5-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2-fluorophenoxy) heptanoic acid | 3.48 LC (1) 633.21 $[M+H]^+$ | Procedures 4, 5, 6, 2, 59 68 and 23 |
| 408 |  | 1-((R)-3,3-difluorocyclopentyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 4.011 LC (3) 573.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 409 |  | 1-((S)-3,3-difluorocyclopentyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.455 LC (3) 573.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 410 |  | 1-((1S,2R,3S,4S)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.736 LC (3) 599.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 411 |  | (R)-1-(4,4-difluorocyclohexyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 4.046 LC (3) 585.3 $[M-H]^-$ | Procedures 3, 4, 5, 6, 130 and 12 |

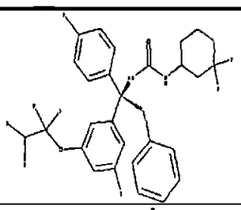
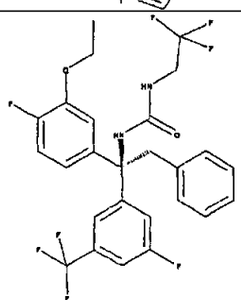
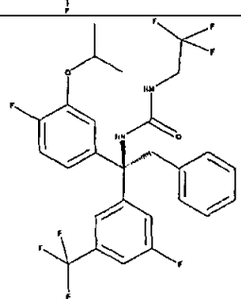
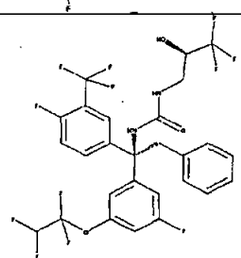
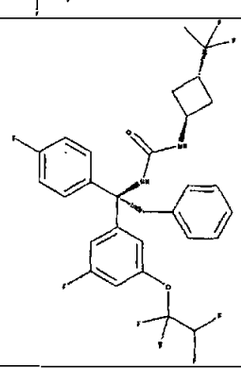
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 412 |  | (R)-methyl 6-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenoxy)hexanoate | 3.69 LC (1) 647.11 $[M+H]^+$ | Procedures 4, 5, 6, 10, 59 and 68 |
| 413 |  | (R)-1-(1-(4-fluoro-3-(2-hydroxyethoxy)phenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.03 LC (1) 563.17 $[M+H]^+$ | Procedures 4, 5, 6, 10, 59 and 68 |
| 414 |  | (R)-6-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl) ureido)ethyl)phenoxy)hexanoic acid | 3.28 LC (1) 633.17 $[M+H]^+$ | Procedures 4, 5, 6, 10, 59, 68 and 23 |
| 415 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((R)-2-oxotetrahydrofuran-3-yl)urea | 3.85 LC (1) 553.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |

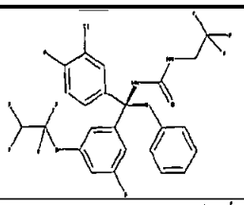
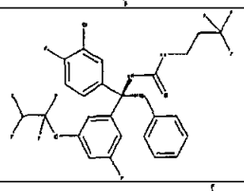
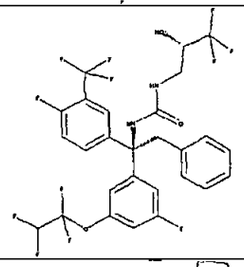
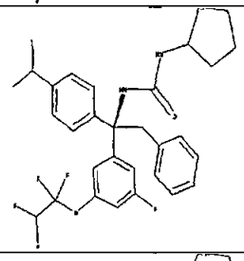
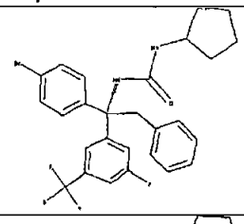
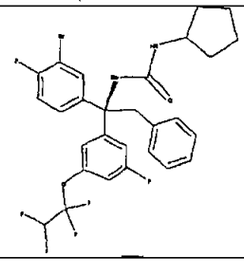
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 416 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(3-hydroxy-2,2-dimethylpropyl) urea | 3.97 LC (1) 555.14 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 417 |  | (R)-1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methoxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.438 LC (1) 515.10 $[M+H]^+$ | Procedures 4, 5, 6 and 10 |
| 418 |  | (S)-1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-methoxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.436 LC (1) 515.11 $[M+H]^+$ | Procedures 4, 5, 6 and 10 |
| 419 |  | 1-((S)-3,3-difluorocyclopentyl)-3-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.66 LC (1) 641.68 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 420 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(2,2,3,3,3-pentafluoropropyl) urea | 4.06 LC (1) 601.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 421 |  | (1S,3R,4R)-methyl 3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)-4-hydroxycyclopentanecarboxylate | 3.87 LC (3) 611.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |

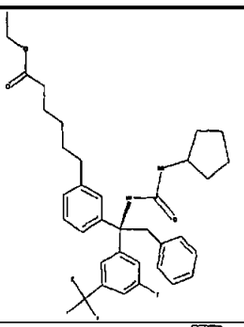
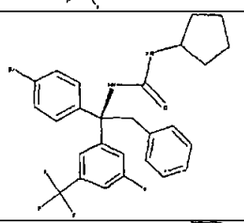
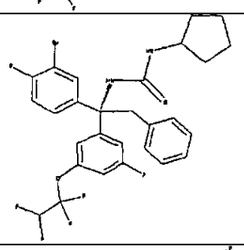
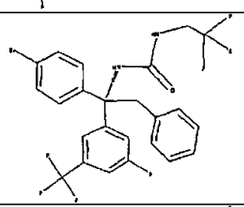
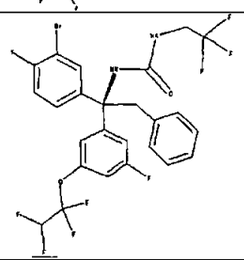
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 422 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((2S,3S)-4,4,4-trifluoro-3-hydroxybutan-2-yl)urea | 3.99 LC (1) 595.12 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 423 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1,1,1-trifluoropropan-2-yl)urea | 4.05 LC (1) 565.65 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 424 |  | (R)-1-cyclopropyl-3-(1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.46 LC (1) 577.03 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 425 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(4-(trifluoromethyl) phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.62 LC (1) 600.98 $[M+H]^+$ | Procedures 3, 4, 5, 6, 2 and 9 |
| 426 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(4-(trifluoromethyl) phenyl)ethyl)-3-(3,3,3-trifluoropropyl)urea | 3.64 LC (1) 615.65 $[M+H]^+$ | Procedures 3, 4, 5, 6, 2 and 9 |
| 427 |  | (S)-1-(1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.30 LC (4) 549.13 $[M+H]^+$ | Procedures 4, 5, 6 and 2 |

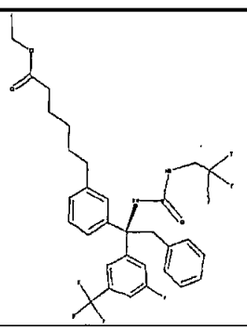
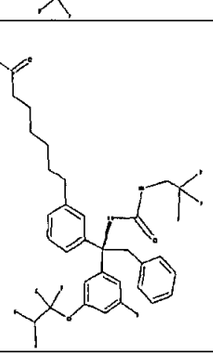
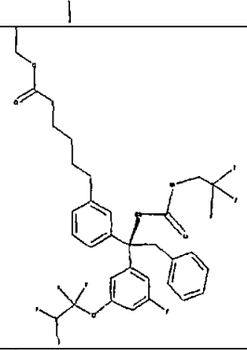
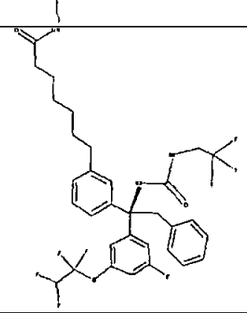
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 428 |  | (S)-1-(1-(3-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.23 LC (4) 597.15 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 429 |  | (S)-1-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.30 LC (4) 567.14 $[M+H]^+$ | Procedures 62, 5, 6 and 2 |
| 430 |  | (R)-1-cyclopentyl-3-(1-(4-(difluoromethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 4.10 LC (4) 585.20 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 431 |  | (S)-1-(1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.21 LC (4) 563.07 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 432 |  | (S)-1-(1-(3-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.13 LC (4) 611.06 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 433 |  | (S)-1-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.19 LC (4) 581.04 $[M+H]^+$ | Procedures 62, 5, 6 and 12 |

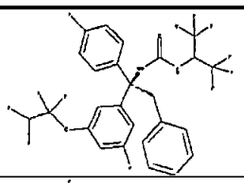
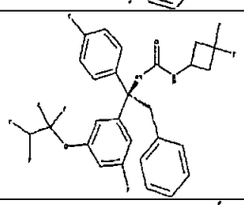
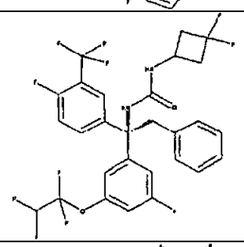
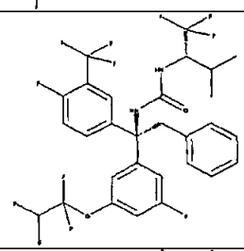
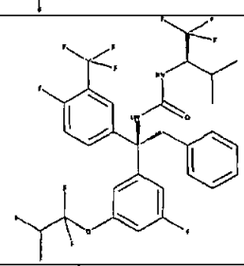
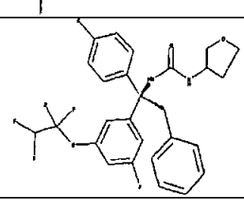
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 434 |  | (R)-1-(1-(4-(difluoromethoxy) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.01 LC (4) 599.15 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 435 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-isopropylphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.27 LC (4) 575.23 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 436 |  | (R)-1-(1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.30 LC (4) 549.13 $[M+H]^+$ | Procedures 4, 5, 6 and 2 |
| 437 |  | (R)-1-(1-(3-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.22 LC (4) 597.12 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 438 |  | (R)-1-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.30 LC (4) 567.11 $[M+H]^+$ | Procedures 62, 5, 6 and 2 |
| 439 |  | (R)-1-(4-cyano-1-methyl-1H-pyrazol-5-yl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.91 LC (3) 574.67 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |

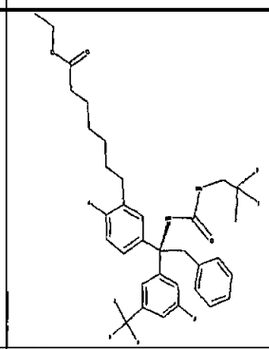
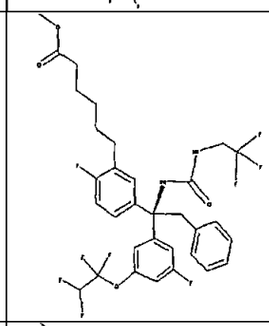
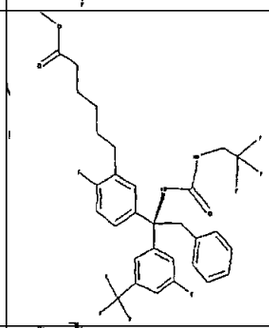
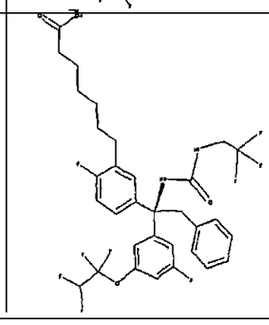
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 440 |  | 1-(3,3-difluorocyclohexyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 4.048 LC (3) 587.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 130 and 12 |
| 441 |  | (R)-1-(1-(3-ethoxy-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.57 LC (1) 547.3 $[M+H]^+$ | Procedures 4, 5, 6, 2, 9, 59 and 68 |
| 442 |  | (R)-1-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.68 LC (1) 561.1 $[M+H]^+$ | Procedures 4, 5, 6, 2, 9, 59 and 68 |
| 443 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-((R)-3,3,3-trifluoro-2-hydroxypropyl)urea | 3.81 LC (1) 649.66 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 28 and 10 |
| 444 |  | 1-((1r,3R)-3-(1,1-difluoroethyl)cyclobutyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 4.10 LC (3) 587.13 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |

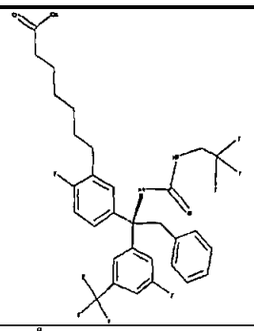
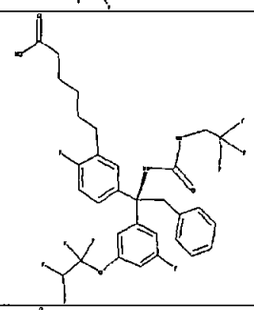
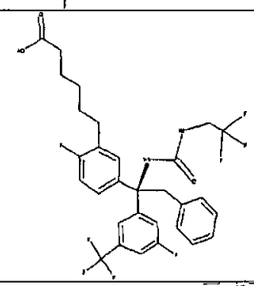
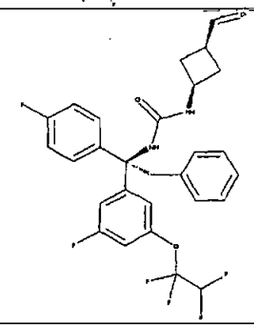
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 445 |  | (S)-1-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.558 LC (1) 585.01 $[M+H]^+$ | Procedures 3, 4, 5, 6, 2 and 9 |
| 446 |  | (S)-1-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(3,3,3-trifluoropropyl)urea | 3.593 LC (1) 599.04 $[M+H]^+$ | Procedures 3, 4, 5, 6, 2 and 9 |
| 447 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-((S)-3,3,3-trifluoro-2-hydroxypropyl)urea | 3.445 LC (1) 649.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 28 and 10 |
| 448 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-isopropylphenyl)-2-phenylethyl)urea | 4.35 LC (4) 561.36 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 449 |  | (S)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.32 LC (4) 549.25 $[M+H]^+$ | Procedures 4, 5, 6 and 2 |
| 450 |  | (S)-1-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.23 LC (4) 615.24 $[M+H]^+$ | Procedures 62, 3, 5, 6 and 2 |

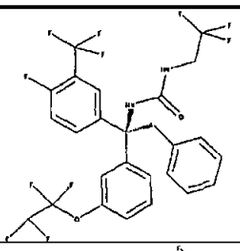
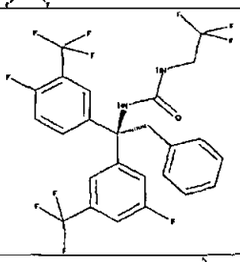
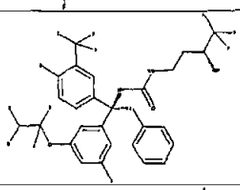
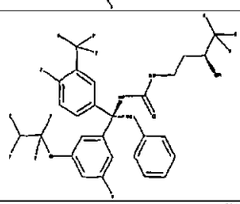
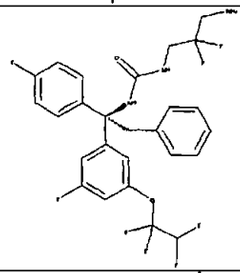
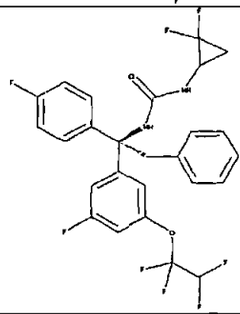
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 451 |  | (R)-ethyl 6-(3-(1-(3-cyclopentylureido)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)phenyl)hexanoate | 4.48 LC (4) 613.43 $[M+H]^+$ | Procedures 4, 5, 6, 24 and 2 |
| 452 |  | (R)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.33 LC (4) 549.21 $[M+H]^+$ | Procedures 4, 5, 6 and 2 |
| 453 |  | (R)-1-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-cyclopentylurea | 4.23 LC (4) 615.26 $[M+H]^+$ | Procedures 62, 3, 5, 6 and 2 |
| 454 |  | (S)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.22 LC (4) 563.16 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 455 |  | (S)-1-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.14 LC (4) 629.11 $[M+H]^+$ | Procedures 62, 3, 5, 6 and 12 |

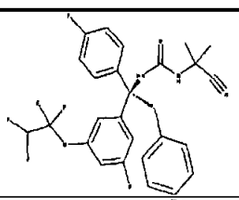
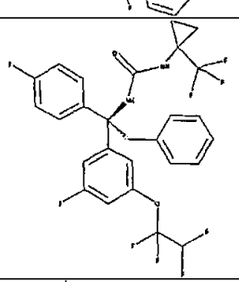
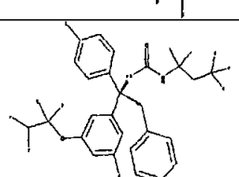
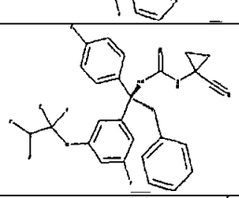
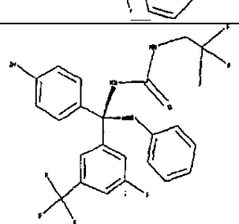
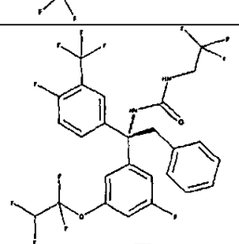
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 456 |  | (R)-ethyl 6-(3-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl) ureido)ethyl)phenyl)hexanoate | 4.36 LC (4) 627.31 $[M+H]^+$ | Procedures 4, 5, 6, 12 and 22 |
| 457 |  | (R)-ethyl 7-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)heptanoate | 4.36 LC (4) 689.31 $[M+H]^+$ | Procedures 3, 4, 5, 6, 12 and 22 |
| 458 |  | (R)-ethyl 6-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)hexanoate | 4.29 LC (4) 675.31 $[M+H]^+$ | Procedures 3, 4, 5, 6, 12 and 22 |
| 459 |  | (R)-7-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl) ureido)ethyl)phenyl)heptanoic acid | 4.17 LC (4) 661.31 $[M+H]^+$ | Procedures 3, 4, 5, 6, 12, 22 and 23 |

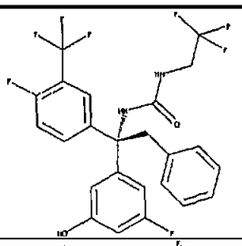
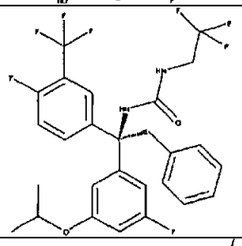
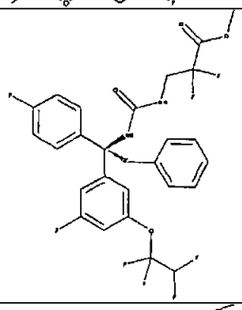
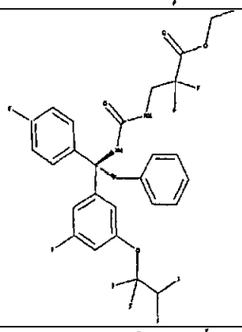
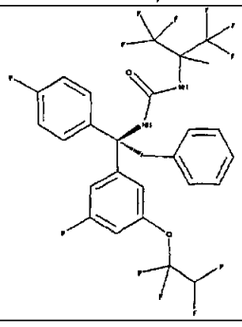
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 460 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea | 4.23 LC (1) 619.04 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 461 |  | (R)-1-(3,3-difluorocyclobutyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.383 LC (3) 559.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 116, 117, 118, 119, 120 and 25 |
| 462 |  | (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.611 LC (3) 627.15 $[M+H]^+$ | Procedures 3, 4, 5, 6, 116, 117, 118, 119, 120 and 10 |
| 463 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-((S)-1,1,1-trifluoro-3-methylbutan-2-yl)urea | 3.891 LC (1) 661.11 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 464 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-((R)-1,1,1-trifluoro-3-methylbutan-2-yl)urea | 3.885 LC (1) 661.12 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 10 |
| 465 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(tetrahydrofuran-3-yl)urea | 3.97 LC (1) 539.09 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |

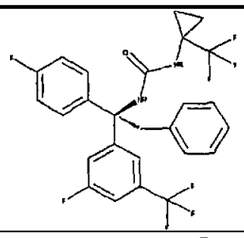
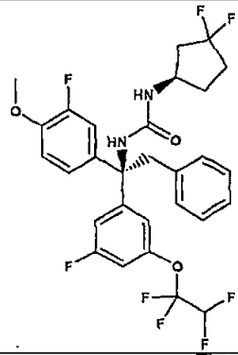
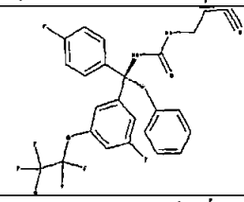
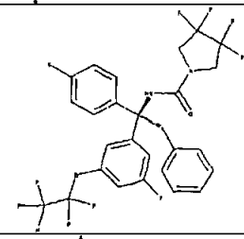
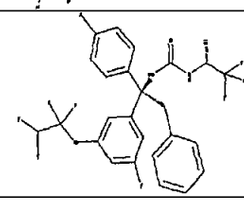
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 466 |  | (R)-ethyl 7-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)heptanoate | 4.45 LC (4) 659.46 $[M+H]^+$ | Procedures 62, 3, 5, 6, 12 and 22 |
| 467 |  | (R)-methyl 6-(2-fluoro-5-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)hexanoate | 4.24 LC (4) 679.45 $[M+H]^+$ | Procedures 62, 3, 5, 6, 12 and 22 |
| 468 |  | (R)-methyl 6-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)hexanoate | 4.30 LC (4) 631.41 $[M+H]^+$ | Procedures 62, 5, 6, 12 and 22 |
| 469 |  | (R)-7-(2-fluoro-5-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)heptanoic acid | 4.18 LC (4) 679.43 $[M+H]^+$ | Procedures 62, 3, 5, 6, 12, 22 and 23 |

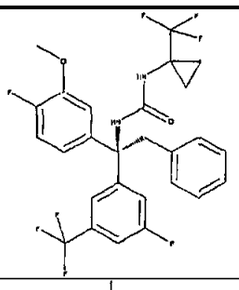
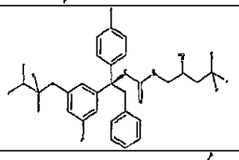
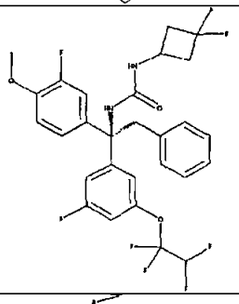
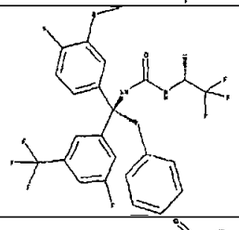
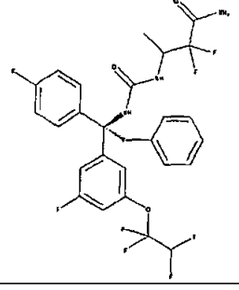
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 470 |  | (R)-7-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl) ureido)ethyl)phenyl)heptanoic acid | 4.23 LC (4) 631.42 $[M+H]^+$ | Procedures 62, 3, 5, 6, 12, 22 and 23 |
| 471 |  | (R)-6-(2-fluoro-5-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) phenyl)hexanoic acid | 4.11 LC (4) 665.40 $[M+H]^+$ | Procedures 62, 3, 5, 6, 12, 22 and 23 |
| 472 |  | (R)-6-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl) ureido)ethyl)phenyl)hexanoic acid | 4.17 LC (4) 617.37 $[M+H]^+$ | Procedures 62, 3, 5, 6, 12, 22 and 23 |
| 473 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((1s,3S)-3-formylcyclobutyl)urea | 2.01 LC (3) 550.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 39, 40 and 41 |

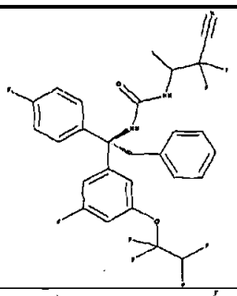
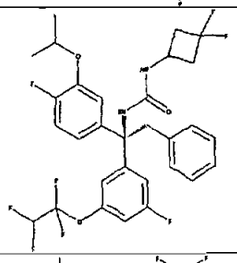
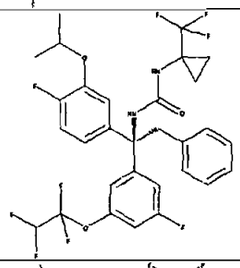
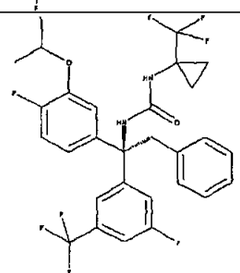
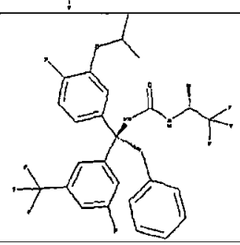
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 474 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(1,1,2,2-tetrafluoroethoxy)phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 4.13 LC (1) 601.9 $[M+H]^+$ | Procedures 3, 4, 5, 6, 2 and 9 |
| 475 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 4.21 LC (1) 571.08 $[M+H]^+$ | Procedures 4, 5, 6, 2 and 9 |
| 476 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-((R)-4,4,4-trifluoro-3-hydroxybutyl)urea | 3.486 LC (1) 663.15 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 28 and 10 |
| 477 |  | 1-((R)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-((S)-4,4,4-trifluoro-3-hydroxybutyl)urea | 3.486 LC (1) 663.16 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 28 and 25 |
| 478 |  | (R)-1-(3-amino-2,2-difluoropropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 1.86 LC (2) 562.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25 and 39 |
| 479 |  | 1-(2,2-difluorocyclopropyl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 2.05 LC (2) 545.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |

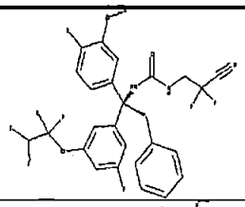
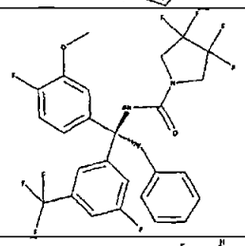
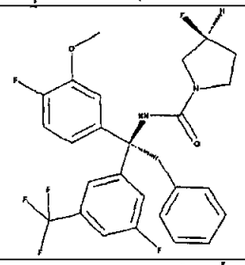
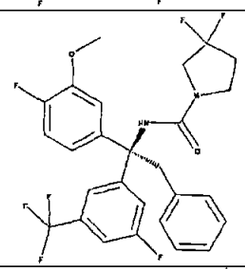
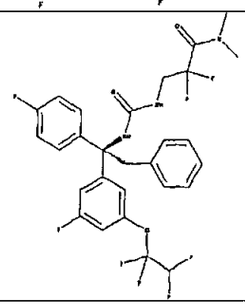
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 480 |  | (R)-1-(2-cyanopropan-2-yl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.93 LC (1) 536.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 481 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 2.08 LC (2) 577.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 30 |
| 482 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(4,4,4-trifluoro-2-methylbutan-2-yl)urea | 2.16 LC (2) 593.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 30 |
| 483 |  | (R)-1-(1-cyanocyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 1.97 LC (2) 534.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 30 |
| 484 |  | (R)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.68 LC (4) 561.1 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 485 |  | (S)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 2.16 LC (2) 619.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 2 and 9 |

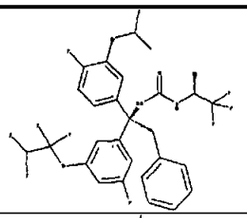
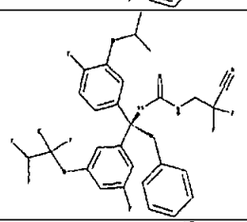
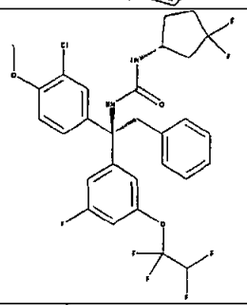
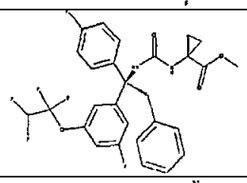
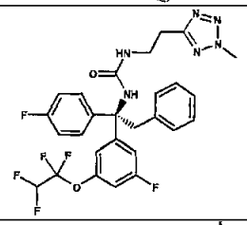
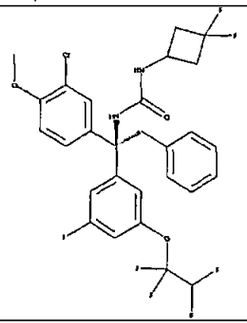
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 486 |  | (S)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-hydroxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 2.0 LC (2) 519.1 $[M+H]^+$ | Procedures 49 and 10 |
| 487 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-isopropoxyphenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 2.20 LC (2) 561.2 $[M+H]^+$ | Procedures 49, 10 and 68 |
| 488 |  | (R)-methyl 2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)propanoate | 4.01 LC (1) 591.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 46, 25 and 127 |
| 489 |  | (R)-ethyl 2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)propanoate | 4.06 LC (1) 605.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 46, 25 and 127 |
| 490 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)urea | 2.19 LC (2) 633.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 30 |

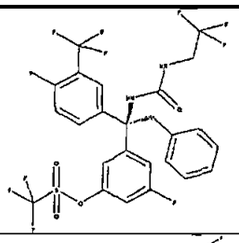
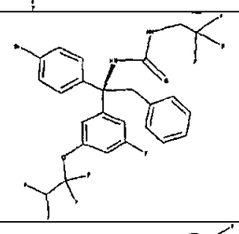
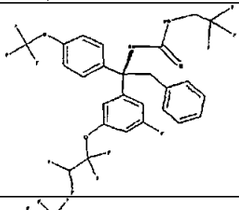
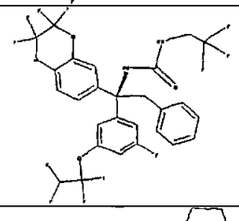
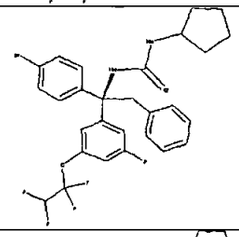
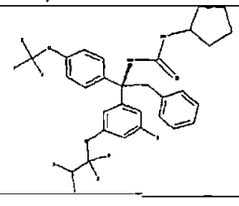
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 491 |  | (R)-1-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 2.12 LC (2) 529.31 $[M+H]^+$ | Procedures 4, 5, 6 and 30 |
| 492 |  | 1-((R)-3,3-difluorocyclopentyl)-3-((R)-1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 10.11 LC (7) 603 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 493 |  | (R)-1-(2-cyanoethyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.075 LC (3) 522.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 494 |  | (R)-3,3,4,4-tetrafluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) pyrrolidine-1-carboxamide | 3.603 LC (3) 595.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 495 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((R)-1,1,1-trifluoropropan-2-yl)urea | 2.12 LC (2) 565.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |

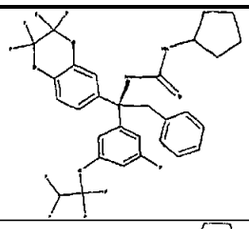
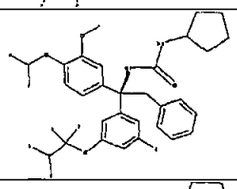
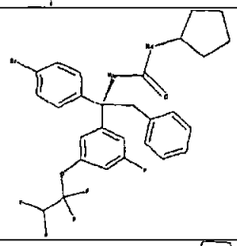
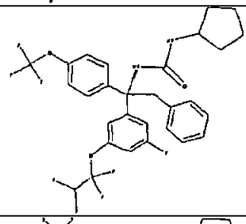
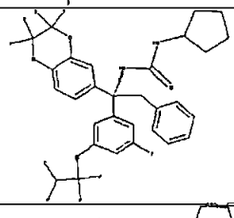
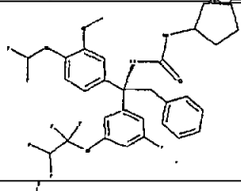
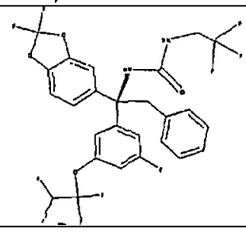
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 496 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 3.50 LC (1) 559.3 $[M+H]^+$ | Procedures 4, 5, 6 and 30 |
| 497 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-((R)-4,4,4-trifluoro-2-hydroxybutyl)urea | 4.271 LC (1) 595.27 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 28 and 25 |
| 498 |  | (R)-1-(3,3-difluorocyclobutyl)-3-(1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 9.97 LC (7) 589 $[M+H]^+$ | Procedures 3, 4, 5, 6, 116, 117, 118, 119, 120 and 10 |
| 499 |  | 1-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-((R)-1,1,1-trifluoropropan-2-yl)urea | 2.10 LC (2) 547.3 $[M+H]^+$ | Procedures 4, 5, 6 and 25 |
| 500 |  | 2,2-difluoro-3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)butanamide | 2.00 LC (2) 590.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 46 and 47 |

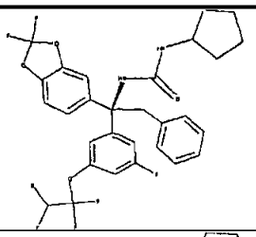
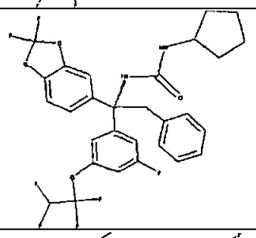
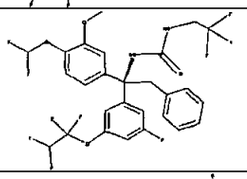
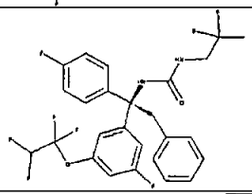
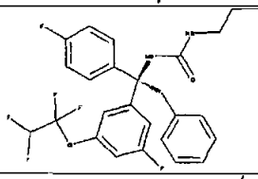
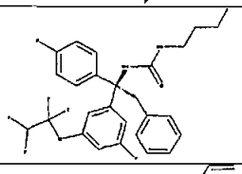
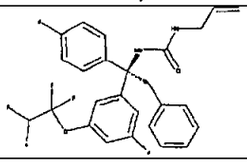
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 501 |  | 1-(1-cyano-1,1-difluoropropan-2-yl)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 2.10 LC (2) 572.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 46, 47 and 48 |
| 502 |  | (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.72 LC (1) 617.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 116, 117, 118, 119, 120, 59, 68 and 10 |
| 503 |  | (R)-1-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 3.60 LC (1) 635.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68 and 30 |
| 504 |  | (R)-1-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 3.745 LC (1) 587.4 $[M+H]^+$ | Procedures 4, 5, 6, 59, 68 and 30 |
| 505 |  | 1-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-((R)-1,1,1-trifluoropropan-2-yl)urea | 2.20 LC (2) 575.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68 and 25 |

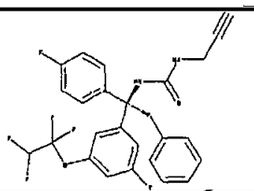
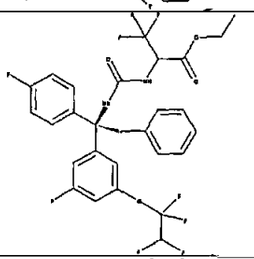
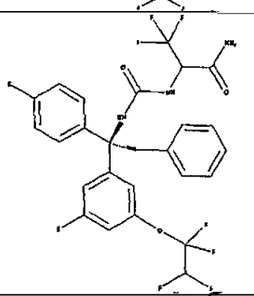
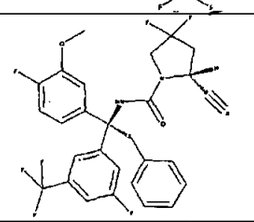
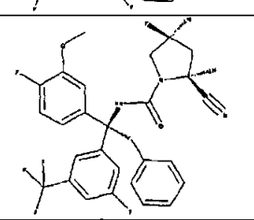
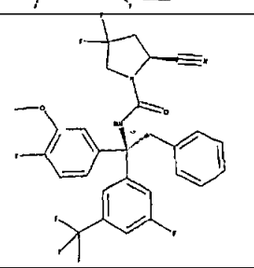
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 506 |  | (R)-1-(2-cyano-2,2-difluoroethyl)-3-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.96 LC (1) 588.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 46, 47 and 48 |
| 507 |  | (R)-3,3,4,4-tetrafluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) pyrrolidine-1-carboxamide | 3.596 LC (3) 577.2 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 508 |  | (S)-3-fluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)pyrrolidine-1-carboxamide | 3.233 LC (3) 523.2 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 509 |  | (R)-3,3-difluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)pyrrolidine-1-carboxamide | 3.403 LC (3) 541.2 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 510 |  | (R)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)-N,N-dimethylpropanamide | 3.21 LC (1) 604.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25 and 127 |

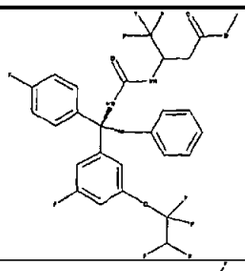
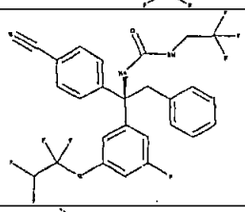
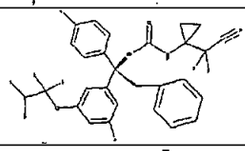
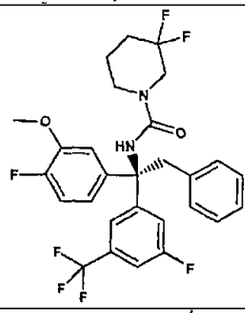
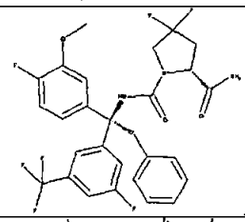
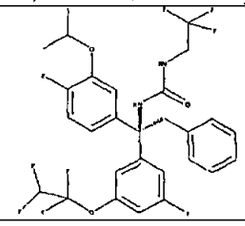
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 511 |  | 1-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-((R)-1,1,1-trifluoropropan-2-yl)urea | 3.66 LC (1) 623.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68 and 25 |
| 512 |  | (R)-1-(2-cyano-2,2-difluoroethyl)-3-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 2.26 LC (2) 616.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68, 46, 25, 47 and 48 |
| 513 |  | 1-((S)-1-(3-chloro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-((R)-3,3-difluorocyclopentyl)urea | 10.28 LC (7) 619 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 514 |  | (R)-methyl 1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)ureido)cyclopropanecarboxylate | 3.89 LC (1) 567.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 515 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(2-(2-methyl-2H-tetrazol-5-yl)ethyl)urea | 3.005 LC (3) 579.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 12 and 55 |
| 516 |  | (S)-1-(1-(3-chloro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(3,3-difluorocyclobutyl)urea | 10.16 LC (7) 606 $[M+H]^+$ | Procedures 3, 4, 5, 6, 116, 117, 118, 119, 120 and 25 |

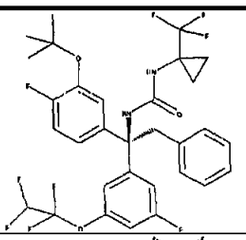
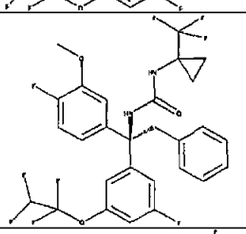
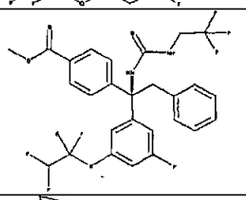
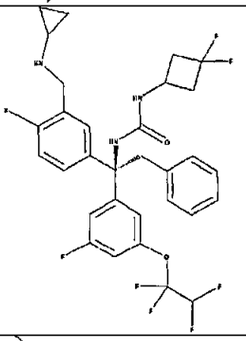
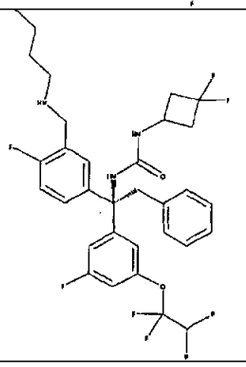
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 517 |  | (R)-3-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl) ureido)ethyl)phenyl trifluoromethanesulfonate | 2.34 LC (2) 651.4 $[M+H]^+$ | Procedures 49 and 66 |
| 518 |  | (R)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.76 LC (4) 611.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 519 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(4-(trifluoromethoxy) phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.79 LC (4) 617.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 520 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-3-(2,2,2-trifluoroethyl) urea | 3.88 LC (4) 663.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 521 |  | (R)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea | 3.87 LC (4) 597.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 522 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(4-(trifluoromethoxy)phenyl)ethyl) urea | 3.90 LC (4) 603.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |

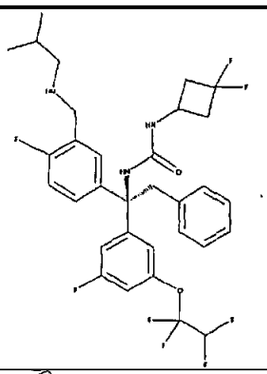
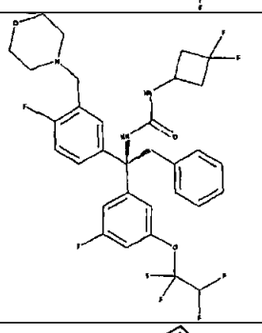
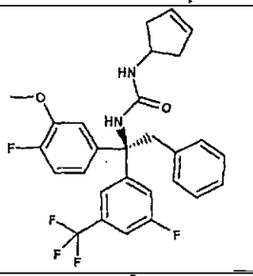
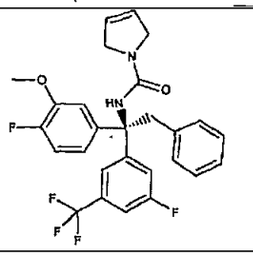
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 523 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)ethyl)urea | 4.02 LC (4) 649.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 524 |  | (R)-1-cyclopentyl-3-(1-(4-(difluoromethoxy)-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.68 LC (4) 615.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 525 |  | (S)-1-(1-(4-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-cyclopentylurea | 3.87 LC (4) 597.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 526 |  | (S)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(4-(trifluoromethoxy)phenyl)ethyl) urea | 3.90 LC (4) 603.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 527 |  | (S)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)ethyl)urea | 4.02 LC (4) 649.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 528 |  | (S)-1-cyclopentyl-3-(1-(4-(difluoromethoxy)-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.68 LC (4) 615.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 529 |  | (R)-1-(1-(2,2-difluorobenzo[d] [1,3]dioxol-5-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.74 LC (4) 613.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 530 |  | (R)-1-cyclopentyl-3-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.85 LC (4) 599.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 531 |  | (S)-1-cyclopentyl-3-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.85 LC (4) 599.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 532 |  | (R)-1-(1-(4-(difluoromethoxy)-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.59 LC (4) 629.09 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 2 |
| 533 |  | (R)-1-(2,2-difluoropropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.955 LC (3) 547.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 534 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-propylurea | 3.985 LC (3) 511.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 535 |  | (R)-1-butyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 4.063 LC (3) 525.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 536 |  | (R)-1-allyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.948 LC (3) 509.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 537 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(prop-2-ynyl)urea | 3.866 LC (3) 507.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 12 |
| 538 |  | ethyl 3,3,3-trifluoro-2-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)propanoate | 2.15 LC (2) 623.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 539 |  | 3,3,3-trifluoro-2-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)propanamide | 3.04 LC (8) 594.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 23 and 47 |
| 540 |  | (R)-2-cyano-4,4-difluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) pyrrolidine-1-carboxamide | 3.895 LC (3) 566.3 $[M+H]^+$ | Procedures 4, 5, 6, 12 and 48 |
| 541 |  | (2S,4S)-2-cyano-4-fluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)pyrrolidine-1-carboxamide | 3.82 LC (3) 548.3 $[M+H]^+$ | Procedures 4, 5, 6, 12 and 48 |
| 542 |  | (S)-2-cyano-4,4-difluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) pyrrolidine-1-carboxamide | 3.925 LC (3) 566.3 $[M+H]^+$ | Procedures 4, 5, 6, 12 and 48 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 543 |  | methyl 4,4,4-trifluoro-3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) ureido)butanoate | 4.0 LC (1) 623.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 544 |  | (R)-1-(1-(4-cyanophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 1.12 LC (9) 558 $[M+H]^+$ | Procedures 3, 4, 5, 6, 56 and 25 |
| 545 |  | (R)-1-(1-(cyanodifluoromethyl) cyclopropyl)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)urea | 3.44 LC (8) 584.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 34, 35, 47 and 48 |
| 546 |  | (R)-3,3-difluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)piperidine-1-carboxamide | 4.023 LC (3) 555.3 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 547 |  | (R)-4,4-difluoro-N1-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) pyrrolidine-1,2-dicarboxamide | 3.901 LC (3) 584.3 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 548 |  | (R)-1-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 3.633 LC (1) 609.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 10, 59 and 68 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 549 |  | (R)-1-(1-(3-tert-butoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 3.798 LC (1) 649.6 $[M+H]^+$ | Procedures 3, 4, 5, 6, 30, 59 and 108 |
| 550 |  | (R)-1-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(1-(trifluoromethyl)cyclopropyl) urea | 3.46 LC (1) 607.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 30 |
| 551 |  | (R)-methyl 4-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(3-(2,2,2-trifluoroethyl)ureido)ethyl) benzoate | 1.19 LC (12) 591 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 56 and 57 |
| 552 |  | (R)-1-(1-(3-((cyclopropylamino) methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(3,3-difluorocyclobutyl)urea | 3.331 LC (15) 628 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 116-120, 12, 147 and 148 |
| 553 |  | (R)-1-(1-(3-((butylamino) methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(3,3-difluorocyclobutyl)urea | 3.488 LC (15) 644 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 116-120, 12, 147 and 148 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 554 |  | (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-((isobutylamino) methyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.458 LC (15) 644 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 116-120, 12, 147 and 148 |
| 555 |  | (R)-1-(3,3-difluorocyclobutyl)-3-(1-(4-fluoro-3-(morpholinomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)urea | 3.636 LC (15) 658 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 116-120, 12, 147 and 148 |
| 556 |  | (R)-1-(cyclopent-3-enyl)-3-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)urea | 4.068 LC (3) 517.3 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |
| 557 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-2,5-dihydro-1H-pyrrole-1-carboxamide | 3.986 LC (3) 503.3 $[M+H]^+$ | Procedures 4, 5, 6 and 12 |

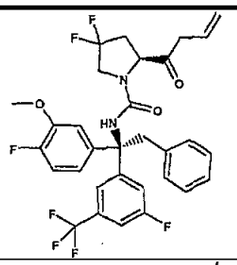
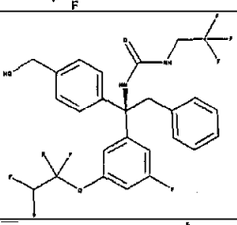
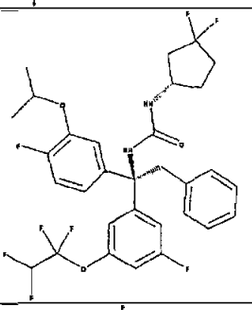
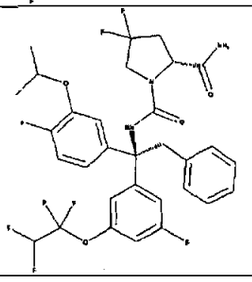
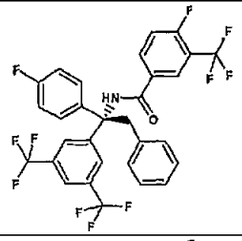
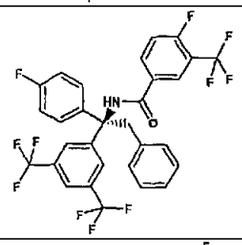
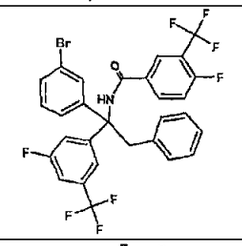
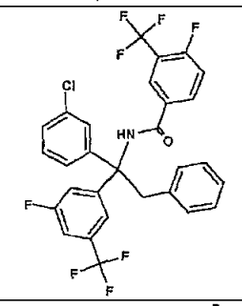
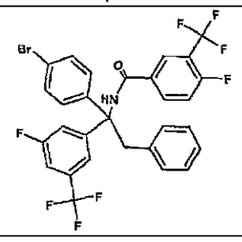
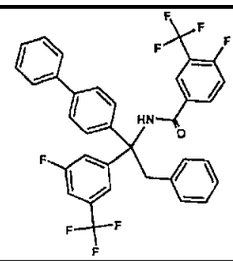
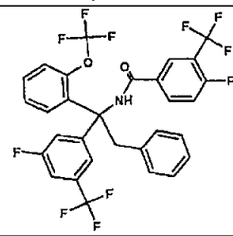
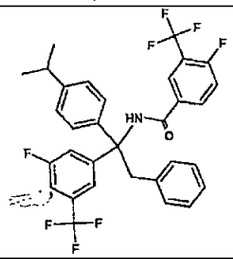
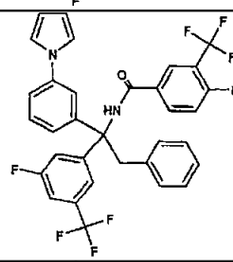
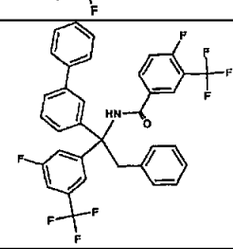
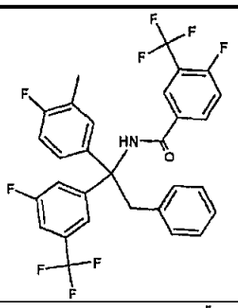
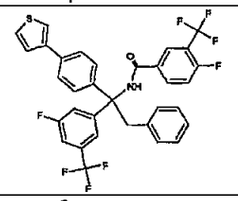
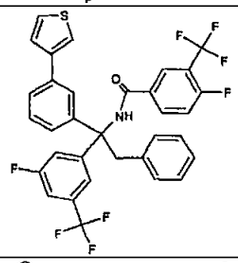
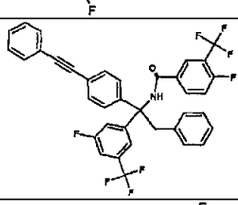
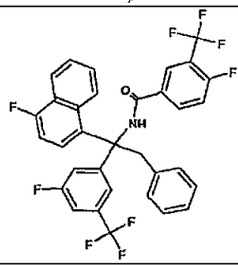
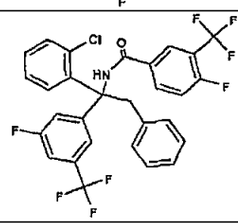
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 558 |  | (S)-2-but-3-enoyl-4,4-difluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)pyrrolidine-1-carboxamide | 4.09 LC (3) 609.3 $[M+H]^+$ | Procedure 4, 5, 6 and 12 |
| 559 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-(hydroxymethyl)phenyl)-2-phenylethyl)-3-(2,2,2-trifluoroethyl)urea | 1.78 LC (9) 563 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 56, 57 and 100 |
| 560 |  | 1-((S)-3,3-difluorocyclopentyl)-3-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)urea | 3.633 LC (3) 661.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 12, 59 and 68 |
| 561 |  | (R)-4,4-difluoro-N1-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)pyrrolidine-1,2-dicarboxamide | 3.221 LC (3) 660.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 12, 59 and 68 |

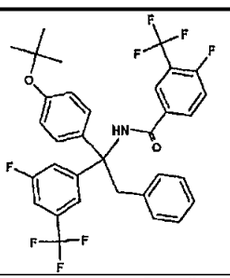
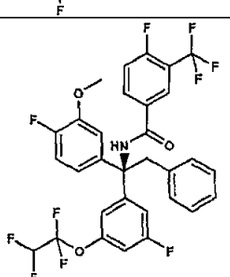
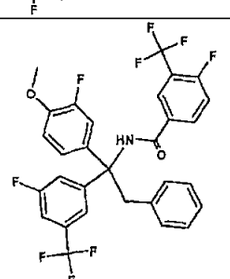
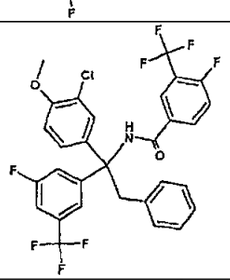
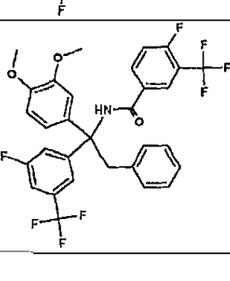
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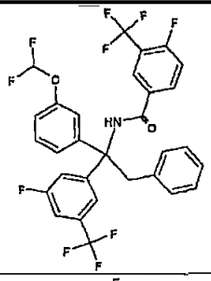
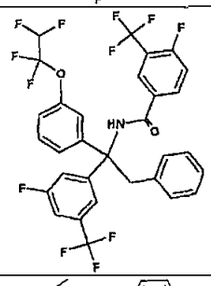
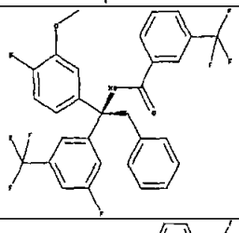
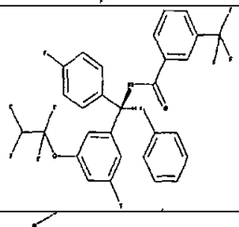
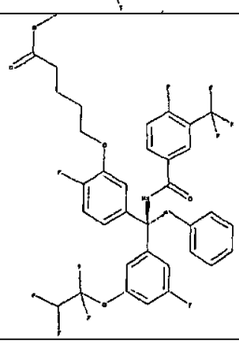
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
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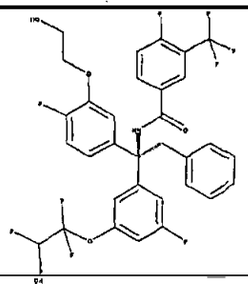
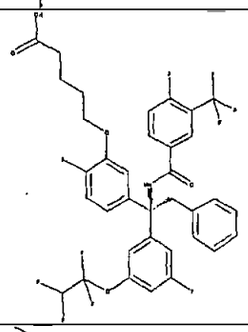
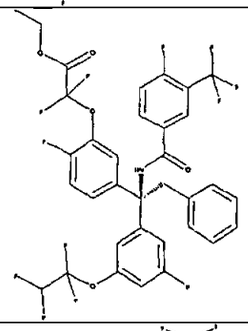
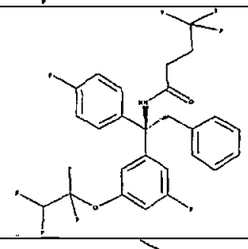
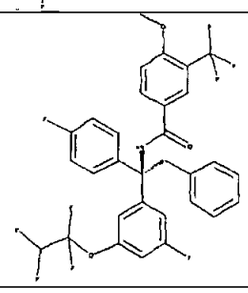
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 562 |  | (S)-N-(1-(3,5-bis(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.120 LC (1) 617.97 $[M+H]^+$ | Procedures 4, 5, 6 and 7 |
| 563 |  | (R)-N-(1-(3,5-bis(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.528 LC (1) 617.97 $[M+H]^+$ | Procedures 4, 5, 6 and 7 |
| 564 |  | N-(1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.33 LC (4) 628.12 $[M+H]^+$ | Procedures 1 and 7 |
| 565 |  | N-(1-(3-chlorophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.31 LC (4) 584.15 $[M+H]^+$ | Procedures 1 and 7 |
| 566 |  | N-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.37 LC (4) 628.10 $[M+H]^+$ | Procedures 1 and 7 |

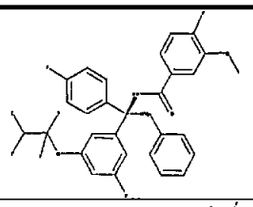
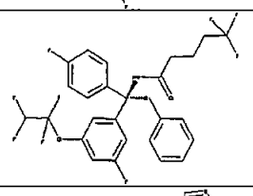
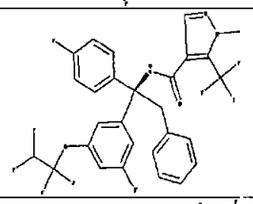
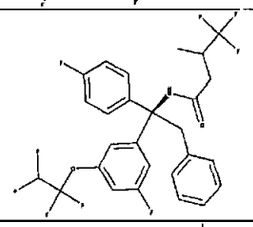
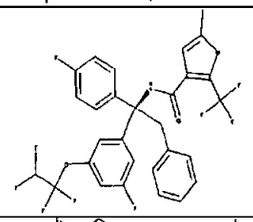
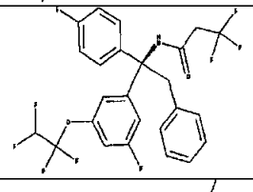
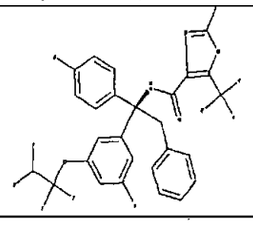
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 567 |  | N-(1-(biphenyl-4-yl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.50 LC (4) 626.26 $[M+H]^+$ | Procedures 1 and 7 |
| 568 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(2-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.32 LC (4) 634.18 $[M+H]^+$ | Procedures 1 and 7 |
| 569 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-isopropylphenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.50 LC (4) 592.23 $[M+H]^+$ | Procedures 1 and 7 |
| 570 |  | N-(1-(3-(1H-pyrrol-1-yl)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.34 LC (4) 615.24 $[M+H]^+$ | Procedures 1 and 7 |
| 571 |  | N-(1-(biphenyl-3-yl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.48 LC (4) 626.25 $[M+H]^+$ | Procedures 1 and 7 |

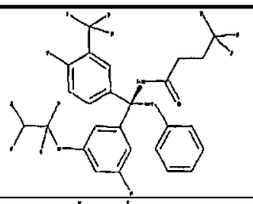
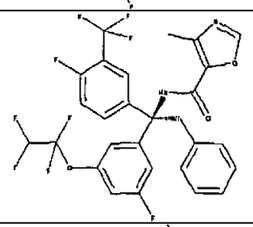
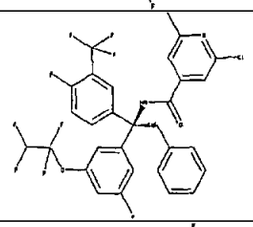
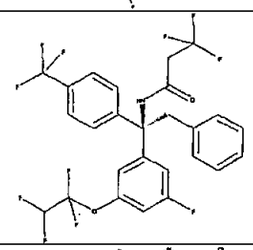
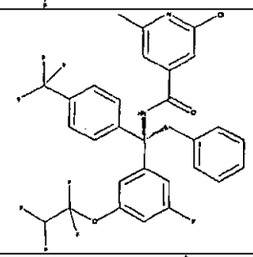
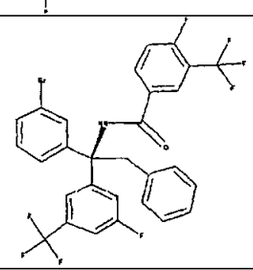
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 572 |  | 4-fluoro-N-(1-(4-fluoro-3-methylphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.33 LC (4) 582.22 $[M+H]^+$ | Procedures 1 and 7 |
| 573 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(4-(thiophen-3-yl)phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.41 LC (4) 632.16 $[M+H]^+$ | Procedures 1 and 7 |
| 574 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(thiophen-3-yl)phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.43 LC (4) 632.18 $[M+H]^+$ | Procedures 1 and 7 |
| 575 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(4-(2-phenylethynyl) phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.59 LC (4) 650.20 $[M+H]^+$ | Procedures 1 and 7 |
| 576 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluoronaphthalen-1-yl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.40 LC (4) 618.20 $[M+H]^+$ | Procedures 1 and 7 |
| 577 |  | N-(1-(2-chlorophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.33 LC (4) 584.19 $[M+H]^+$ | Procedures 1 and 7 |

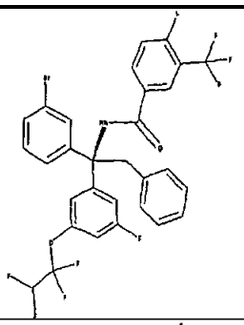
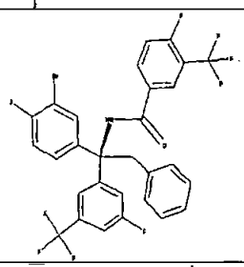
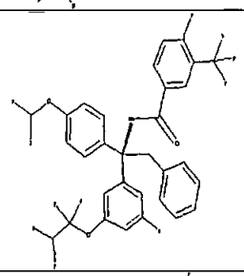
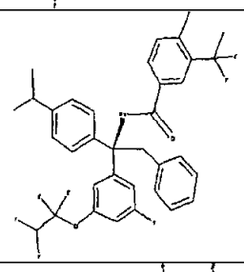
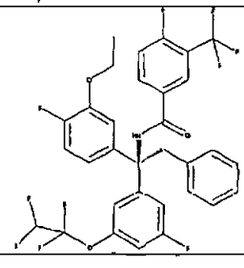
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 578 |  | N-(1-(4-tert-butoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.40 LC (4) 622.28 $[M+H]^+$ | Procedures 1 and 7 |
| 579 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.833 LC (1) 646.14 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 580 |  | 4-fluoro-N-(1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.20 LC (4) 598.10 $[M+H]^+$ | Procedures 1 and 7 |
| 581 |  | N-(1-(3-chloro-4-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.26 LC (4) 614.07 $[M+H]^+$ | Procedures 1 and 7 |
| 582 |  | N-(1-(3,4-dimethoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.15 LC (4) 610.13 $[M+H]^+$ | Procedures 1 and 7 |

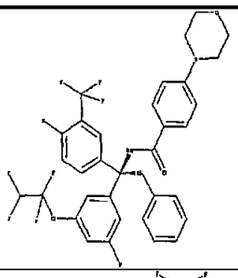
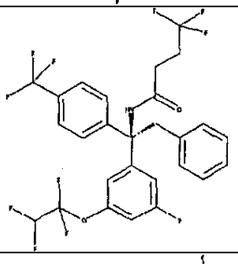
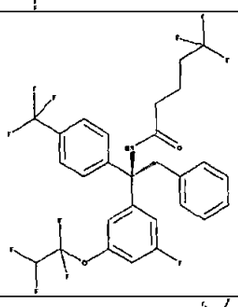
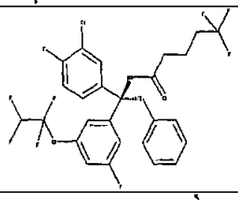
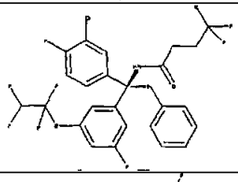
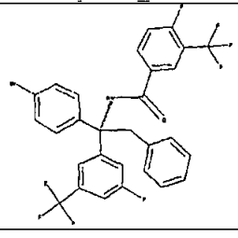
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 583 |  | N-(1-(3-(difluoromethoxy) phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.21 LC (4) 616.10 $[M+H]^+$ | Procedures 1 and 7 |
| 584 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.24 LC (4) 666.13 $[M+H]^+$ | Procedures 1 and 7 |
| 585 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.92 LC (1) 580.1 $[M+H]^+$ | Procedures 4, 5, 6 and 7 |
| 586 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.84 LC (1) 598.15 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 587 |  | (R)-methyl 5-(2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) phenoxy)pentanoate | 3.95 LC (1) 746.12 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

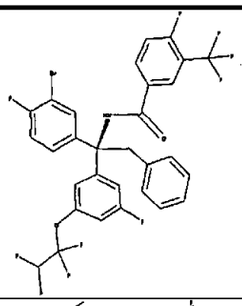
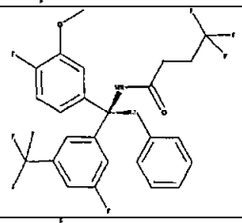
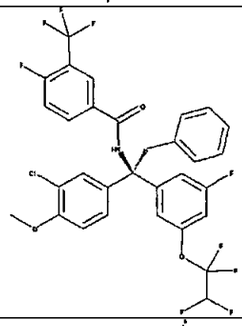
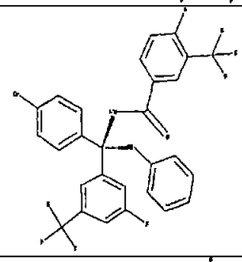
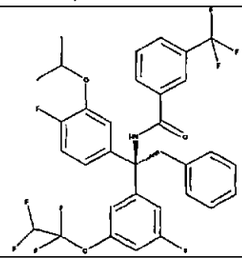
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 588 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(2-hydroxyethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.48 LC (1) 676.10 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 589 |  | (R)-5-(2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) phenoxy)pentanoic acid | 3.59 LC (1) 732.08 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 68 and 23 |
| 590 |  | (R)-ethyl 2,2-difluoro-2-(2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)phenoxy)acetate | 3.92 LC (1) 754.30 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 591 |  | (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide | 3.60 LC (1) 550.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 592 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-4-methoxy-3-(trifluoromethyl)benzamide | 3.81 LC (1) 628.21 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |

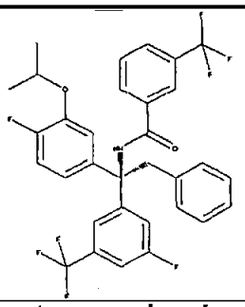
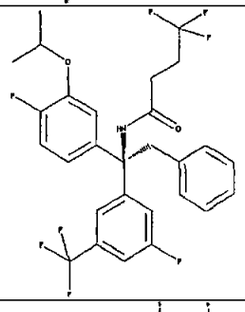
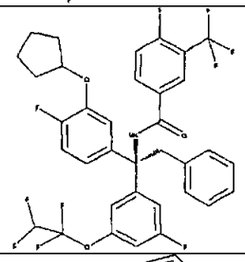
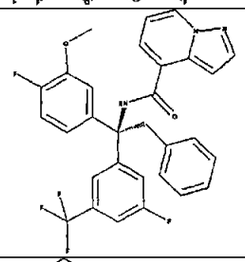
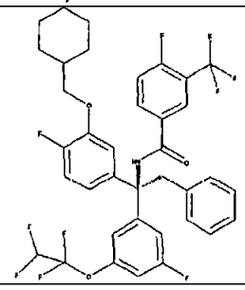
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 593 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-methoxybenzamide | 3.68 LC (1) 578.12 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 594 |  | (R)-5,5,5-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)pentanamide | 3.65 LC (1) 564.09 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 595 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-1-methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide | 4.01 LC (4) 602.17 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 127 |
| 596 |  | 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-methylbutanamide | 4.14 LC (4) 564.21 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 127 |
| 597 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-5-methyl-2-(trifluoromethyl)furan-3-carboxamide | 4.12 LC (4) 602.17 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 127 |
| 598 |  | (R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide | 3.99 LC (4) 535.21 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 127 |
| 599 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-methyl-5-(trifluoromethyl)oxazole-4-carboxamide | 4.15 LC (4) 603.14 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 127 |

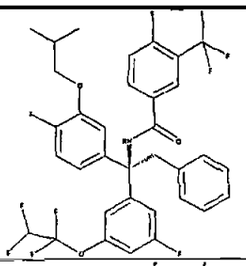
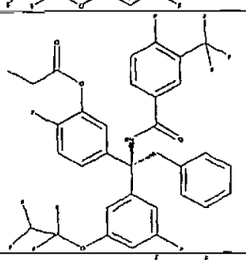
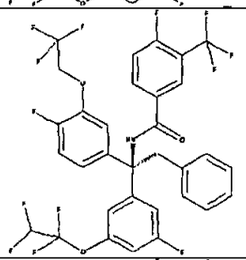
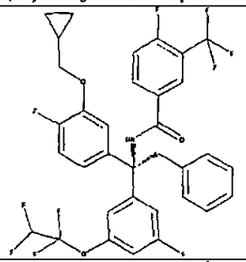
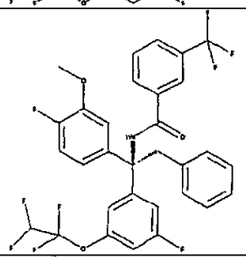
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 600 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide | 3.751 LC (1) 617.96 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 601 |  | (R)-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-methyloxazole-5-carboxamide | 3.513 LC (1) 603.69 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 602 |  | (R)-2-chloro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-6-methylisonicotinamide | 3.836 LC (1) 647.69 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 603 |  | (R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(4-(trifluoromethyl) phenyl)ethyl)propanamide | 3.61 LC (1) 586.67 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 604 |  | (R)-2-chloro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethyl) -6-methylisonicotinamide | 3.72 LC (1) 629.70 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 605 |  | (S)-N-(1-(3-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.41 LC (4) 628.08 $[M+H]^+$ | Procedures 4, 5, 6 and 7 |

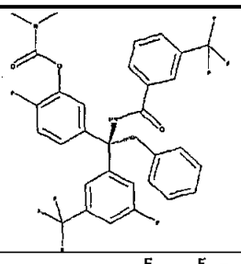
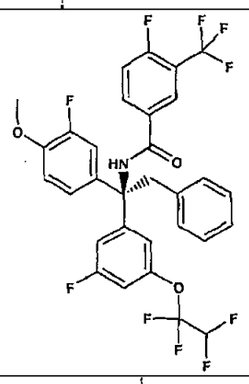
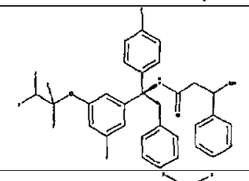
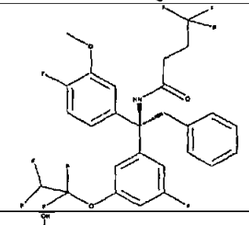
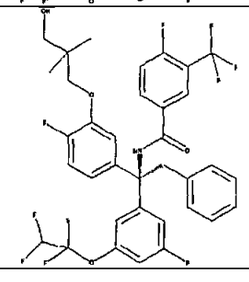
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 606 |  | (S)-N-(1-(3-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.32 LC (4) 676.06 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 607 |  | (S)-N-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.43 LC (4) 646.05 $[M+H]^+$ | Procedures 62, 5, 6 and 7 |
| 608 |  | (R)-N-(1-(4-(difluoromethoxy) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.22 LC (4) 664.14 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 609 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-isopropylphenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.47 LC (4) 640.20 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 610 |  | (R)-N-(1-(3-ethoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 3.606 LC (1) 660.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

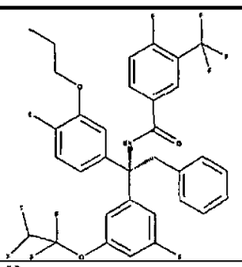
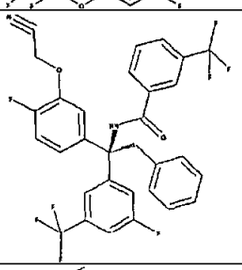
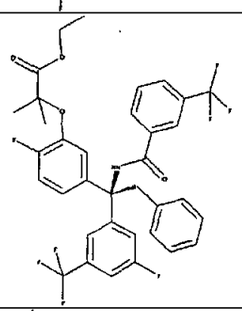
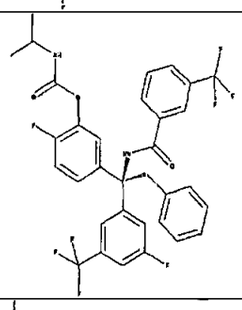
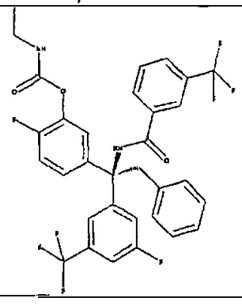
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 611 |  | (R)-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-morpholinobenzamide | 3.66 LC (1) 683.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 612 |  | (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(4-(trifluoromethyl) phenyl)ethyl)butanamide | 3.455 LC (1) 600.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 613 |  | (R)-5,5,5-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-(4-(trifluoromethyl) phenyl)ethyl)pentanamide | 3.773 LC (1) 614.66 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 614 |  | (S)-N-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-5,5,5-trifluoropentanamide | 3.76 LC (1) 598.05 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 615 |  | (S)-N-(1-(3-chloro-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4,4,4-trifluorobutanamide | 3.73 LC (1) 587.04 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 616 |  | (S)-N-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.44 LC (4) 628.19 $[M+H]^+$ | Procedures 4, 5, 6 and 7 |

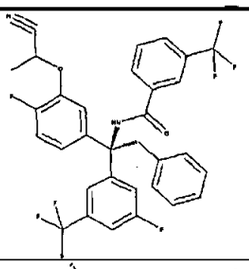
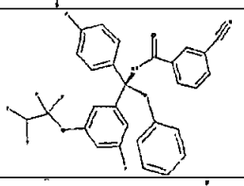
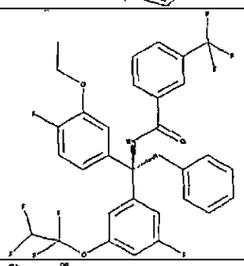
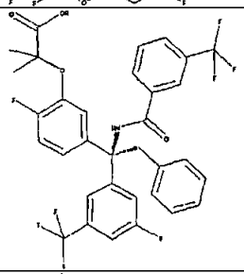
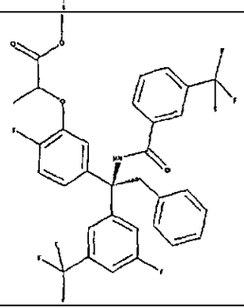
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 617 |  | (S)-N-(1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.33 LC (4) 694.21 $[M+H]^+$ | Procedures 62, 3, 5, 6 and 7 |
| 618 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) butanamide | 3.628 LC (1) 532.15 $[M+H]^+$ | Procedures 4, 5, 6 and 128 |
| 619 |  | (S)-N-(1-(3-chloro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 10.93 LC (7) 662.0 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 620 |  | (R)-N-(1-(4-bromophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.43 LC (4) 628.30 $[M+H]^+$ | Procedures 4, 5, 6 and 7 |
| 621 |  | (R)-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.00 LC (1) 656.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

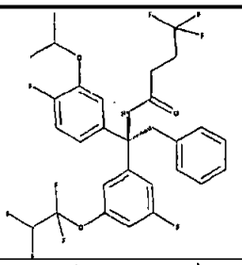
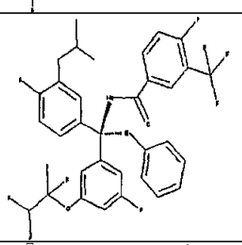
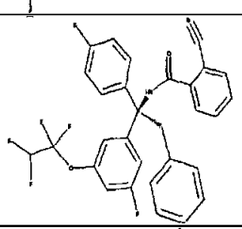
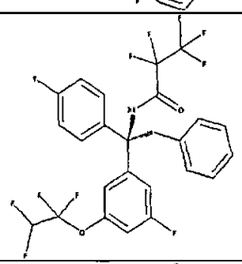
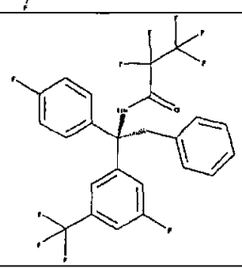
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 622 |  | (R)-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.10 LC (1) 608.4 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |
| 623 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) butanamide | 3.85 LC (1) 560.2 $[M+H]^+$ | Procedures 4, 5, 6, 128, 59 and 68 |
| 624 |  | (R)-N-(1-(3-(cyclopentyloxy)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.24 LC (1) 700.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 625 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)pyrazolo[1,5-a]pyridine-4-carboxamide | 2.12 LC (1) 552.3 $[M+H]^+$ | Procedures 4, 5, 6 and 127 |
| 626 |  | (R)-N-(1-(3-(cyclohexylmethoxy)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.51 LC (1) 729.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

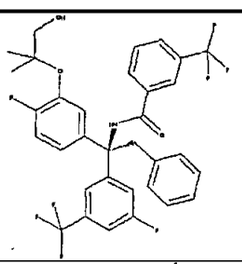
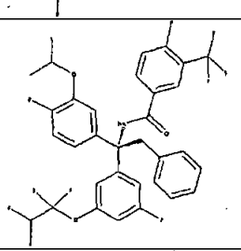
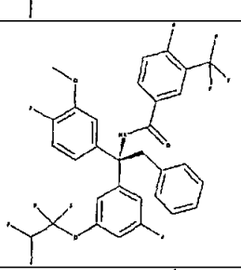
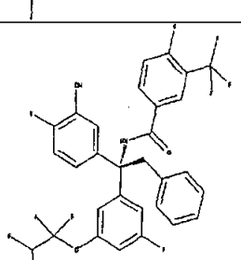
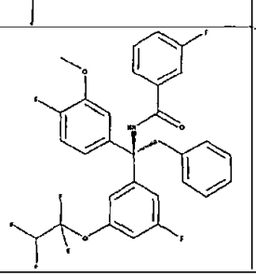
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 627 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isobutoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.23 LC (1) 688.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 628 |  | (R)-2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)phenyl propionate | 3.905 LC (1) 688.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 629 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.95 LC (1) 714.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 630 |  | (R)-N-(1-(3-(cyclopropylmethoxy)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.04 LC (1) 686.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 631 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.88 LC (1) 628.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |

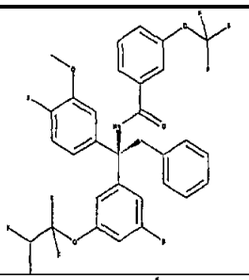
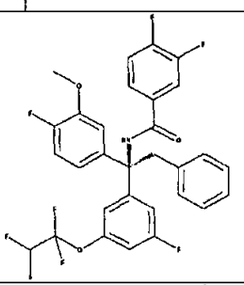
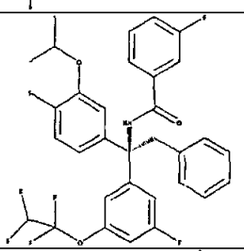
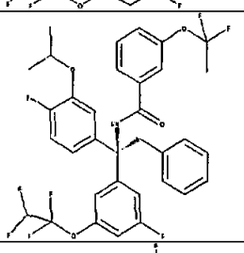
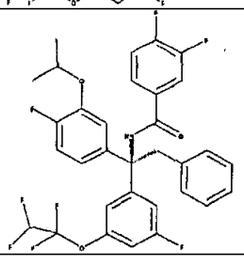
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 632 |  | (R)-2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl) benzamido)ethyl)phenyl dimethylcarbamate | 2.21 LC (2) 637.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 633 |  | (R)-4-fluoro-N-(1-(3-fluoro-4-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 645.487 | Procedures 3, 4, 5, 6 and 7 |
| 634 |  | N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-phenylpropanamide | 4.28 LC (11) 574.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 60 and 23 |
| 635 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide | 3.56 LC (1) 580.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 636 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(3-hydroxy-2,2-dimethylpropoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.833 LC (1) 718.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

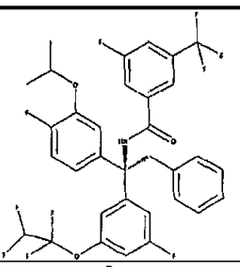
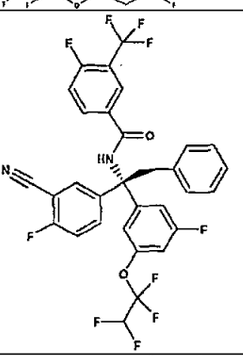
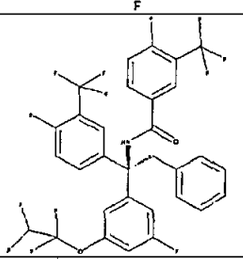
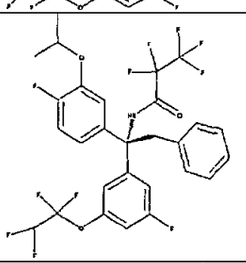
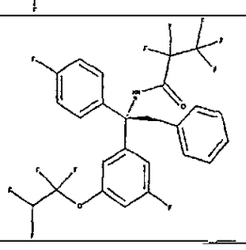
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 637 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-propoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.08 LC (1) 674.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 638 |  | (R)-N-(1-(3-(cyanomethoxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.24 LC (1) 605.2 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |
| 639 |  | (R)-ethyl 2-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenyl-1-(3-(trifluoromethyl)benzamido) ethyl)phenoxy)-2-methylpropanoate | 4.44 LC (1) 680.2 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |
| 640 |  | (R)-2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl) benzamido)ethyl)phenyl isopropylcarbamate | 2.20 LC (2) 651.3 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |
| 641 |  | (R)-2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl) benzamido)ethyl)phenyl ethylcarbamate | 2.15 LC (2) 637.2 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |

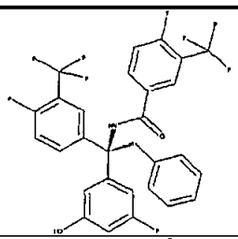
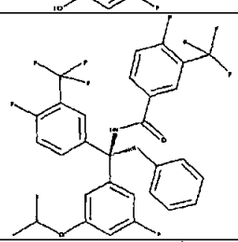
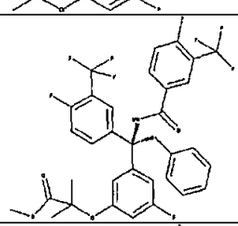
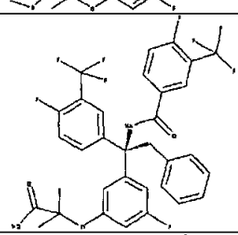
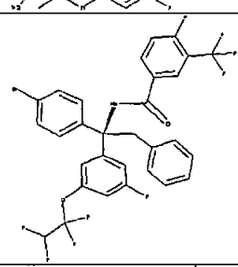
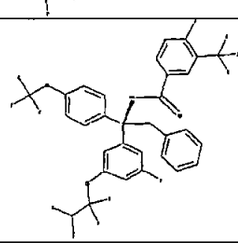
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 642 |  | N-((1R)-1-(3-(1-cyanoethoxy)-4-fluorophenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 2.18 LC (2) 619.3 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |
| 643 |  | (R)-3-cyano-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)benzamide | 2.07 LC (2) 555.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 644 |  | (R)-N-(1-(3-ethoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.91 LC (1) 642.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 645 |  | (R)-2-(2-fluoro-5-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenyl-1-(3-(trifluoromethyl) benzamido)ethyl)phenoxy)-2-methylpropanoic acid | 2.23 LC (2) 652.3 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59, 68 and 23 |
| 646 |  | methyl 2-(2-fluoro-5-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenyl-1-(3-(trifluoromethyl)benzamido) ethyl)phenoxy)propanoate | 2.24 LC (2) 652.4 $[M+H]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |

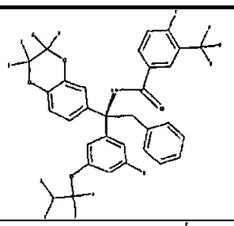
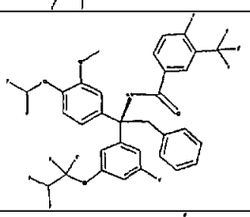
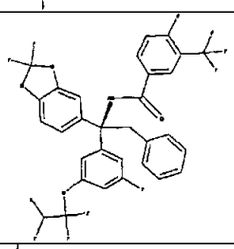
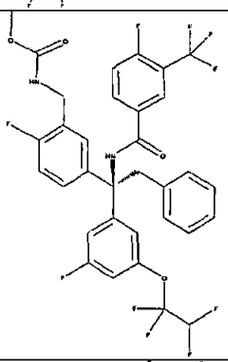
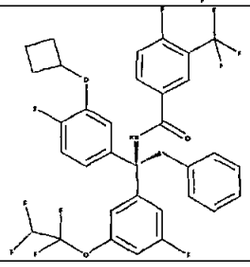
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 647 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide | 3.79 LC (1) 608.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68 and 128 |
| 648 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isobutylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.54 LC (4) 672.40 $[M+H]^+$ | Procedures 3, 62, 5, 6, 122 and 7 |
| 649 |  | (R)-2-cyano-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)benzamide | 2.14 LC (2) 577.4 $[M+Na]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 650 |  | (R)-2,2,3,3,3-pentafluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide | 2.11 LC (2) 409.2 [M-amide] | Procedures 3, 109, 110, 111, 112, 113, 114 and 115 |
| 651 |  | (R)-2,2,3,3,3-pentafluoro-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) propanamide | 2.15 LC (2) no ionizable peak | Procedures 4, 5, 6 and 115 |

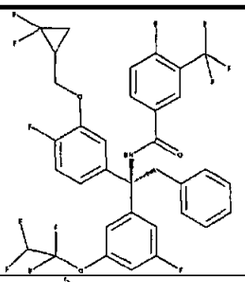
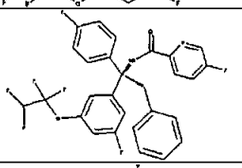
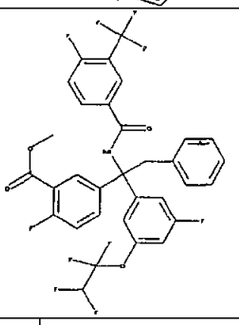
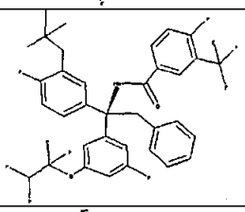
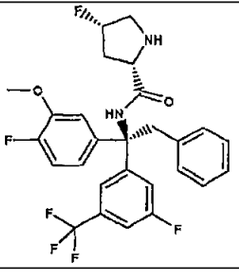
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 652 |  | (R)-N-(1-(4-fluoro-3-(1-hydroxy-2-methylpropan-2-yloxy)phenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 2.33 LC (2) 660.5 $[M+Na]^+$ | Procedures 4, 5, 6, 7, 59 and 68 |
| 653 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.35 LC (4) 674.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 654 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.21 LC (1) 645.14 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 655 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-hydroxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.06 LC (1) 632.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7 and 59 |
| 656 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) benzamide | 3.63 LC (1) 578.2 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |

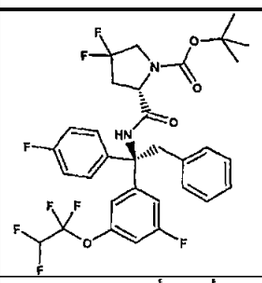
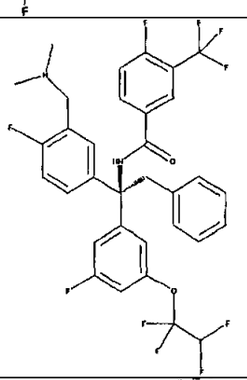
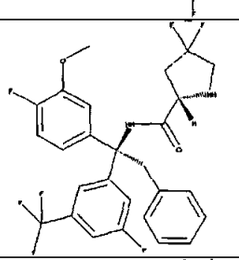
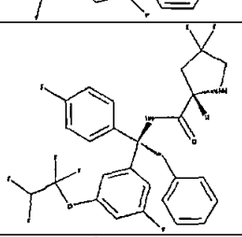
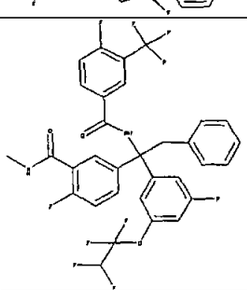
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 657 |  | (R)-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethoxy)benzamide | 3.87 LC (1) 644.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 658 |  | (R)-3,4-difluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.701 LC (1) 596.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 659 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.85 LC (1) 606.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 660 |  | (R)-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethoxy)benzamide | 4.06 LC (1) 672.6 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 661 |  | (R)-3,4-difluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.91 LC (1) 624.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

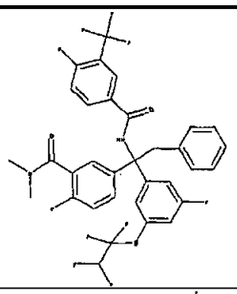
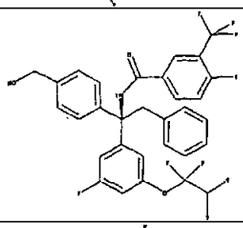
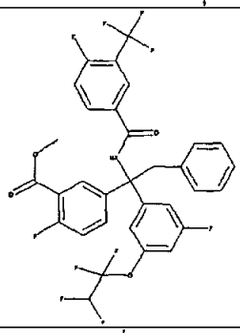
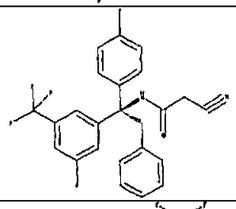
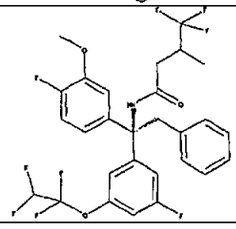
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 662 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-5-(trifluoromethyl)benzamide | 4.08 LC (1) 674.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 663 |  | N-(1-(3-cyano-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 2.335 LC (2) 641.3 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7 and 56 |
| 664 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.30 LC (1) 684.46 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 665 |  | (S)-2,2,3,3,3-pentafluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)propanamide | 2.22 LC (2) no ionizable peak | Procedures 3, 109, 110, 111, 112, 113, 114 and 115 |
| 666 |  | (S)-2,2,3,3,3-pentafluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide | 2.14 LC (2) no ionizable peak | Procedures 3, 4, 5, 6 and 115 |

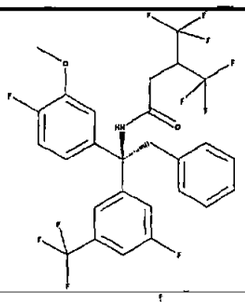
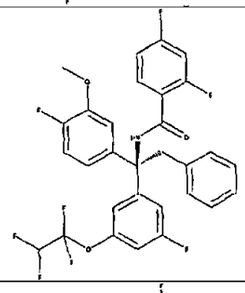
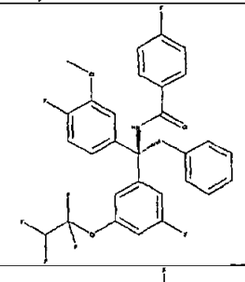
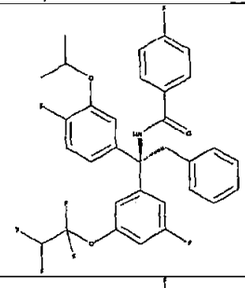
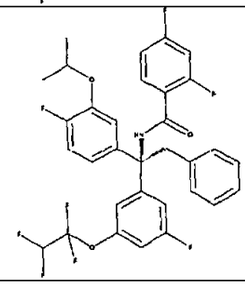
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 667 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-hydroxyphenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 2.19 LC (2) 584.4 $[M+H]^+$ | Procedures 49 and 7 |
| 668 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-isopropoxyphenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 2.34 LC (2) 626.5 $[M+H]^+$ | Procedures 49, 7 and 68 |
| 669 |  | (R)-methyl 2-(3-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)phenoxy)-2-methylpropanoate | 2.26 LC (2) 684.6 $[M+H]^+$ | Procedures 49, 7 and 68 |
| 670 |  | (R)-2-(3-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)phenoxy)-2-methylpropanoic acid | 2.25 LC (2) 670.6 $[M+H]^+$ | Procedures 49, 7, 68 and 23 |
| 671 |  | (R)-N-(1-(4-bromophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.13 LC (4) 676.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 672 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(4-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.13 LC (4) 682.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |

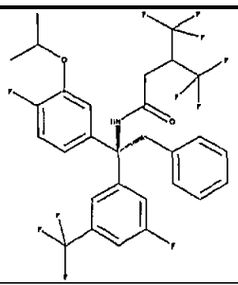
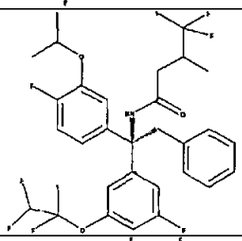
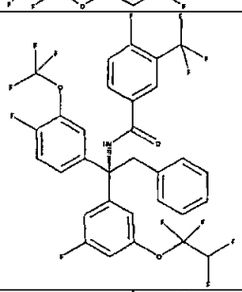
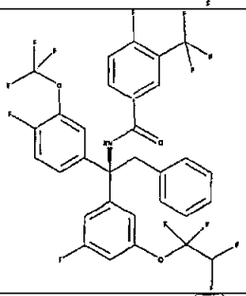
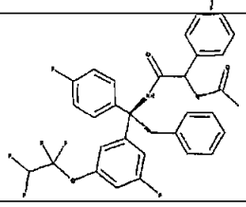
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 673 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-3-(trifluoromethyl) benzamide | 4.21 LC (4) 728.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 674 |  | (R)-N-(1-(4-(difluoromethoxy)-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 3.95 LC (4) 694.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 675 |  | (R)-N-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.10 LC (4) 678.5 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 676 |  | (R)-methyl 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) benzylcarbamate | 10.26 LC (7) 703.1 $[M+H]^+$ | Procedures 3, 62, 63, 7, 64 and 82 |
| 677 |  | (R)-N-(1-(3-cyclobutoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.12 LC (1) 686.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

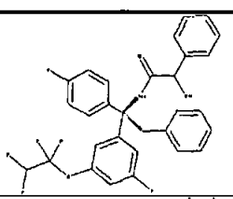
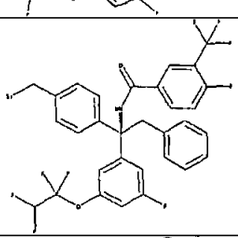
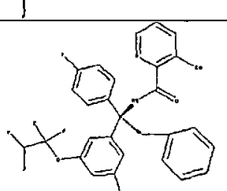
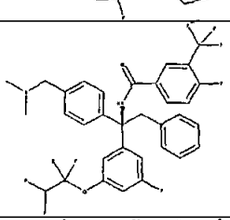
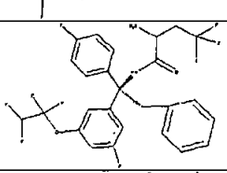
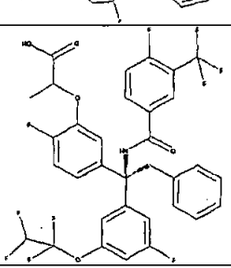
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 678 |  | N-((1R)-1-(3-((2,2-difluorocyclopropyl) methoxy)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 3.94 LC (1) 722.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 679 |  | (R)-5-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)picolinamide | 4.13 LC (1) 549 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 71 |
| 680 |  | methyl 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) benzoate | 2.38 LC (9) 674 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7, 56 and 57 |
| 681 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-neopentylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.60 LC (4) 686.43 $[M+H]^+$ | Procedures 3, 62, 5, 6, 122 and 7 |
| 682 |  | (2S,4S)-4-fluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) pyrrolidine-2-carboxamide | 3.94 LC (3) 523.3 $[M+H]^+$ | Procedures 4, 5, 6, 71 and 39 |

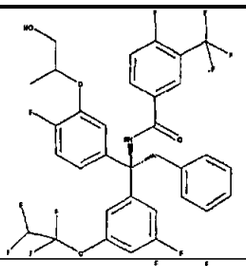
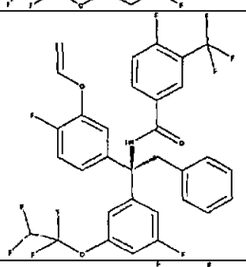
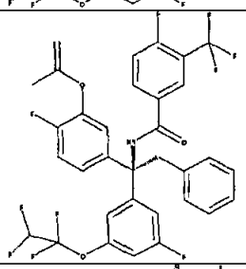
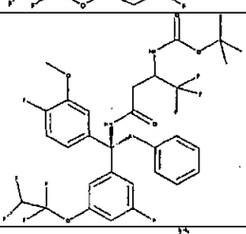
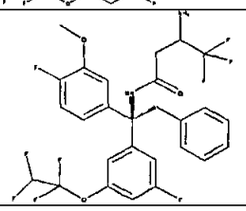
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 683 |  | (S)-tert-butyl 4,4-difluoro-2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylcarbamoyl) pyrrolidine-1-carboxylate | 4.218 LC (3) 659.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 71 |
| 684 |  | (R)-N-(1-(3-((dimethylamino) methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.48 LC (1) 632.4 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7, 56, 57, 100 and 102 |
| 685 |  | (S)-4,4-difluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl) pyrrolidine-2-carboxamide | 4.008 LC (3) 541.2 $[M+H]^+$ | Procedures 4, 5, 6, 71 and 39 |
| 686 |  | (S)-4,4-difluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)pyrrolidine-2-carboxamide | 3.963 LC (3) 559.3 $[M+H]^+$ | Procedures 4, 5, 6, 71 and 39 |
| 687 |  | 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-N-methylbenzamide | 2.28 LC (9) 673 $[M+H]^+$ | Procedures 3, 4, 5, 6, 56, 57, 23 and 103 |

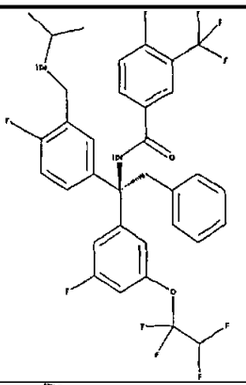
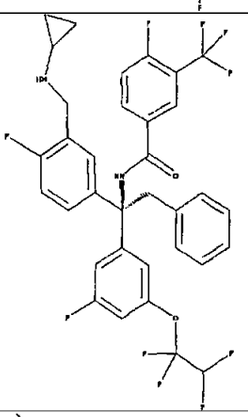
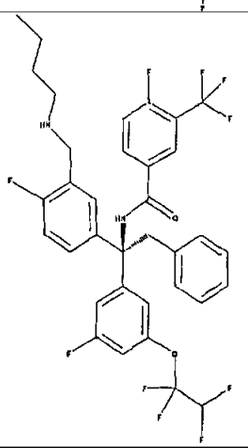
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 688 |  | 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-N,N-dimethylbenzamide | 4.213 LC (11) 687 $[M+H]^+$ | Procedures 3, 4, 5, 6, 56, 57, 23 and 103 |
| 689 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-(hydroxymethyl) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 1.90 LC (12) 628 $[M+H]^+$ | Procedures 3, 4, 5, 6, 56, 57 and 100 |
| 690 |  | methyl 2-fluoro-5-(1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) benzoate | 2.353 LC (2) 674.0 $[M+H]^+$ | Procedures 3, 62, 5, 6, 56 and 57 |
| 691 |  | (R)-2-cyano-N-(1-(3-fluoro-5-(trifluoromethyl)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) acetamide | 2.163 LC (1) 654.3 $[M+H]^+$ | Procedures 4, 5, 6 and 127 |
| 692 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-methylbutanamide | 3.67 LC (1) 594.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |

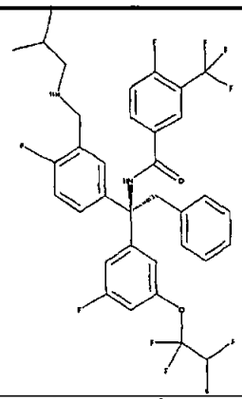
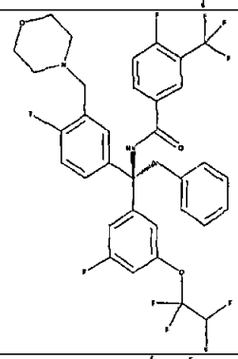
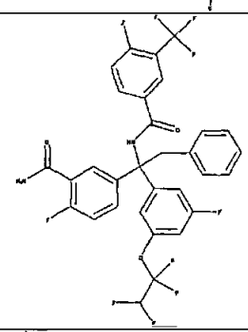
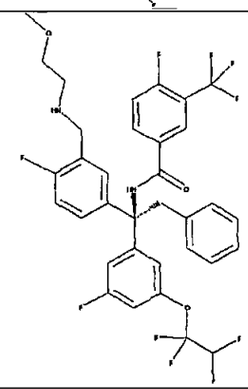
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 693 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(trifluoromethyl)butanamide | 4.09 LC (1) 600.0 $[M+H]^+$ | Procedures 4, 5, 6 and 128 |
| 694 |  | (R)-2,4-difluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.67 LC (1) 596.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 695 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) benzamide | 3.61 LC (1) 578.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 696 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.836 LC (1) 606.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 697 |  | (R)-2,4-difluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.91 LC (1) 624.5 $[M+H]^+$ | Procedures 4, 5, 6, 128, 59 and 68 |

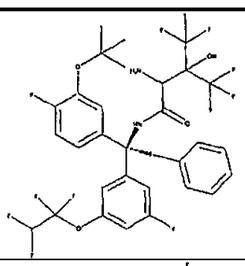
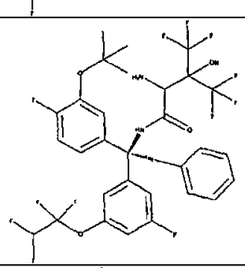
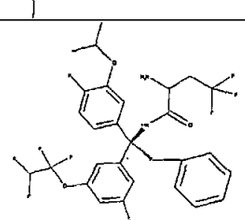
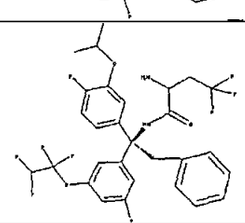
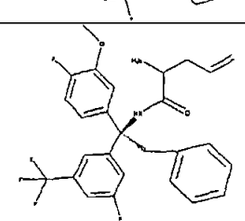
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 698 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-phenylethyl)-3-(trifluoromethyl)butanamide | 4.05 LC (1) 628.5 $[M+H]^+$ | Procedures 4, 5, 6, 128, 59 and 68 |
| 699 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-methylbutanamide | 3.911 LC (1) 622.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 128, 59 and 68 |
| 700 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.36 LC (4) 700.32 $[M+H]^+$ | Procedures 3, 62, 5, 6 and 7 |
| 701 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.36 LC (4) 700.26 $[M+H]^+$ | Procedures 3, 62, 5, 6 and 7 |
| 702 |  | 2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)-2-oxo-1-phenylethyl acetate | 4.05 LC (1) 602.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |

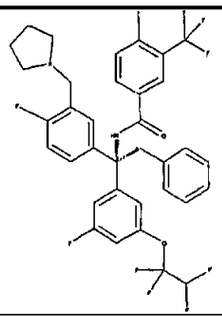
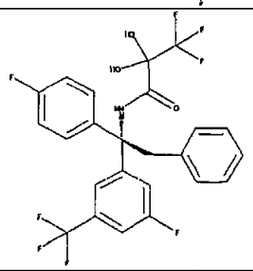
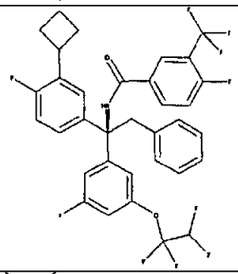
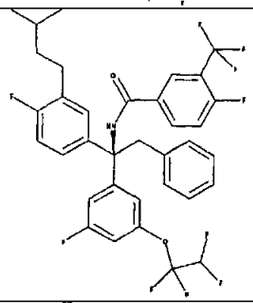
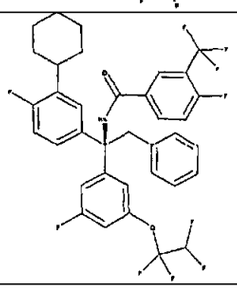
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 703 |  | N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2-hydroxy-2-phenylacetamide | 3.82 LC (1) 560.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7 and 23 |
| 704 |  | (R)-N-(1-(4-(bromomethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 1.77 LC (9) 602.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 56, 57, 100 and 32 |
| 705 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxypicolinamide | 2.22 LC (2) 547.4 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 71 |
| 706 |  | (R)-N-(1-(4-((dimethylamino) methyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 0.89 LC (12) 655 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 56, 57, 100 and 102 |
| 707 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)butanamide | 3.1 LC (1) 565.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 139, 140 and 141 |
| 708 |  | 2-(2-fluoro-5-((R)-1-(4-fluoro-3-(trifluoromethyl) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) phenoxy)propanoic acid | 3.51 LC (1) 704.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 68 and 23 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 709 |  | 4-fluoro-N-((1R)-1-(4-fluoro-3-(1-hydroxypropan-2-yloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.588 LC (1) 690.6 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 68, 23 and 100 |
| 710 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(vinyloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.948 LC (1) 658.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 106 |
| 711 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(prop-1-en-2-yloxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.053 LC (1) 672.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 712 |  | tert-butyl 1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-4-oxobutan-2-ylcarbamate | 3.7 LC (1) 695.3 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 128 |
| 713 |  | 3-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) butanamide | 2.518 LC (1) 595.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 128 and 39 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 714 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-((isopropylamino)methyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 8.099 LC (7) 687 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |
| 715 |  | (R)-N-(1-(3-((cyclopropylamino)methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 3.656 LC (15) 685 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |
| 716 |  | (R)-N-(1-(3-((butylamino) methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 3.723 LC (15) 701 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 717 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-((isobutylamino)methyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.725 LC (15) 701 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |
| 718 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(morpholinomethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.650 LC (15) 715 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |
| 719 |  | N-(1-(3-carbamoyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.243 LC (13) 659 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7, 56, 57, 23 and 136 |
| 720 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-((2-methoxyethylamino) methyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.636 LC (15) 703 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 721 |  | 2-amino-N-((R)-1-(3-tert-butoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butanamide | 2.09 LC (1) 721.0 $[M+H]^+$ | Procedures 3, 109, 110, 111, 112, 108, 90, 91 and 92 |
| 722 |  | 2-amino-N-((R)-1-(3-tert-butoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl) butanamide | 2.11 LC (1) 721.0 $[M+H]^+$ | Procedures 3, 109, 110, 111, 112, 108, 90, 91 and 92 |
| 723 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide | 2.01 LC (2) 623.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68, 139, 140 and 141 |
| 724 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide | 2.04 LC (2) 623.4 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68, 139, 140 and 141 |
| 725 |  | 2-amino-N-((R)-1-(4-fluoro-3-methoxyphenyl)-1-(3-fluoro-5-(trifluoromethyl)phenyl)-2-phenylethyl)pent-4-enamide | 2.2 LC (2) 505.2 $[M+H]^+$ | Procedures 4, 5, 6, 140 and 39 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 726 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(pyrrolidin-1-ylmethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 3.606 LC (15) 699 $[M+H]^+$ | Procedures 3, 62, 5, 6, 146, 7, 147 and 148 |
| 727 |  | (S)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-2,2-dihydroxypropanamide | 1.70 LC (14) 518.1 $[M-H]^-$ | Procedure 4, 149, 150, 151, 152 and 159 |
| 728 |  | (R)-N-(1-(3-cyclobutyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 8.654 LC (16) 670.29 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7 and 121 |
| 729 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopentylphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-(trifluoromethyl)benzamide | 4.62 LC (4) 686.33 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7 and 162 |
| 730 |  | (R)-N-(1-(3-cyclohexyl-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-4-fluoro-3-(trifluoromethyl) benzamide | 4.67 LC (4) 698.37 $[M+H]^+$ | Procedures 3, 62, 5, 6, 7 and 162 |

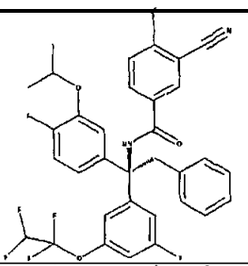
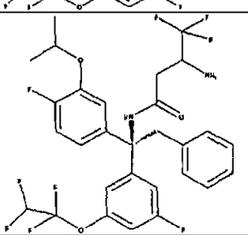
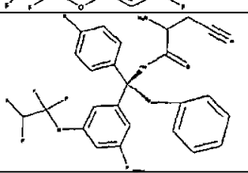
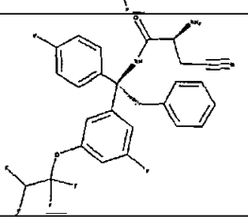
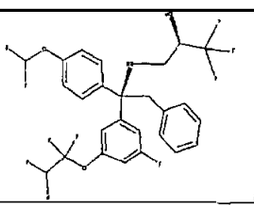
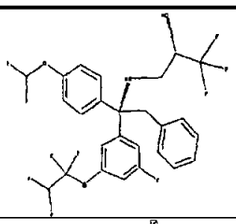
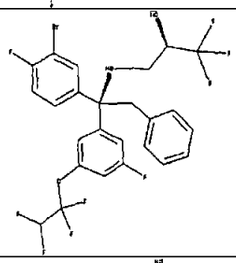
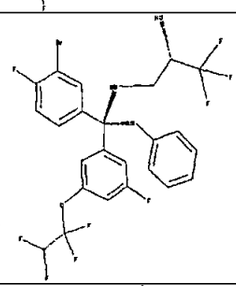
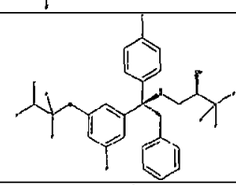
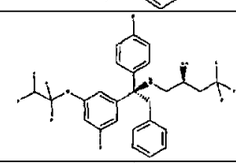
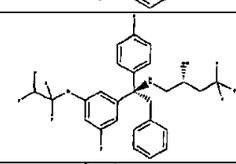
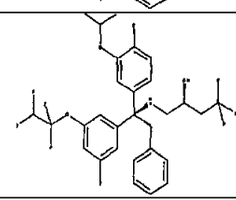
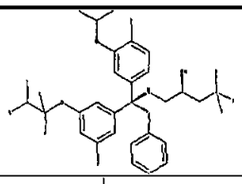
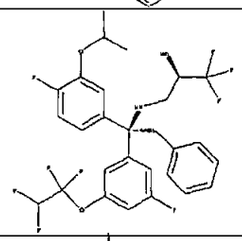
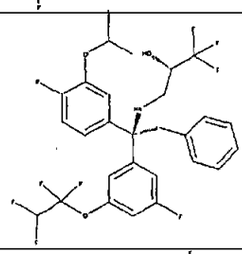
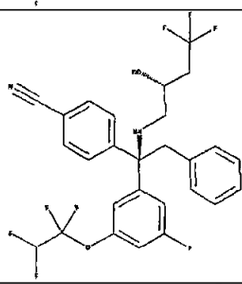
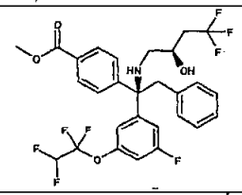
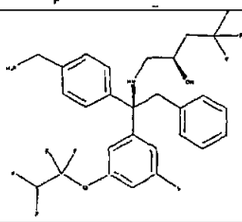
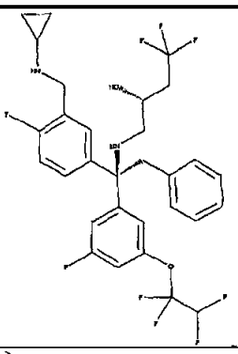
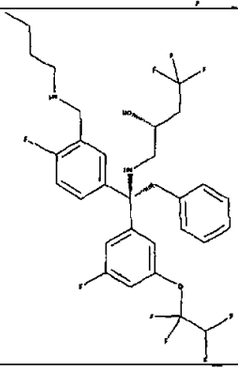
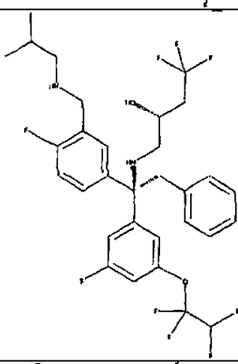
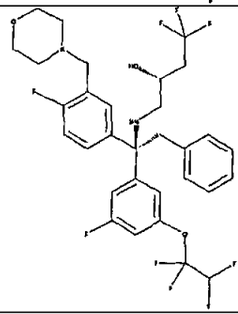
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 731 |  | (R)-3-cyano-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)benzamide | 3.785 LC (1) 631.6 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68 and 7 |
| 732 |  | 3-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethyl)butanamide | 2.69 LC (1) 623.5 $[M+H]^+$ | Procedures 3, 4, 5, 6, 59, 68, 143 and 144 |
| 733 |  | 2-amino-3-cyano-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide | 1.83 LC (2) 522.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 140 and 39 |
| 734 |  | (S)-2-amino-3-cyano-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl)propanamide | 3.12 LC (8) 522.0 $[M+H]^+$ | Procedures 3, 4, 5, 6, 140 and 39 |

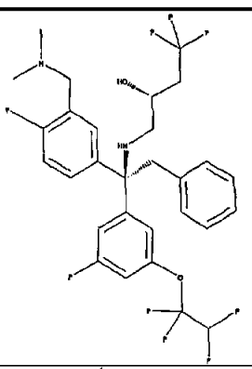
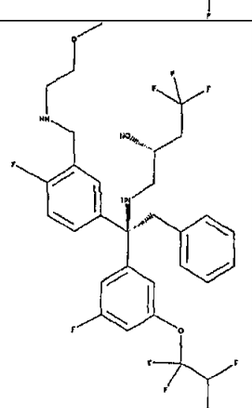
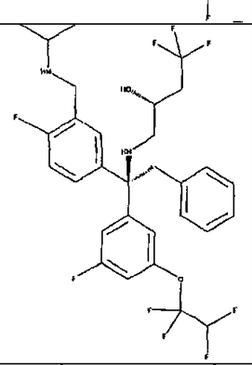
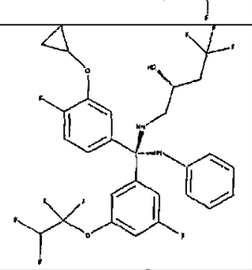
**TABLE 11**

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 735 |  | (R)-3-((R)-1-(4-(difluoromethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 3.97 LC (4) 586.39 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27 and 8 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 736 |  | (S)-3-((R)-1-(4-(difluoromethoxy)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 3.98 LC (4) 586.41 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27 and 8 |
| 737 |  | (R)-3-((S)-1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 4.23 LC (4) 616.31 $[M+H]^+$ | Procedures 3, 62, 5, 6, 27 and 8 |
| 738 |  | (S)-3-((S)-1-(3-bromo-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 4.21 LC (4) 616.32 $[M+H]^+$ | Procedures 3, 62, 5, 6, 27 and 8 |
| 739 |  | (R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)propan-2-ol | 2.097 LC (2) 538.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27 and 8 |
| 740 |  | (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)butan-2-ol | 3.805 LC (1) 552.33 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27 and 8 |
| 741 |  | (R)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethylamino)butan-2-ol | 1.835 LC (2) 552.33 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27 and 8 |
| 742 |  | (S)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)butan-2-ol | 2.00 LC (2) 610.4 $[M+H]^+$ | Procedures 3, 109, 110, 111, 112, 113, 114, 27 and 8 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 743 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)butan-2-ol | 2.002 LC (2) 610.4 $[M+H]^+$ | Procedures 3, 109, 110, 111, 112, 113, 114, 27 and 8 |
| 744 |  | (R)-1,1,1-trifluoro-3-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)propan-2-ol | 2.25 LC (2) 596.2 $[M+H]^+$ | Procedures 3, 109, 110, 111, 112, 113, 114, 27 and 8 |
| 745 |  | (S)-1,1,1-trifluoro-3-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)propan-2-ol | 2.21 LC (2) 596.1 $[M+H]^+$ | Procedures 3, 109, 110, 111, 112, 113, 114, 27 and 8 |
| 746 |  | 4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenyl-1-((R)-4,4,4-trifluoro-2-hydroxybutylamino)ethyl) benzonitrile | 0.92 LC (12) 592 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, and 56 |
| 747 |  | methyl 4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenyl-1-((R)-4,4,4-trifluoro-2-hydroxybutylamino) ethyl)benzoate | 0.91 LC (12) 592 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, 56 and 57 |
| 748 |  | (R)-1-((R)-1-(4-(aminomethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)-4,4,4-trifluorobutan-2-ol | 1.33 LC (2) | Procedures 3, 4, 5, 6, 27, 8, 56 and 101 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 749 |  | (R)-1-((R)-1-(3-((cyclopropylamino)methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-4,4,4-trifluorobutan-2-ol | 7.418 LC (7) 621 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, 146, 147 and 148 |
| 750 |  | (R)-1-((R)-1-(3-((butylamino)methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-4,4,4-trifluorobutan-2-ol | 7.418 LC (7) 637 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, 146, 147 and 148 |
| 751 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-((isobutylamino) methyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino) butan-2-ol | 4.46 LC (15) 637 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, 146, 147 and 148 |
| 752 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-(morpholinomethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)butan-2-ol | 7.033 LC (7) 651 $[M+H]^+$ | Procedures 3, 62, 5, 6, 27, 8, 146, 147 and 148 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 753 |  | (R)-1-((R)-1-(3-((dimethylamino)methyl)-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-4,4,4-trifluorobutan-2-ol | 7.133 LC (7) 609 $[M+H]^+$ | Procedures 3, 62, 5, 6, 27, 8, 146, 147 and 148 |
| 754 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-((2-methoxyethylamino)methyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethylamino)butan-2-ol | 6.90 LC (7) 639 $[M+H]^+$ | Procedures 3, 62, 5, 6, 27, 8, 146, 147 and 148 |
| 755 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-((isopropylamino) methyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino) butan-2-ol | 7.241 LC (7) 623 $[M+H]^+$ | Procedures 3, 62, 5, 6, 27, 8, 146, 147 and 148 |
| 756 |  | (R)-1-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-4,4,4-trifluorobutan-2-ol | 3.99 LC (1) 608.0 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, 59, 106 and 107 |

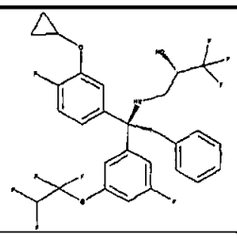
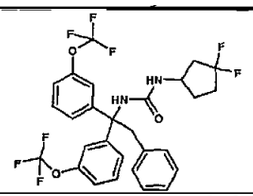
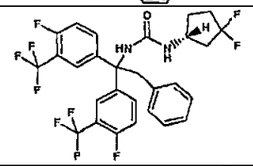
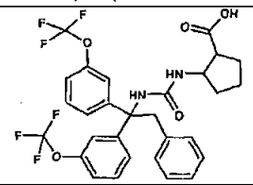
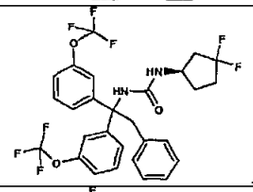
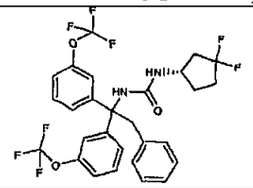
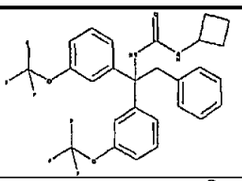
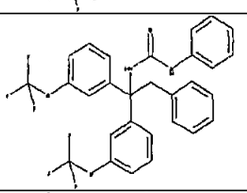
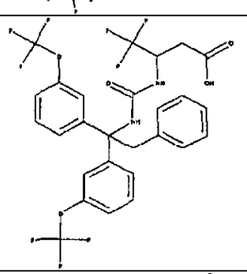
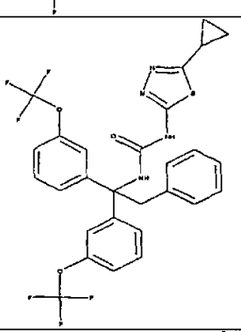
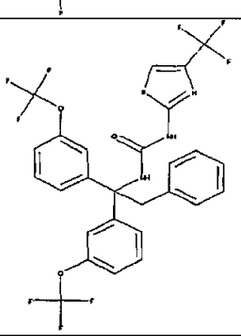
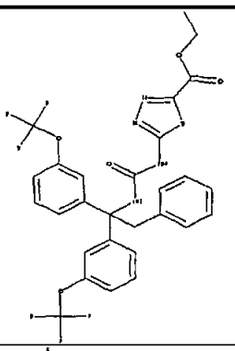
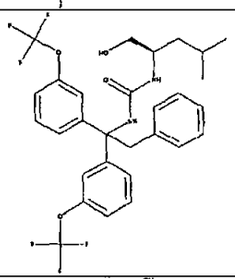
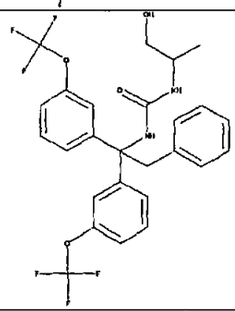
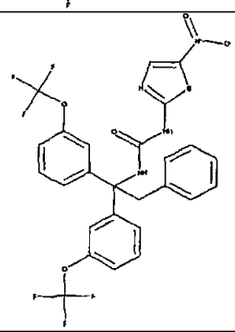
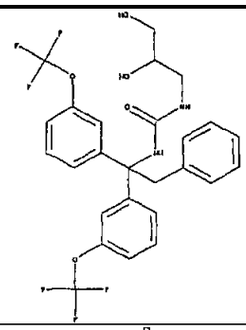
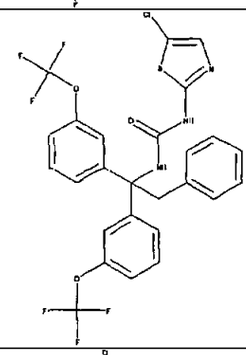
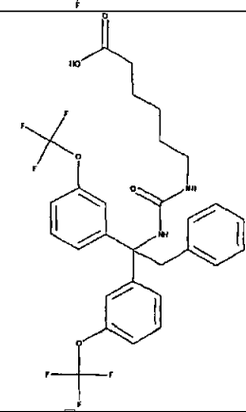
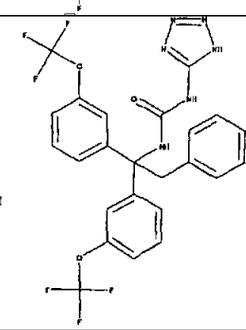
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 757 |  | (S)-3-((R)-1-(3-cyclopropoxy-4-fluorophenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-1,1,1-trifluoropropan-2-ol | 4.19 LC (1) 594.0 $[M+H]^+$ | Procedures 3, 4, 5, 6, 27, 8, 59, 106 and 107 |

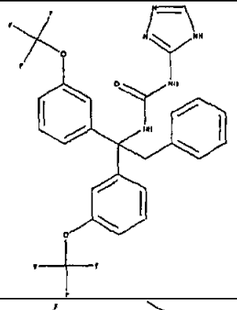
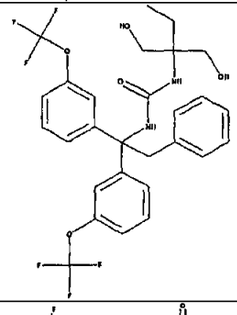
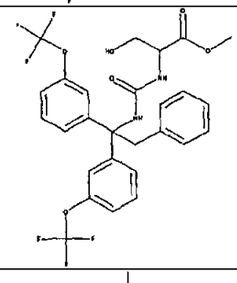
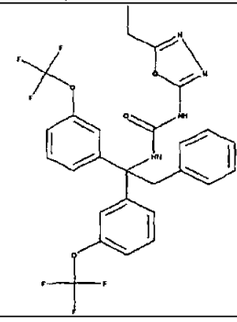
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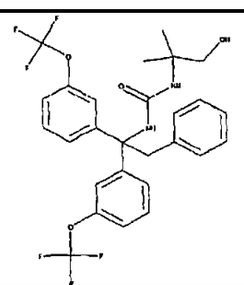
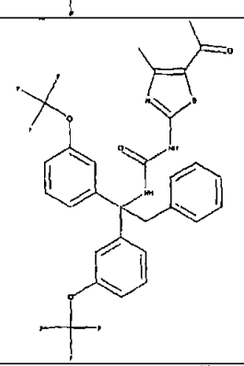
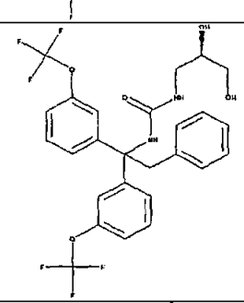
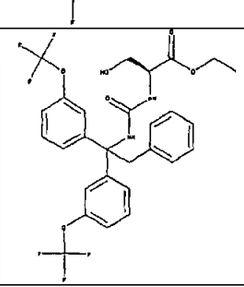
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 758 |  | 1-(3,3-difluorocyclopentyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.25 LC (3) 589.3 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 759 |  | (R)-1-(1,1-bis(4-fluoro-3-(trifluoromethyl)phenyl)-2-phenylethyl)-3-(3,3-difluorocyclopentyl)urea | 4.13 LC (3) 593.3 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 760 |  | 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido) cyclopentanecarboxylic acid | 3.408 LC (1) 597.03 $[M+H]^+$ | Procedures 11, 6 and 10 |
| 761 |  | (R)-1-(3,3-difluorocyclopentyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.21 LC (3) 589.2 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 762 |  | (S)-1-(3,3-difluorocyclopentyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.206 LC (3) 589.2 $[M+H]^+$ | Procedures 11, 6 and 12 |

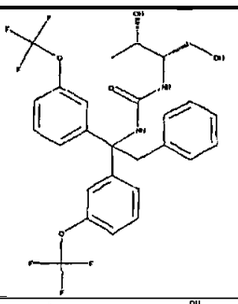
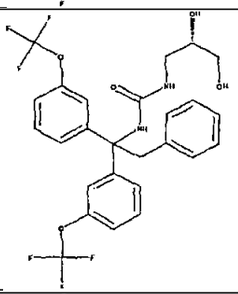
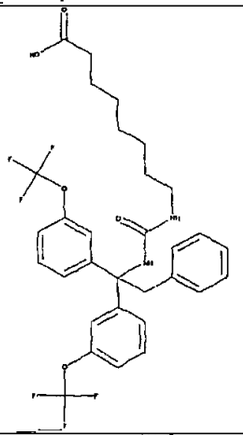
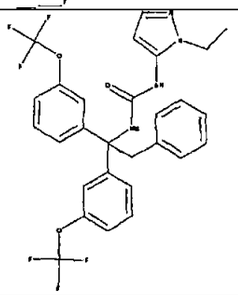
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 763 |  | 1-cyclobutyl-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.25 LC (4) 539.11 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 764 |  | 1-phenyl-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.281 LC (4) 561.06 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 765 |  | 4,4,4-trifluoro-3-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido)butanoic acid | 624.452 LC (4) LC 625.10 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 766 |  | 1-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.39 LC (4) 609.11 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 767 |  | 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(4-(trifluoromethyl) thiazol-2-yl)urea | 4.44 LC (4) 636.06 $[M+H]^+$ | Procedures 11, 6 and 12 |

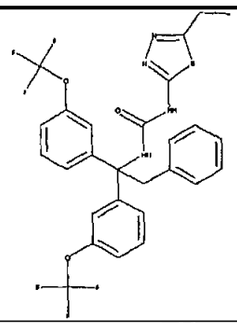
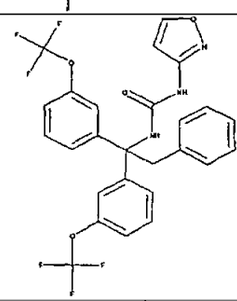
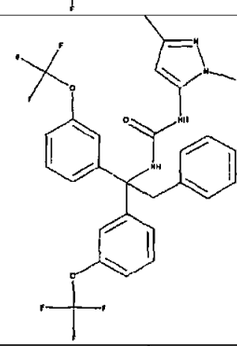
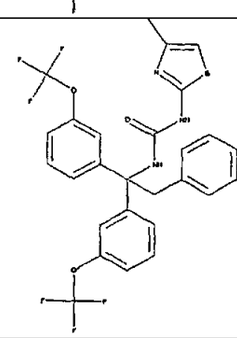
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 768 |  | ethyl 5-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)-1,3,4-thiadiazole-2-carboxylate | 4.42 LC (4) 641.09 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 769 |  | (R)-1-(1-hydroxy-4-methylpentan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.27 LC (4) 585.23 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 770 |  | 1-(1-hydroxypropan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.18 LC (4) 543.21 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 771 |  | 1-(5-nitrothiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.40 LC (4) 612.50 $[M+H]^+$ | Procedures 11, 6 and 12 |

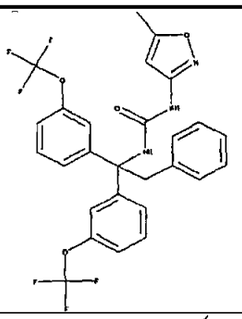
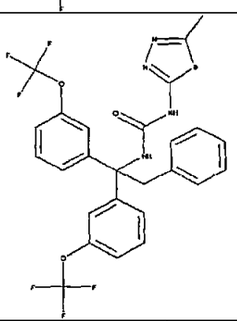
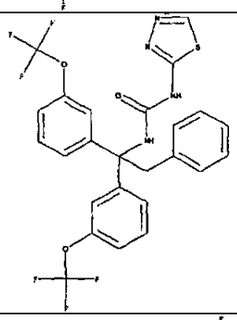
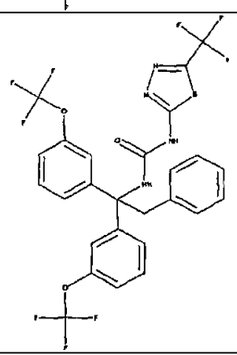
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 772 |  | 1-(2,3-dihydroxypropyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.11 LC (4) 559.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 773 |  | 1-(5-chlorothiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.56 LC (4) 602.05 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 774 |  | 6-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)hexanoic acid | 4.20 LC (4) 599.18 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 775 |  | 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(1H-tetrazol-5-yl)urea | 4.06 LC (4) 553.16 $[M+H]^+$ | Procedures 11, 6 and 12 |

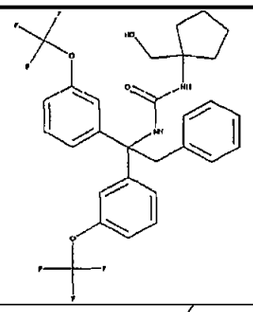
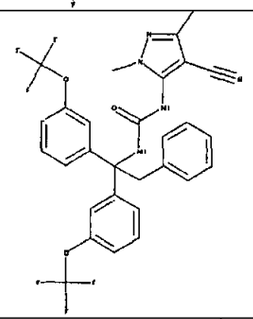
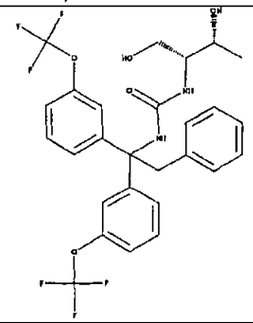
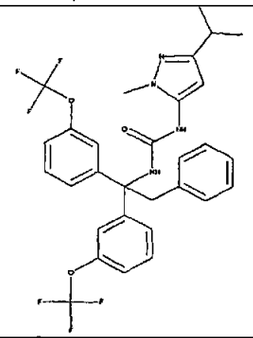
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 776 |  | 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(4H-1,2,4-triazol-3-yl)urea | 4.05 LC (4) 552.17 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 777 |  | 1-(1-hydroxy-2-(hydroxymethyl)butan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.20 LC (4) 587.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 778 |  | methyl 3-hydroxy-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 4.07 LC (4) 587.16 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 779 |  | 1-(5-ethyl-1,3,4-oxadiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.25 LC (4) 581.16 $[M+H]^+$ | Procedures 11, 6 and 12 |

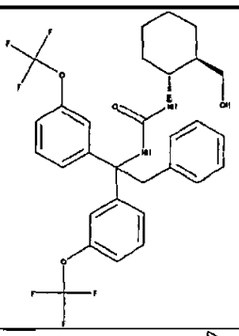
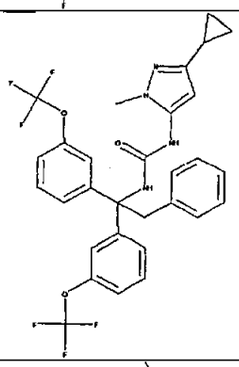
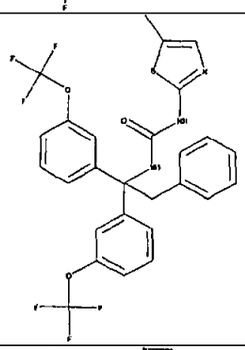
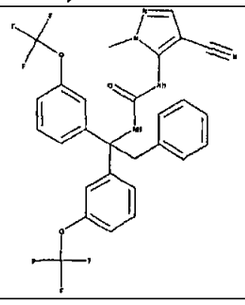
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 780 |  | 1-(1-hydroxy-2-methylpropan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.14 LC (4) 557.25 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 781 |  | 1-(5-acetyl-4-methylthiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.28 LC (4) 624.11 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 782 |  | (R)-1-(2,3-dihydroxypropyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.04 LC (4) 559.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 783 |  | (S)-ethyl 3-hydroxy-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 4.13 LC (4) 601.17 $[M+H]^+$ | Procedures 11, 6 and 12 |

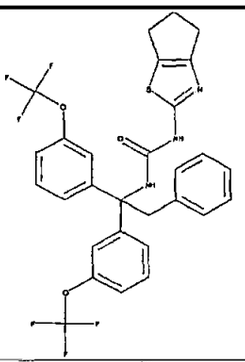
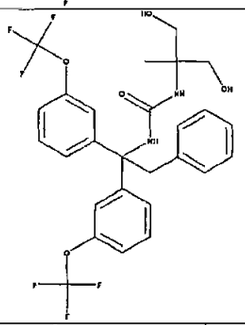
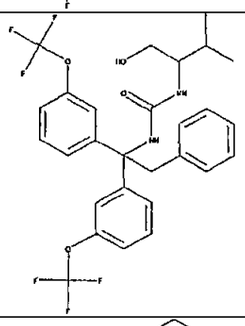
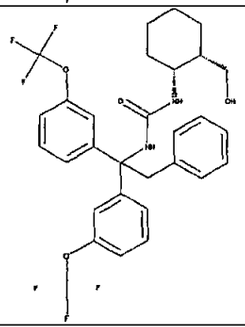
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 784 |  | 1-((2S,3S)-1,3-dihydroxybutan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.07 LC (4) 573.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 785 |  | (S)-1-(2,3-dihydroxypropyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.03 LC (4) 559.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 786 |  | 8-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)octanoic acid | 4.22 LC (4) 627.26 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 787 |  | 1-(1-ethyl-1H-pyrazol-5-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.09 LC (4) 579.21 $[M+H]^+$ | Procedures 11, 6 and 12 |

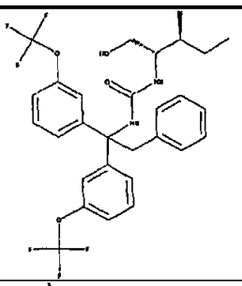
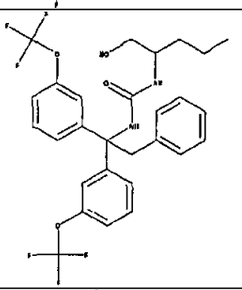
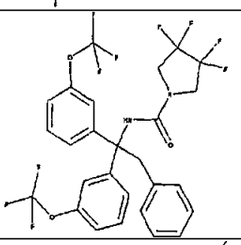
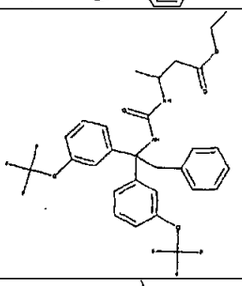
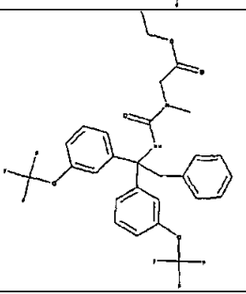
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 788 |  | 1-(5-ethyl-1,3,4-thiadiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.27 LC (4) 597.11 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 789 |  | 1-(isoxazol-3-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.16 LC (4) 552.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 790 |  | 1-(1,3-dimethyl-1H-pyrazol-5-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.99 LC (4) 579.20 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 791 |  | 1-(4-methylthiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.21 LC (4) 582.12 $[M+H]^+$ | Procedures 11, 6 and 12 |

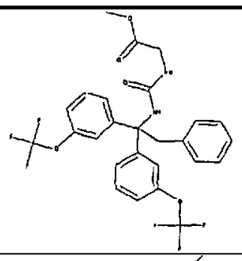
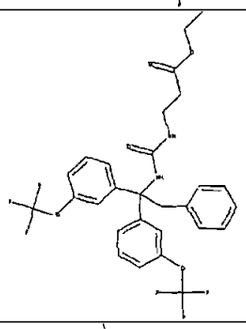
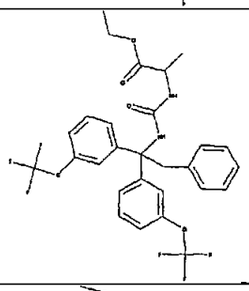
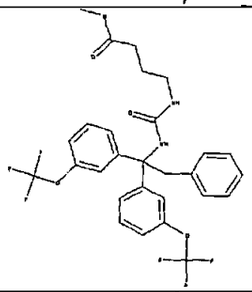
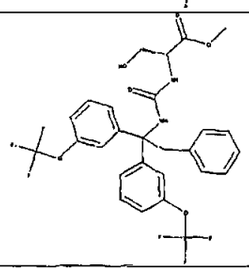
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 792 |  | 1-(5-methylisoxazol-3-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.23 LC (4) 566.18 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 793 |  | 1-(5-methyl-1,3,4-thiadiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.18 LC (4) 583.12 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 794 |  | 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(1,3,4-thiadiazol-2-yl)urea | 4.13 LC (4) 569.13 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 795 |  | 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)urea | 4.49 LC (4) 637.07 $[M+H]^+$ | Procedures 11, 6 and 12 |

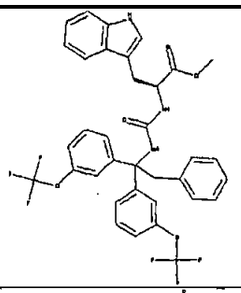
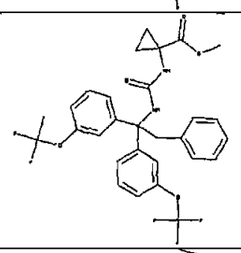
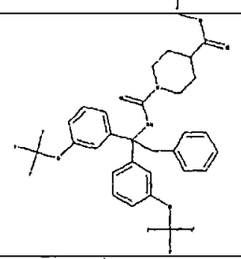
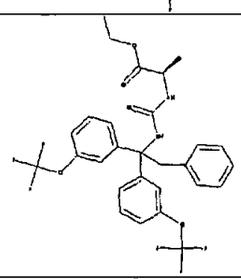
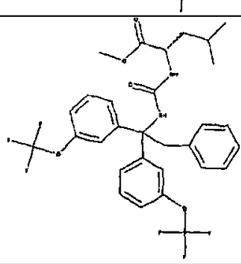
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 796 |  | 1-(1-(hydroxymethyl) cyclopentyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.22 LC (4) 583.23 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 797 |  | 1-(4-cyano-1,3-dimethyl-1H-pyrazol-5-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.04 LC (4) 603.98 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 798 |  | 1-((2R,3R)-1,3-dihydroxybutan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.07 LC (4) 573.19 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 799 |  | 1-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.12 LC (4) 607.23 $[M+H]^+$ | Procedures 11, 6 and 12 |

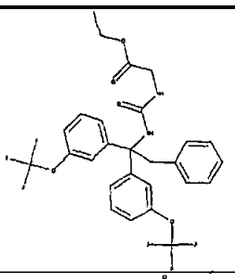
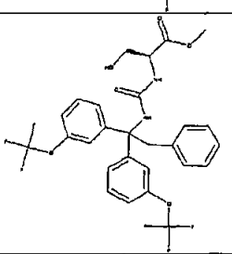
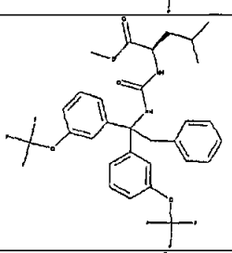
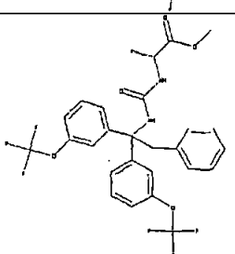
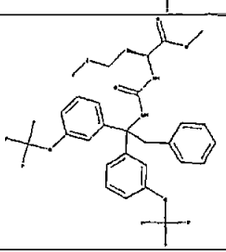
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 800 |  | 1-((1R,2R)-2-(hydroxymethyl) cyclohexyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.24 LC (4) 597.21 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 801 |  | 1-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.09 LC (4) 605.21 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 802 |  | 1-(5-methylthiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.21 LC (4) 582.12 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 803 |  | 1-(4-cyano-1-methyl-1H-pyrazol-5-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.05 LC (4) 590.18 $[M+H]^+$ | Procedures 11, 6 and 12 |

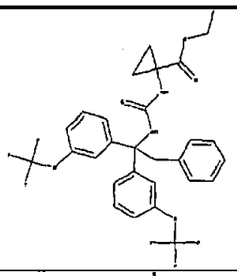
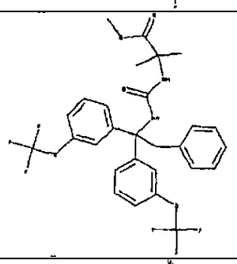
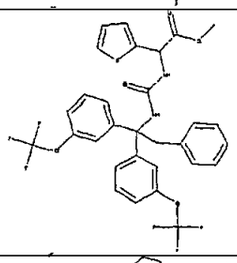
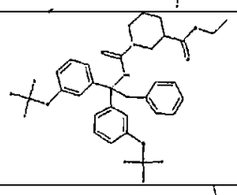
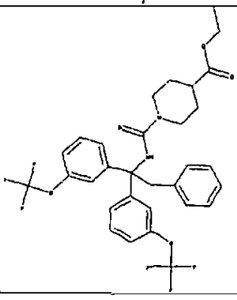
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 804 |  | 1-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.40 LC (4) 608.12 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 805 |  | 1-(1,3-dihydroxy-2-methylpropan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.08 LC (4) 573.22 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 806 |  | 1-(1-hydroxy-3-methylbutan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.20 LC (4) 571.24 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 807 |  | 1-((1R,2S)-2-(hydroxymethyl) cyclohexyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)urea | 4.23 LC (4) 597.23 $[M+H]^+$ | Procedures 11, 6 and 12 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 808 |  | 1-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.26 LC (4) 585.24 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 809 |  | 1-(1-hydroxypentan-2-yl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.21 LC (4) 571.23 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 810 |  | 3,3,4,4-tetrafluoro-N-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)pyrrolidine-1-carboxamide | 3.868 LC (3) 611.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 811 |  | ethyl 3-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)butanoate | 3.81 LC (10) 599.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 812 |  | ethyl 2-(1-methyl-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido)acetate | 3.85 LC (10) 585.4 $[M+H]^+$ | Procedures 11, 6 and 12 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 813 |  | methyl 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido)acetate | 3.57 LC (10) 557.4 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 814 |  | ethyl 3-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 3.71 LC (10) 585.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 815 |  | ethyl 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 3.78 LC (10) 585.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 816 |  | methyl 4-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido)butanoate | 3.62 LC (10) 585.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 817 |  | (R)-methyl 3-hydroxy-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 3.39 LC (10) 587.4 $[M+H]^+$ | Procedures 11, 6 and 12 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 818 |  | (S)-methyl 3-(1H-indol-3-yl)-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 3.85 LC (10) 685.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 819 |  | methyl 1-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido) cyclopropanecarboxylate | 3.63 LC (10) 583.4 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 820 |  | methyl 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamoyl)piperidine-4-carboxylate | 3.81 LC (10) 611.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 821 |  | (R)-ethyl 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido) propanoate | 3.79 LC (10) 585.5 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 822 |  | (S)-methyl 4-methyl-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)pentanoate | 4.04 LC (10) 613.2 $[M+H]^+$ | Procedures 11, 6 and 12 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 823 |  | ethyl 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)acetate | 3.74 LC (10) 571.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 824 |  | (S)-methyl 3-hydroxy-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 3.44 LC (10) 587.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 825 |  | (R)-methyl 4-methyl-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)pentanoate | 4.04 LC (10) 613.2 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 826 |  | (R)-methyl 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido) propanoate | 3.73 LC (10) 571.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 827 |  | (R)-methyl 4-(methylthio)-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)butanoate | 3.88 LC (10) 631.1 $[M+H]^+$ | Procedures 11, 6 and 12 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 828 |  | ethyl 1-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido) cyclopropanecarboxylate | 3.80 LC (10) 597.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 829 |  | methyl 2-methyl-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoate | 3.80 LC (10) 585.0 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 830 |  | methyl 2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)ureido)-2-(thiophen-2-yl)acetate | 3.92 LC (10) 639.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 831 |  | ethyl 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamoyl)piperidine-3-carboxylate | 3.99 LC (10) 625.2 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 832 |  | ethyl 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamoyl)piperidine-4-carboxylate | 3.90 LC (10) 625.2 $[M+H]^+$ | Procedures 11, 6 and 12 |

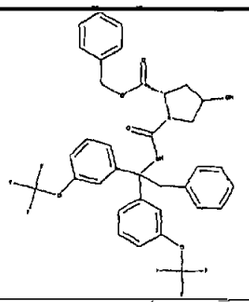
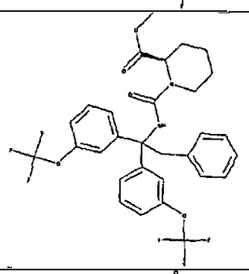
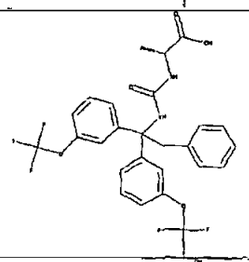
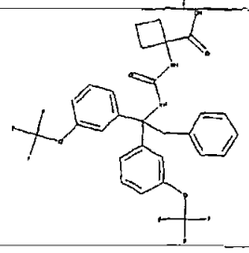
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 833 |  | (2S)-benzyl 4-hydroxy-1-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamoyl)pyrrolidine-2-carboxylate | 3.76 LC (10) 689.2 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 834 |  | (R)-methyl 1-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethylcarbamoyl) piperidine-2-carboxylate | 3.95 LC (10) 611.1 $[M+H]^+$ | Procedures 11, 6 and 12 |
| 835 |  | (R)-2-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido)propanoic acid | 2.62 LC (10) 557.1 $[M+H]^+$ | Procedures 11, 6, 12 and 23 |
| 836 |  | 1-(3-(2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)ureido) cyclobutanecarboxylic acid | 2.94 LC (10) 583.1 $[M+H]^+$ | Procedures 11, 6, 12 and 23 |

**TABLE 13**

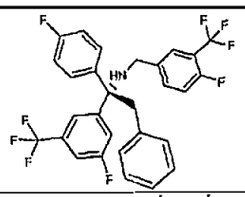
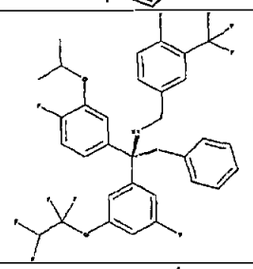
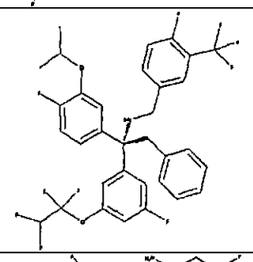
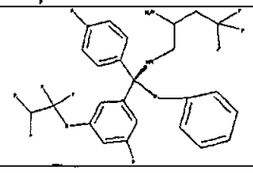
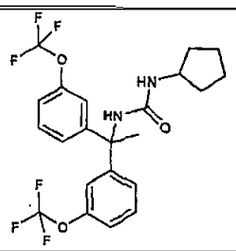
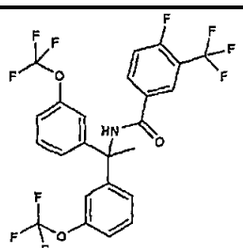
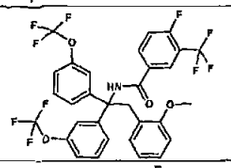
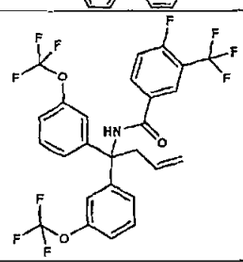
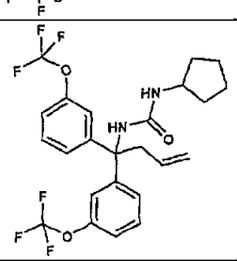
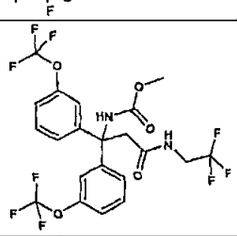
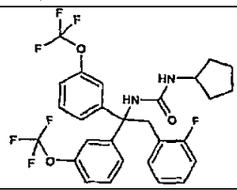
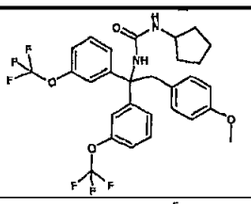
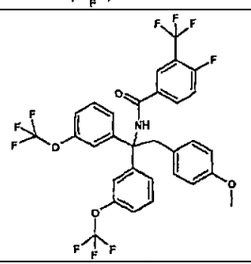
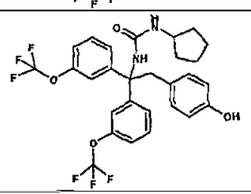
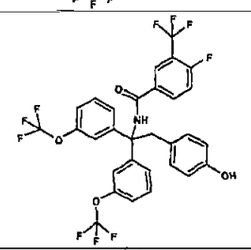
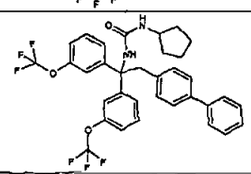
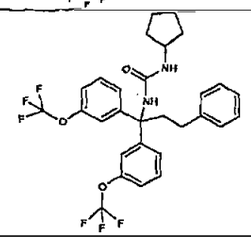
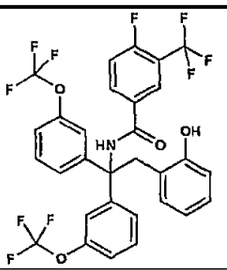
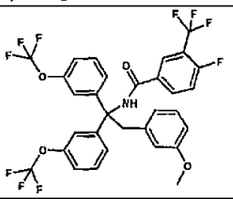
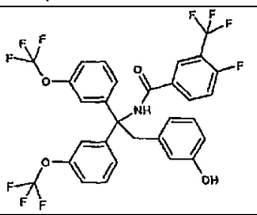
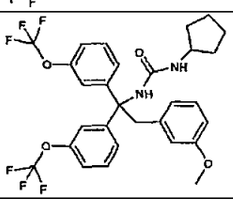
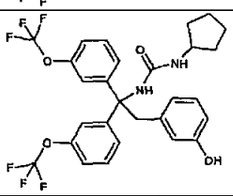
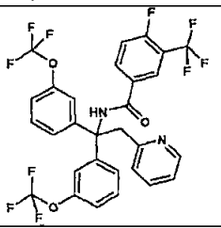
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 837 |  | (S)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethanamine | 4.32 LC (1) 553.90 $[M+H]^+$ | Procedures 4, 5, 6 and 13 |
| 838 |  | (R)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine | 2.23 LC (2) 660.39 $[M+H]^+$ | Procedures 109, 110, 111, 112, 113, 114 and 13 |
| 839 |  | (S)-N-(4-fluoro-3-(trifluoromethyl)benzyl)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-phenylethanamine | 2.23 LC (2) 660.38 $[M+H]^+$ | Procedures 109, 110, 111, 112, 113, 114 and 13 |
| 840 |  | 4,4,4-trifluoro-N1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-phenylethyl) butane-1,2-diamine | 3.55 LC (1) 551.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 13 and 141 |

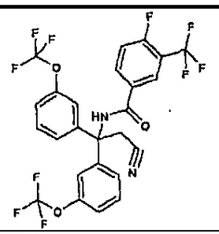
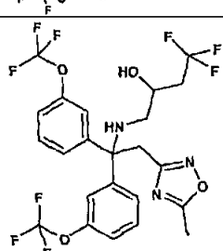
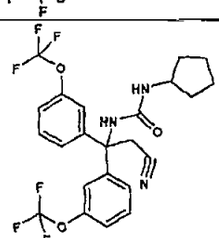
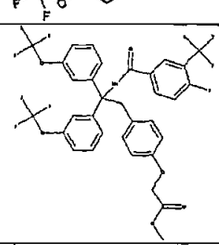
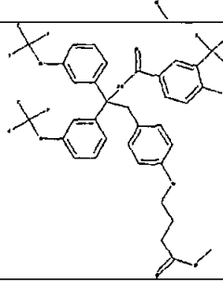
**TABLE 14**

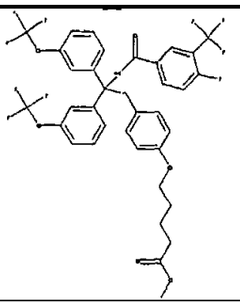
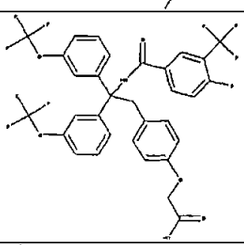
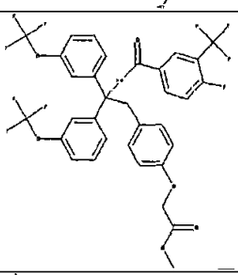
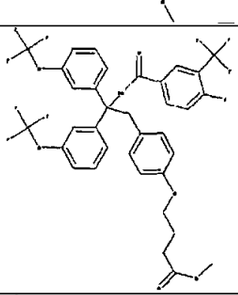
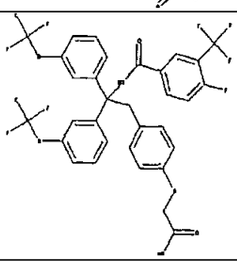
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 841 |  | 1-(1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-cyclopentylurea | 4.26 LC (1) 477.34 $[M+H]^+$ | Procedures 11, 6 and 2 |

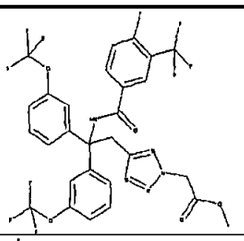
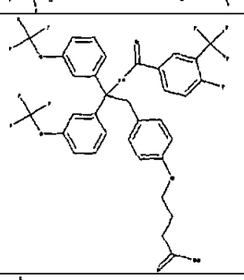
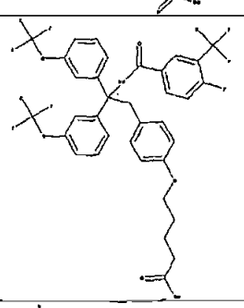
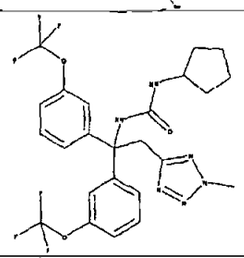
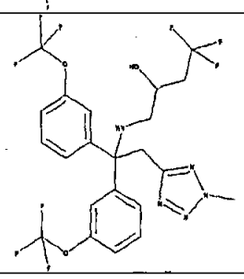
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 842 |  | N-(1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.38 LC (1) 556.24 $[M+H]^+$ | Procedures 11, 6 and 7 |
| 843 |  | 4-fluoro-N-(2-(2-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.116 LC (1) 661.98 $[M+H]^+$ | Procedures 11, 6 and 7 |
| 844 |  | N-(1,1-bis(3-(trifluoromethoxy)phenyl)but-3-enyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.37 LC (1) 582.25 $[M+H]^+$ | Procedures 11, 6 and 7 |
| 845 |  | 1-(1,1-bis(3-(trifluoromethoxy)phenyl)but-3-enyl)-3-cyclopentylurea | 4.26 LC (1) 503.33 $[M+H]^+$ | Procedures 11, 6 and 2 |
| 846 |  | methyl 3-oxo-3-(2,2,2-trifluoroethylamino)-1,1-bis(3-(trifluoromethoxy)phenyl) propylcarbamate | 3.81 LC (1) 548.90 $[M+H]^+$ | Procedures 11, 6, 14, 23, 128 and 82 |
| 847 |  | 1-cyclopentyl-3-(2-(2-fluorophenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.766 LC (1) 571.06 $[M+H]^+$ | Procedures 11, 6 and 2 |

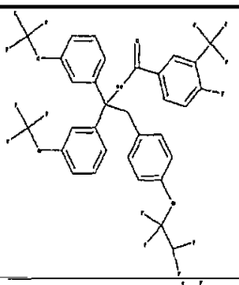
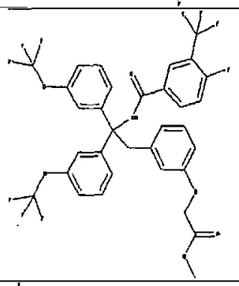
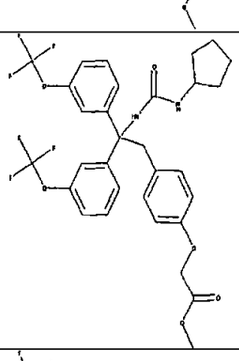
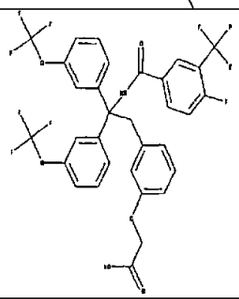
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 848 |  | 1-cyclopentyl-3-(2-(4-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.37 LC (11) 583.03 $[M+H]^+$ | Procedures 11, 6 and 2 |
| 849 |  | 4-fluoro-N-(2-(4-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.52 LC (11) 661.96 $[M+H]^+$ | Procedures 11, 6 and 7 |
| 850 |  | 1-cyclopentyl-3-(2-(4-hydroxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.21 LC (11) 569.17 $[M+H]^+$ | Procedures 11, 6, 2 and 59 |
| 851 |  | 4-fluoro-N-(2-(4-hydroxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.28 LC (11) 648.12 $[M+H]^+$ | Procedures 11, 6, 7 and 59 |
| 852 |  | 1-(2-(biphenyl-4-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-cyclopentylurea | 4.74 LC (11) 629.20 $[M+H]^+$ | Procedures 11, 6 and 2 |
| 853 |  | 1-cyclopentyl-3-(3-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)propyl)urea | 4.54 LC (11) 567.2 $[M+H]^+$ | Procedures 11, 6 and 2 |

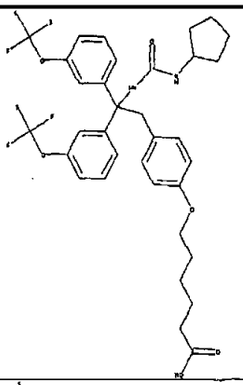
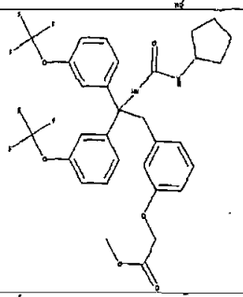
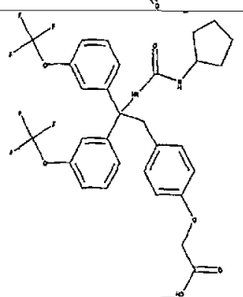
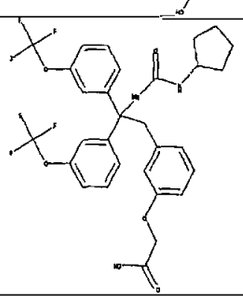
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 854 |  | 4-fluoro-N-(2-(2-hydroxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 3.953 LC (1) 648.2 $[M+H]^+$ | Procedures 11, 6, 7 and 59 |
| 855 |  | 4-fluoro-N-(2-(3-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.50 LC (11) 662.1 $[M+H]^+$ | Procedures 11, 6 and 7 |
| 856 |  | 4-fluoro-N-(2-(3-hydroxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.30 LC (11) 648.1 $[M+H]^+$ | Procedures 11, 6, 7 and 59 |
| 857 |  | 1-cyclopentyl-3-(2-(3-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.44 LC (11) 583.2 $[M+H]^+$ | Procedures 11, 6 and 2 |
| 858 |  | 1-cyclopentyl-3-(2-(3-hydroxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 4.19 LC (11) 569.2 $[M+H]^+$ | Procedures 11, 6, 2 and 59 |
| 859 |  | 4-fluoro-N-(2-(pyridin-2-yl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.03 LC (1) 633.13 $[M+H]^+$ | Procedures 11, 20, 6 and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 860 |  | N-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.04 LC (1) 581.16 $[M+H]^+$ | Procedures 11, 18, 6 and 7 |
| 861 |  | 4,4,4-trifluoro-1-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethylamino)butan-2-ol | 3.78 LC (1) 574.22 $[M+H]^+$ | Procedures 11, 17 and 8 |
| 862 |  | 1-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-cyclopentylurea | 3.83 LC (1) 502.3 $[M+H]^+$ | Procedures 11, 18, 6 and 2 |
| 863 |  | methyl 2-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetate | 4.37 LC (11) 720.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 68 |
| 864 |  | methyl 4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) butanoate | 4.50 LC (11) 748.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 68 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 865 |  | methyl 5-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) pentanoate | 4.59 LC (11) 762.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 68 |
| 866 |  | 2-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetic acid | 4.28 LC (11) 706.1 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |
| 867 |  | methyl 2-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetate | 4.365 LC (11) 720.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 68 |
| 868 |  | methyl 4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) butanoate | 4.503 LC (11) 748.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 68 |
| 869 |  | 2-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetic acid | 4.281 LC (11) 706.1 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 870 |  | methyl 2-(5-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)-2H-tetrazol-2-yl)acetate | 4.04 LC (1) 696.1 $[M+H]^+$ | Procedures 11, 18, 6, 7, 79 and 163 |
| 871 |  | 4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) butanoic acid | 4.336 LC (11) 734.1 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |
| 872 |  | 5-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) pentanoic acid | 4.376 LC (11) 748.2 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |
| 873 |  | 1-cyclopentyl-3-(2-(2-methyl-2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)urea | 3.89 LC (1) 559.26 $[M+H]^+$ | Procedures 11, 18, 6, 2, 79 and 80 |
| 874 |  | 4,4,4-trifluoro-1-(2-(2-methyl-2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)butan-2-ol | 3.72 LC (1) 574.23 $[M+H]^+$ | Procedures 11, 18, 6, 8, 79 and 80 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 875 |  | 4-fluoro-N-(2-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.305 LC (11) 748.1 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 3 |
| 876 |  | methyl 2-(3-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetate | 4.363 LC (11) 720.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 68 |
| 877 |  | methyl 2-(4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy)phenyl) ethyl)phenoxy)acetate | 4.293 LC (11) 641.2 $[M+H]^+$ | Procedures 11, 6, 2, 59 and 68 |
| 878 |  | 2-(3-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetic acid | 4.286 LC (11) 706.1 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 879 |  | 6-(4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) hexanoic acid | 4.39 LC (11) 683.2 $[M+H]^+$ | Procedures 11, 6, 2, 59, 129 and 23 |
| 880 |  | methyl 2-(3-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy)phenyl) ethyl)phenoxy)acetate | 4.278 LC (11) 641.2 $[M+H]^+$ | Procedures 11, 6, 2, 59, and 68 |
| 881 |  | 2-(4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetic acid | 4.223 LC (11) 627.2 $[M+H]^+$ | Procedures 11, 6, 2, 59, 68 and 23 |
| 882 |  | 2-(3-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetic acid | 4.198 LC (11) 627.2 $[M+H]^+$ | Procedures 11, 6, 2, 59, 68 and 23 |

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, -$NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, –$CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, –$COR_{49}$, –$S(O)_pR_{49}$, –$SO_2NHR_{49}$, –$COOR_{49}$, or –$NHC(CN)NHR_{49}$;

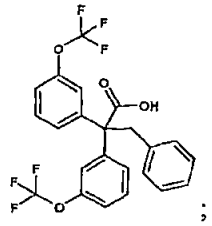
$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl;

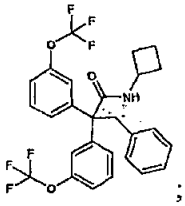
r is 0 to 5;

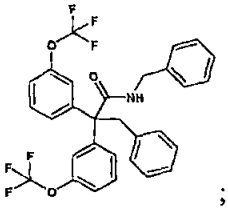
s is 0 to 4; and

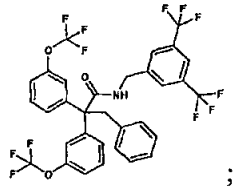
p is 1 or 2;

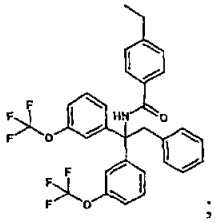
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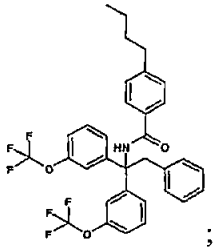


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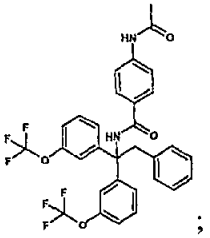
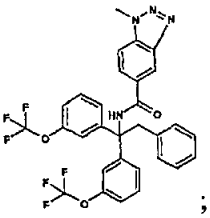
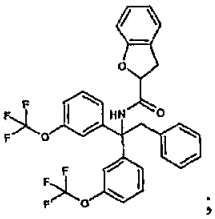
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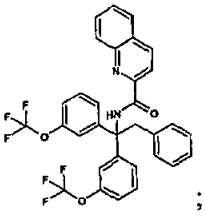
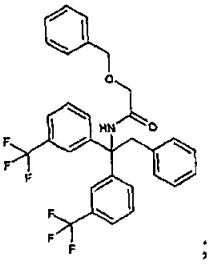
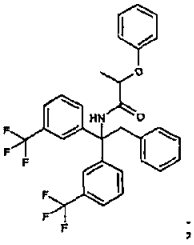
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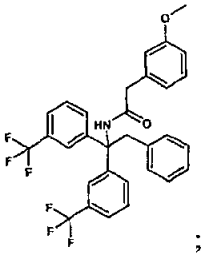
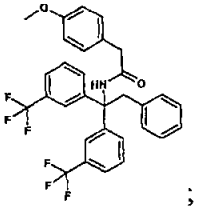
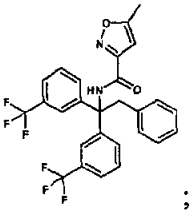
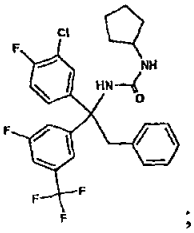
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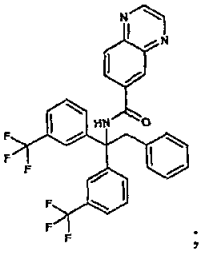
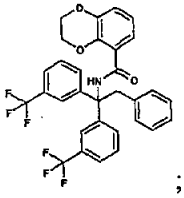
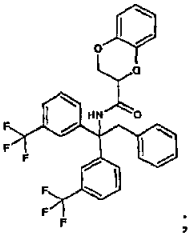
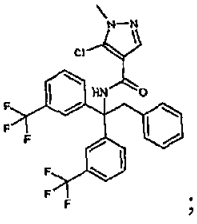
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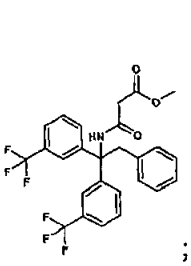
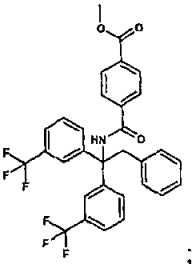
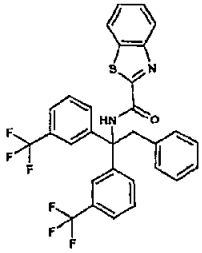
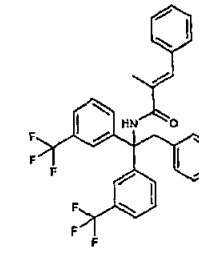
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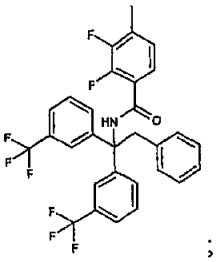
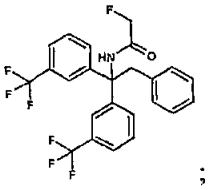
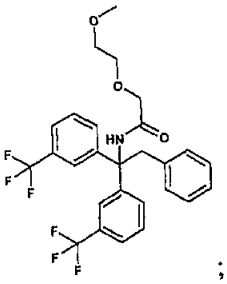

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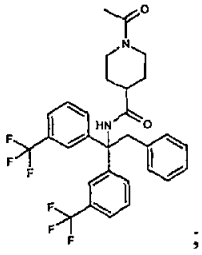
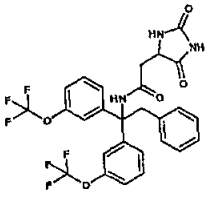
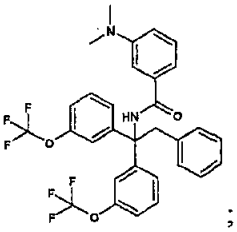

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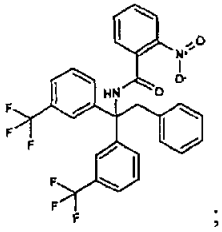
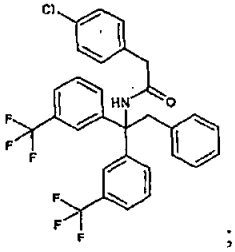
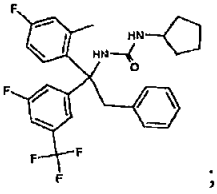
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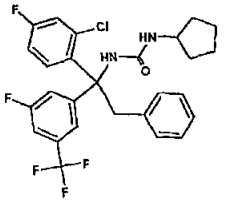
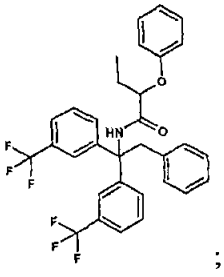
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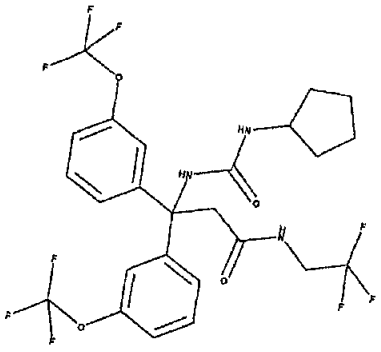

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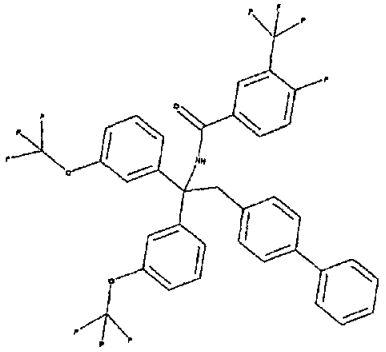
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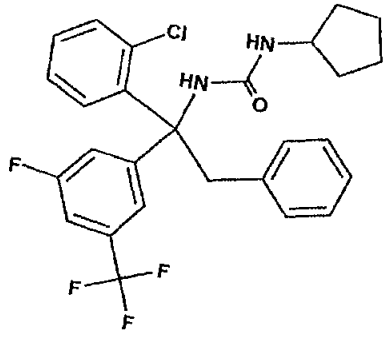

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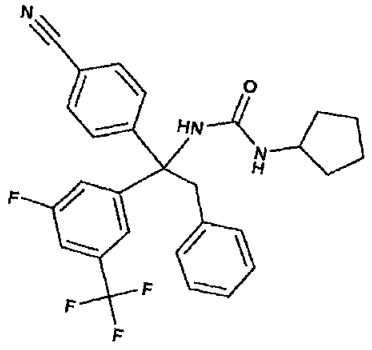
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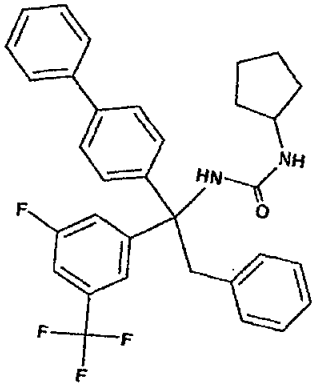
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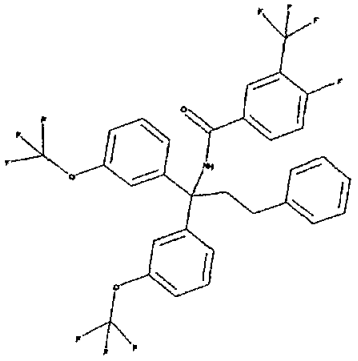
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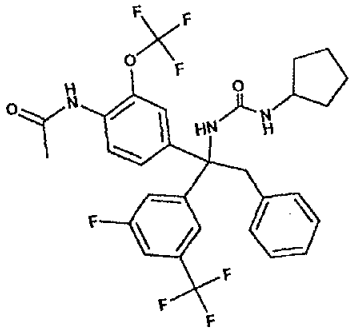
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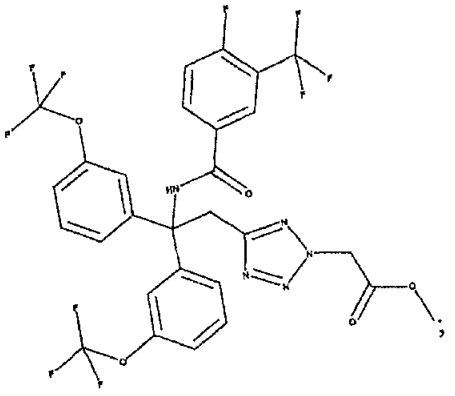
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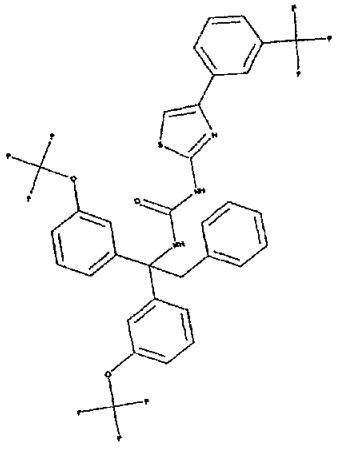
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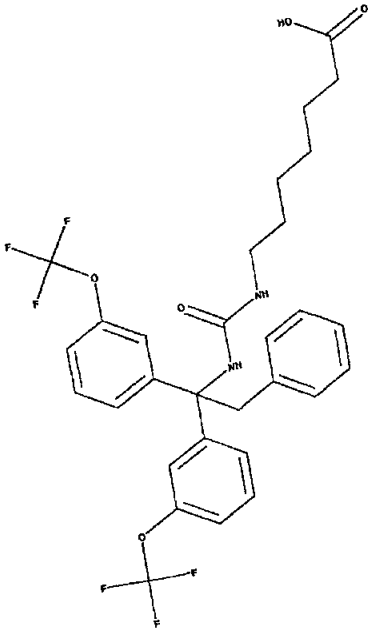
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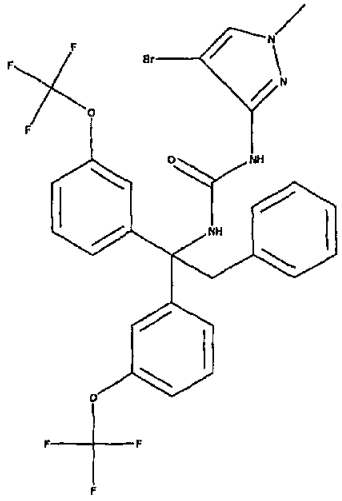


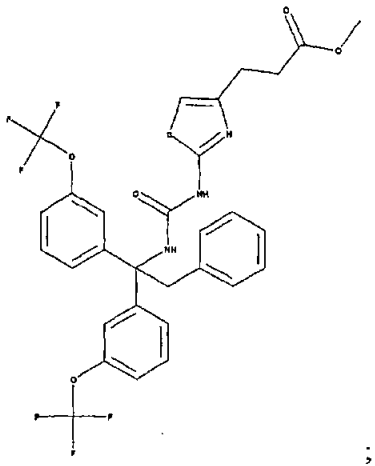
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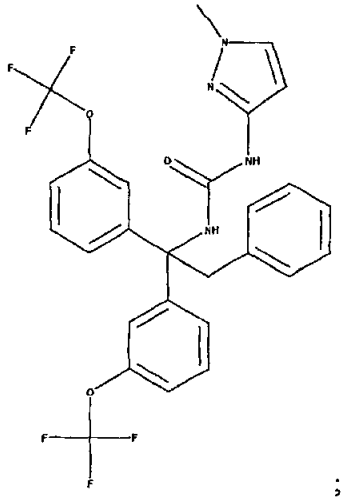


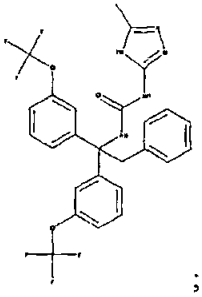
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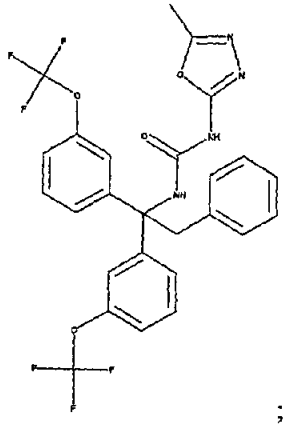
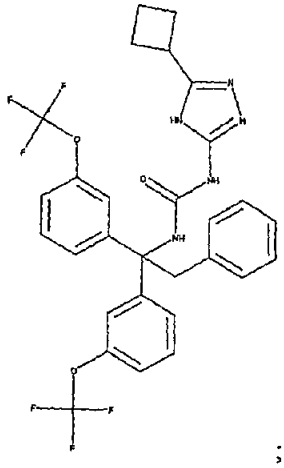
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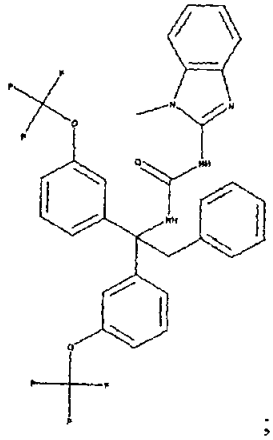
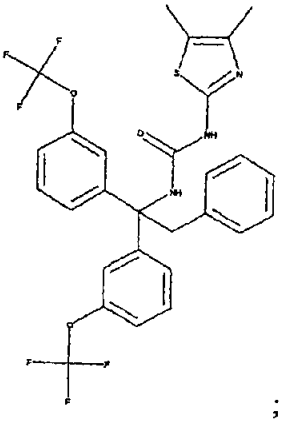

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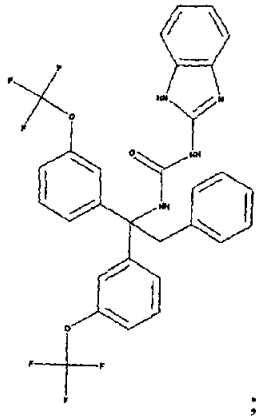
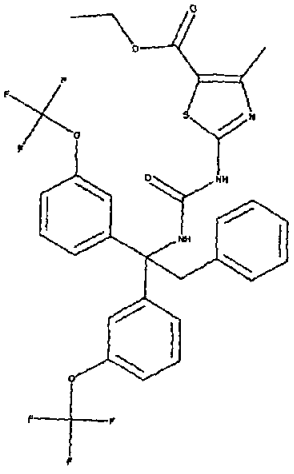

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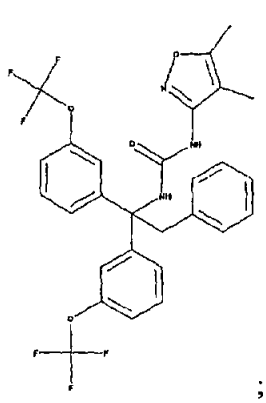
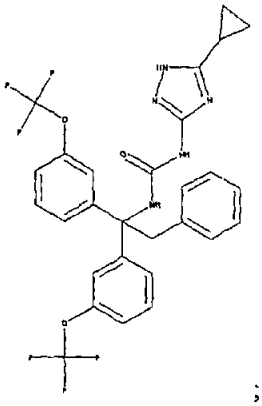

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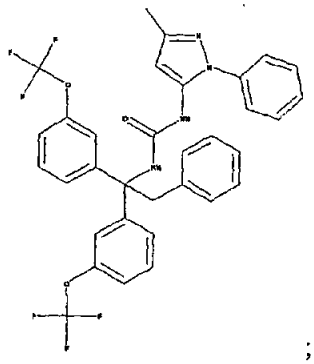
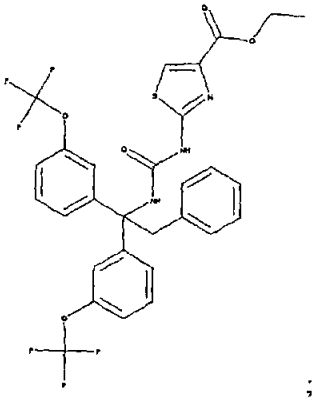

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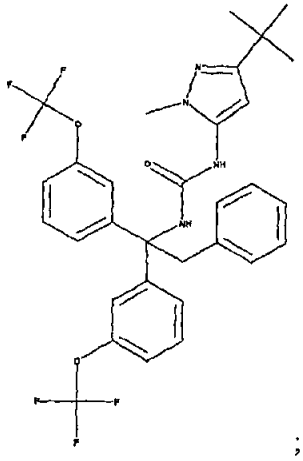
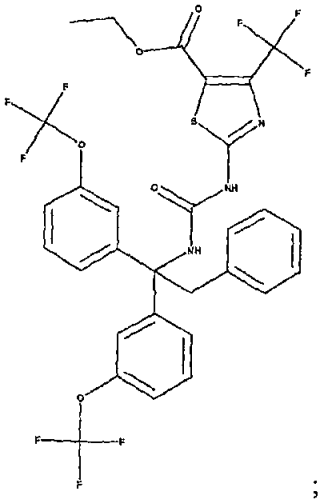

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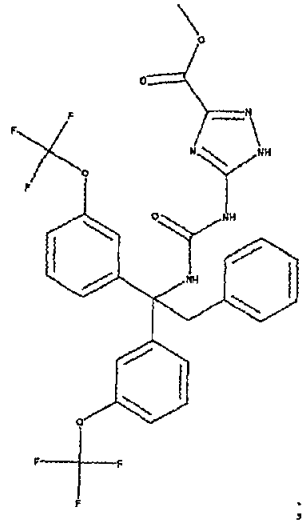
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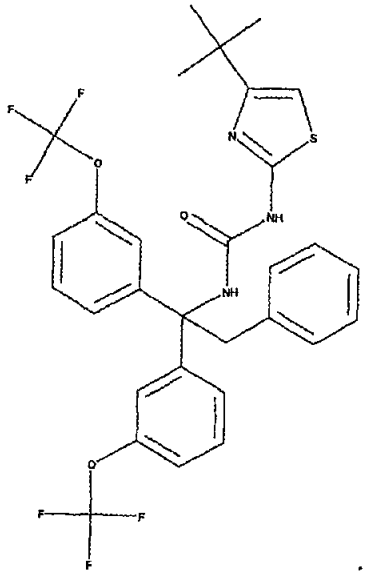

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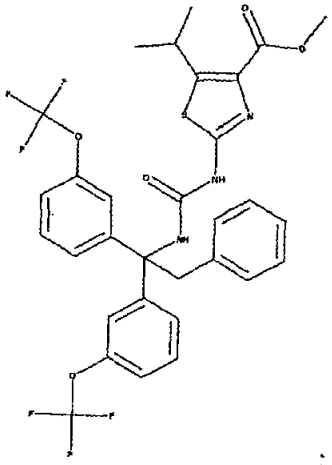

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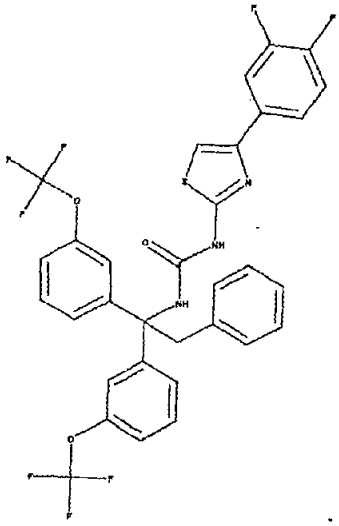
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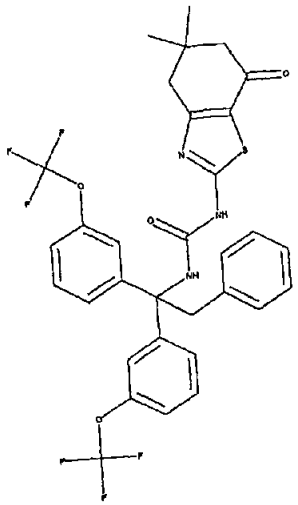


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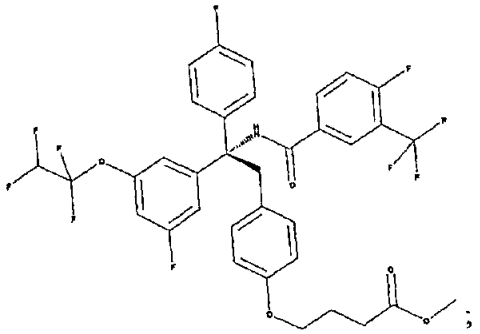


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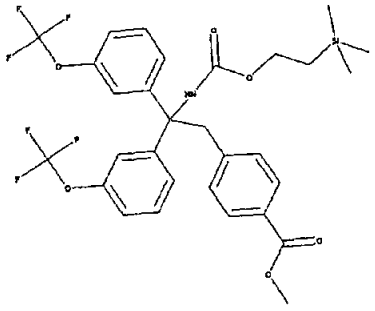
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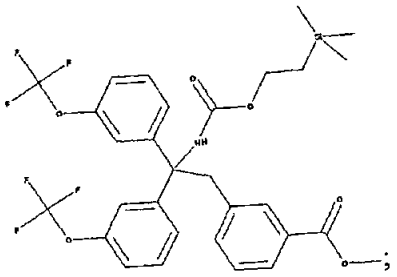
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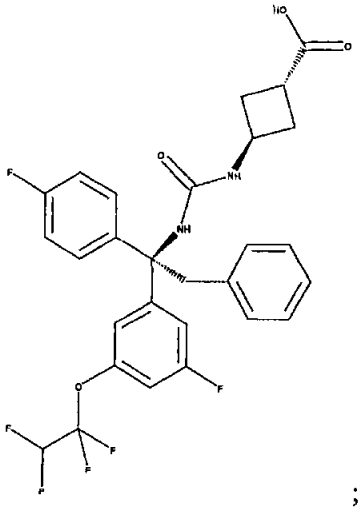


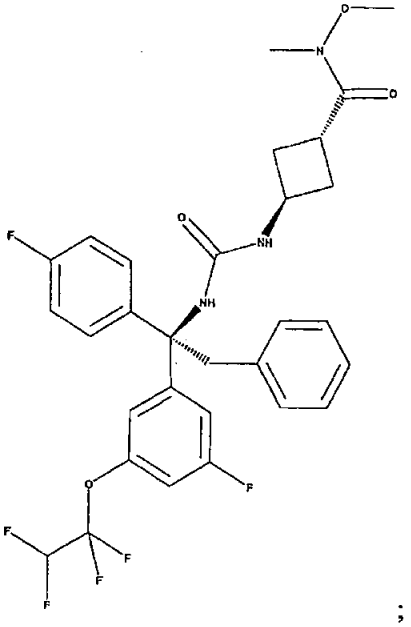
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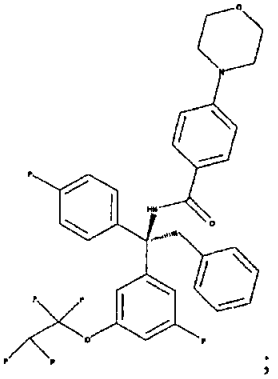


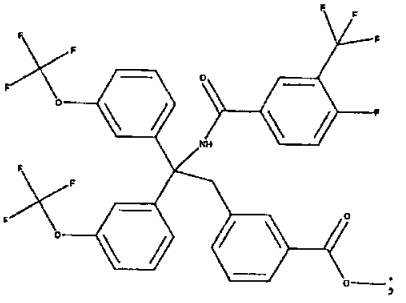
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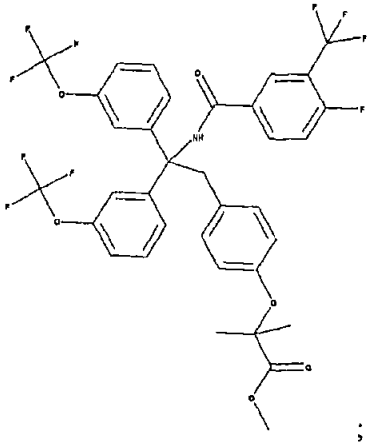
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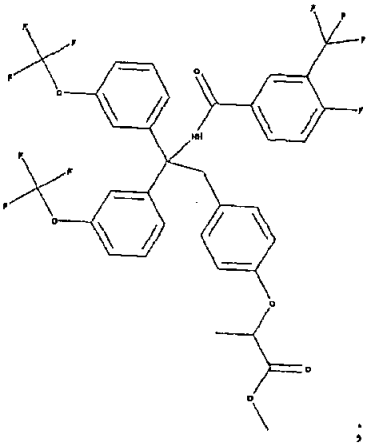

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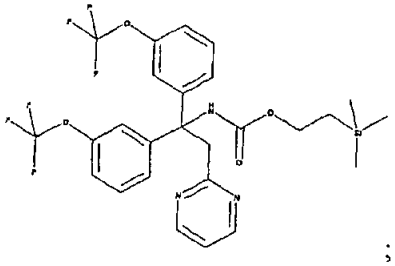

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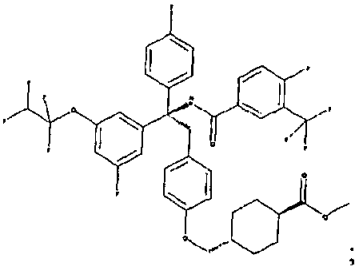

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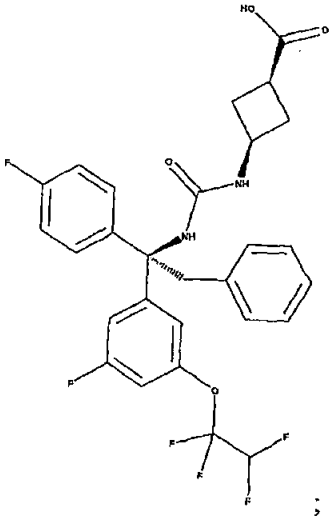

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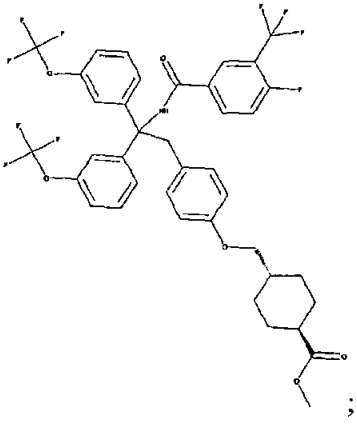

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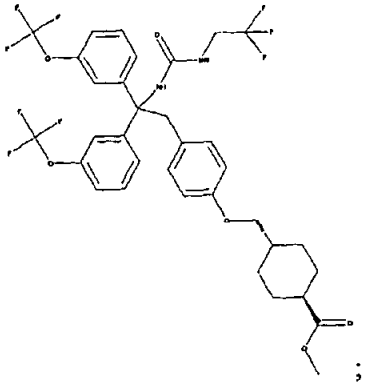

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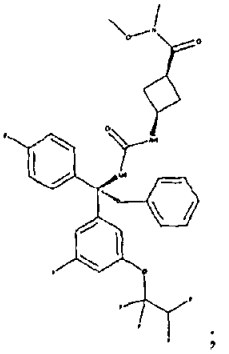

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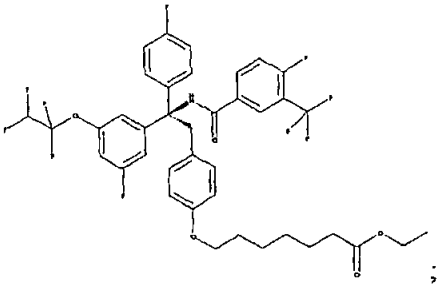

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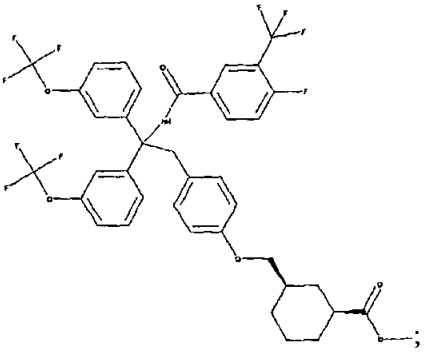

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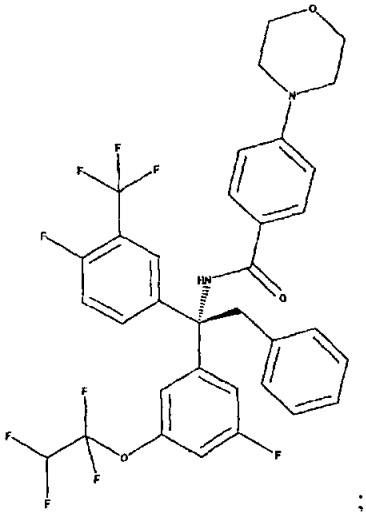

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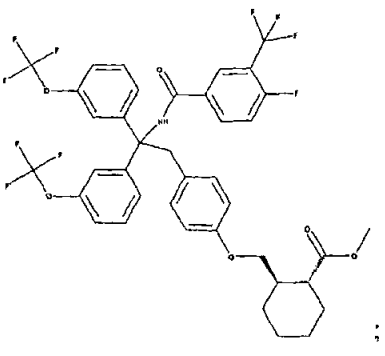

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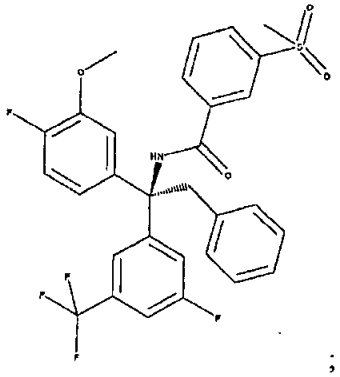

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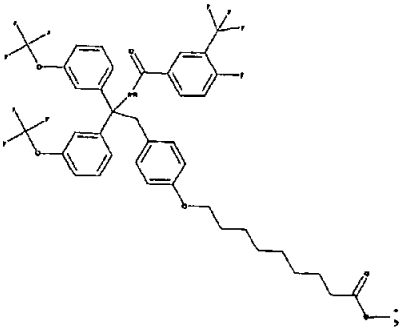

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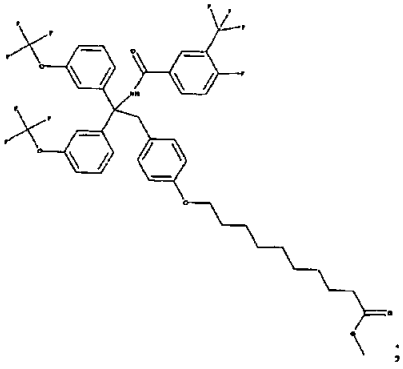

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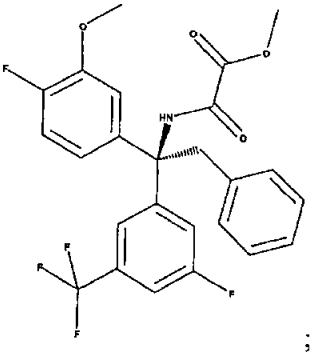

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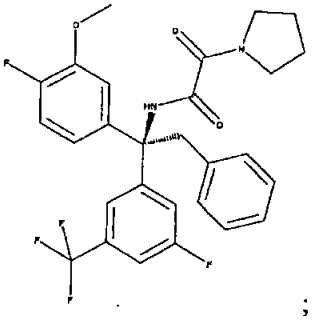

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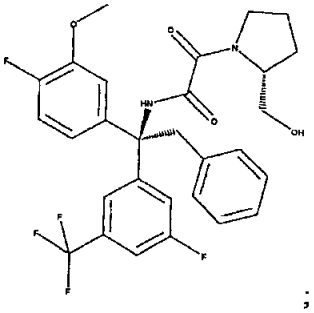

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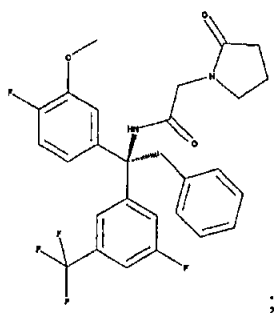
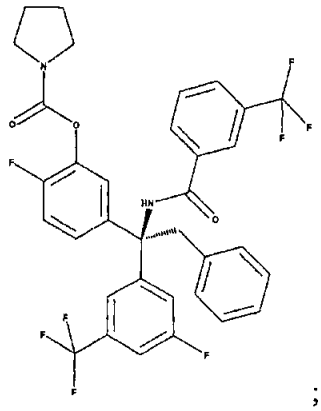
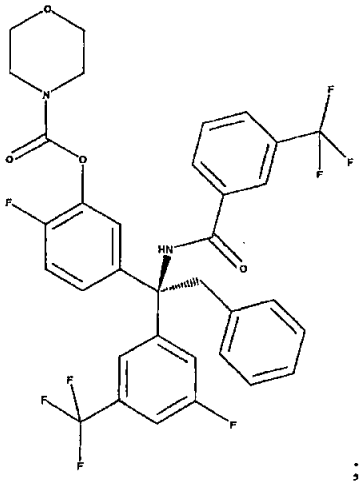
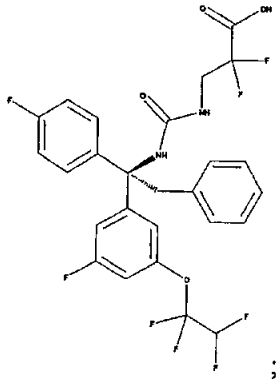
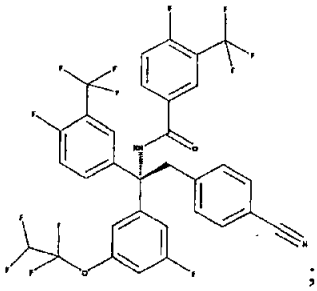
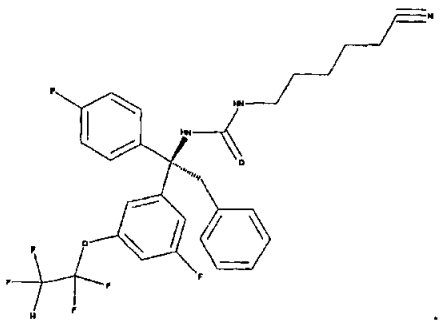

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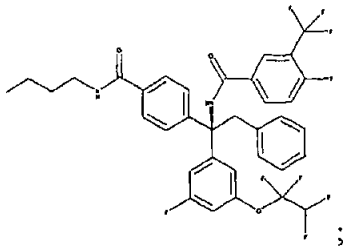

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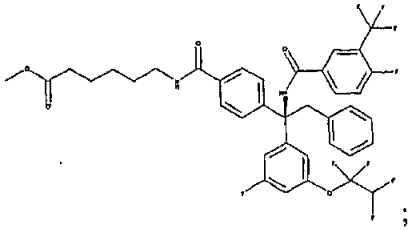

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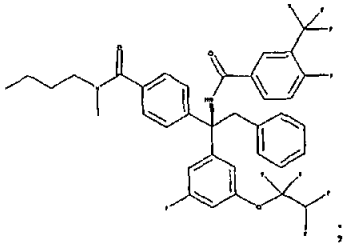

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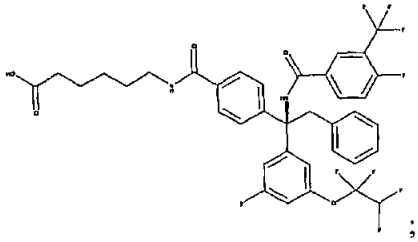

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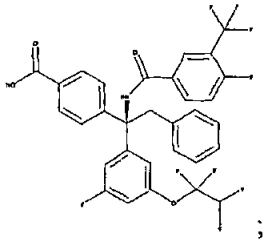
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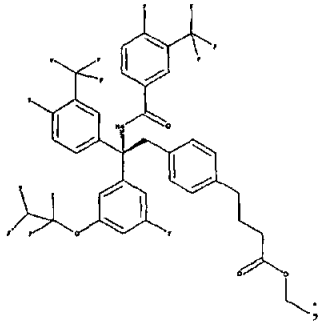

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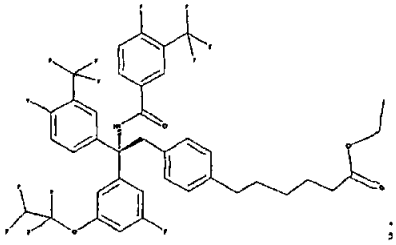

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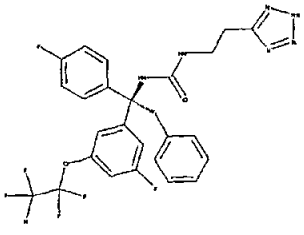

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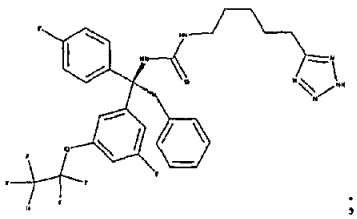
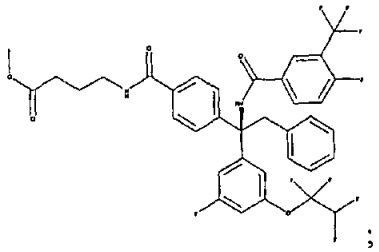

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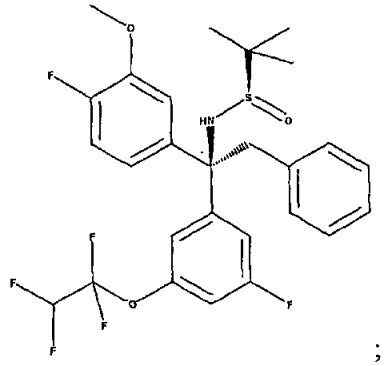
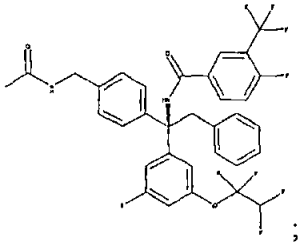

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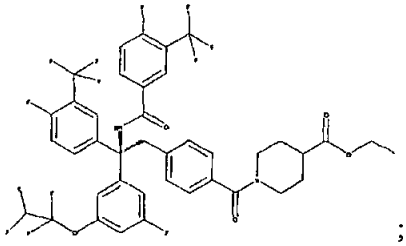
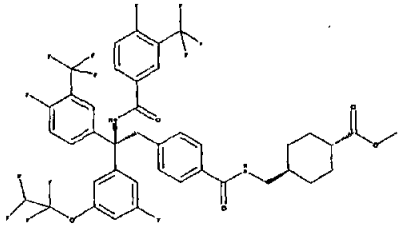

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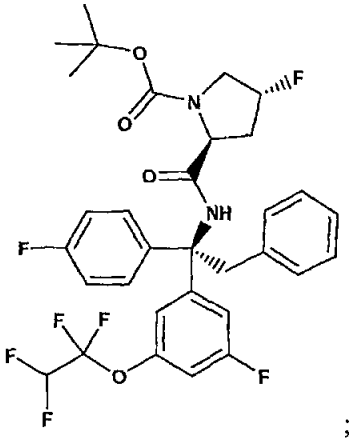
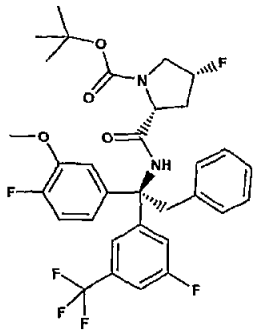

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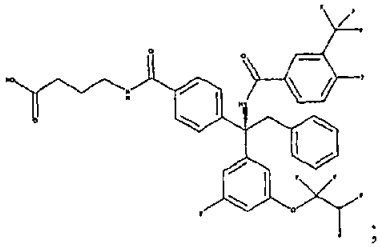

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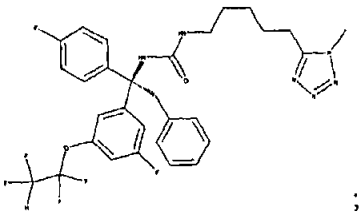

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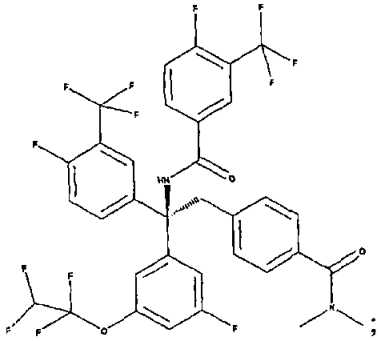

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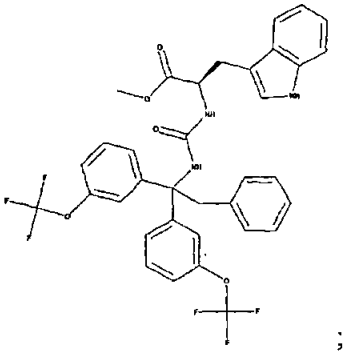

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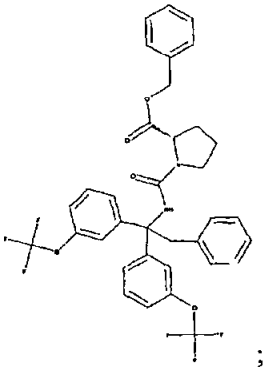

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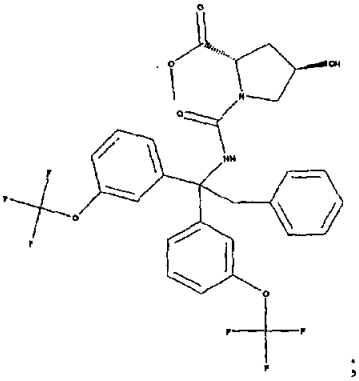

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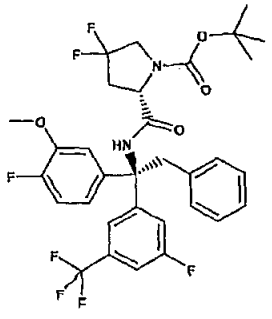

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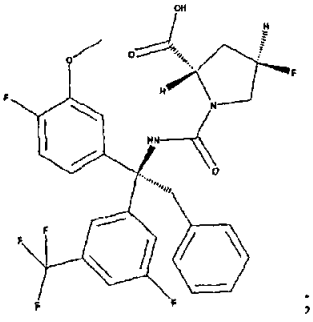

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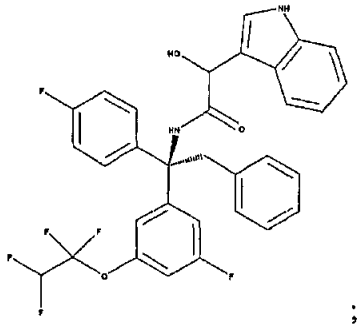
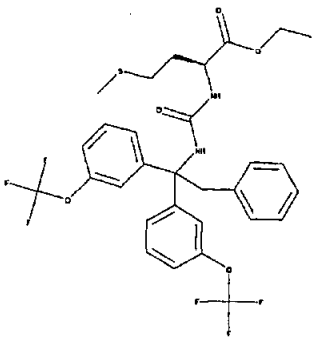
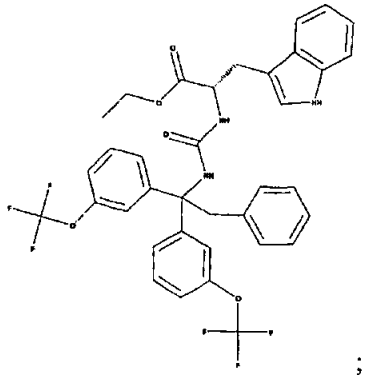
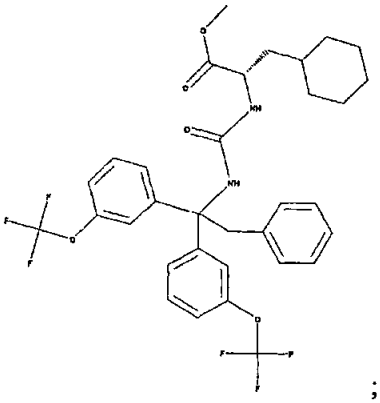
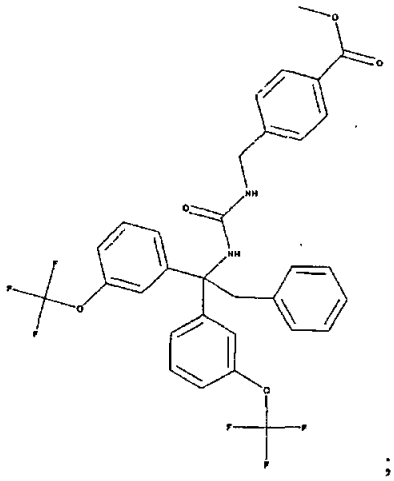
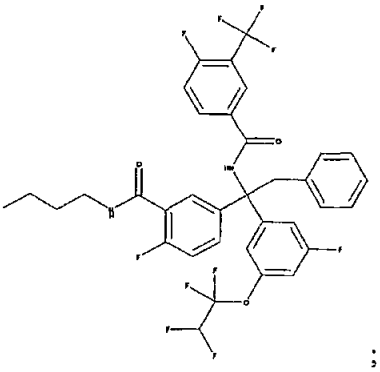

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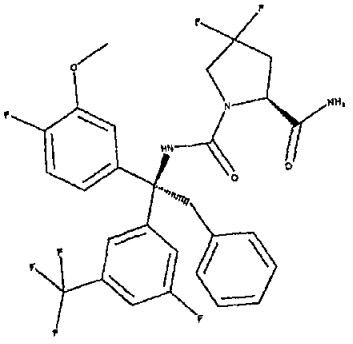
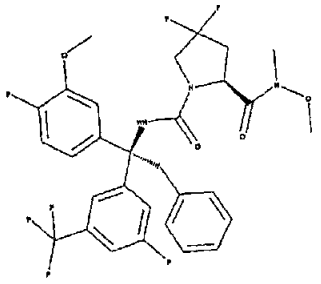
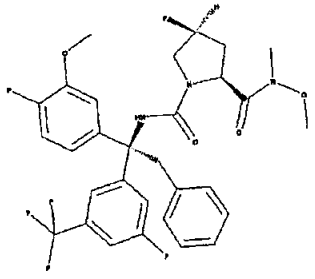
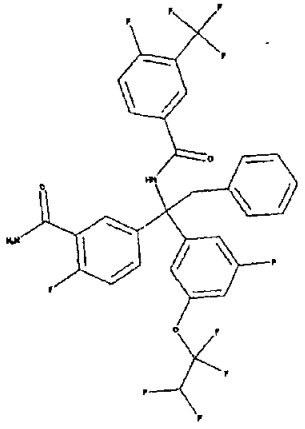
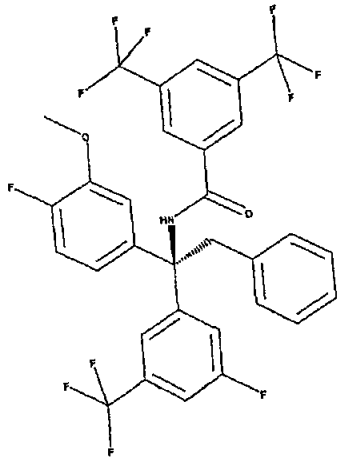
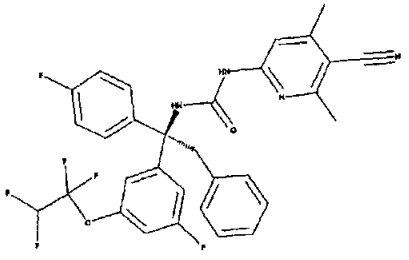

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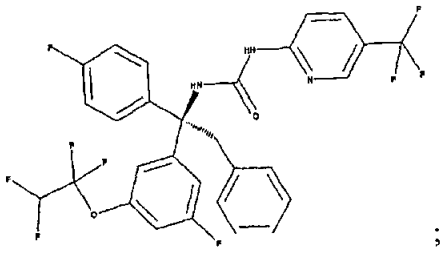
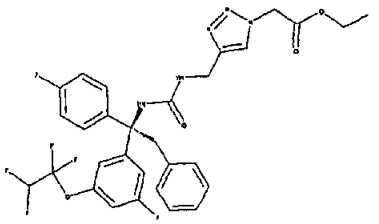
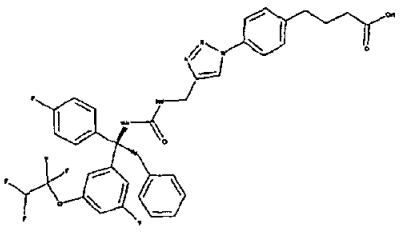
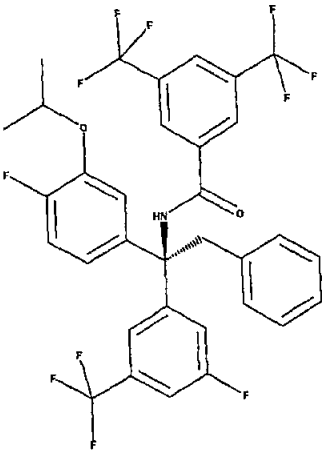
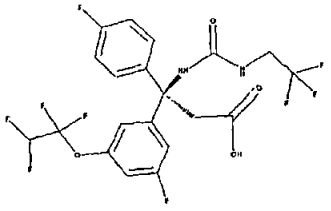
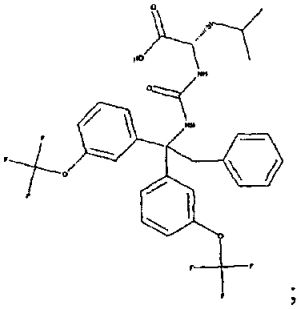

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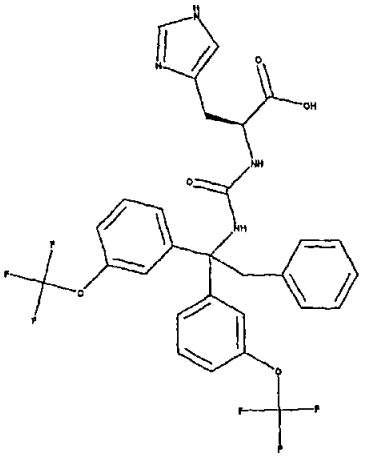
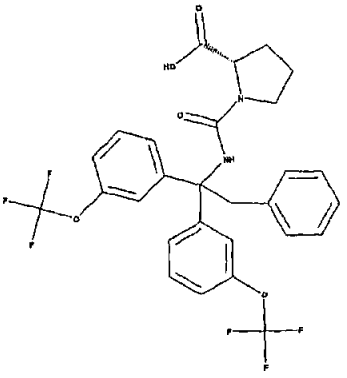
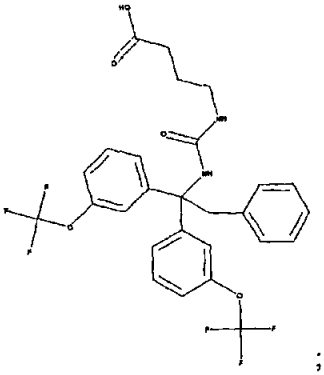
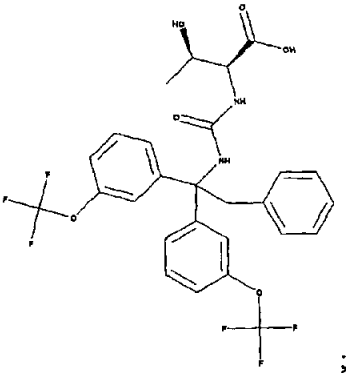
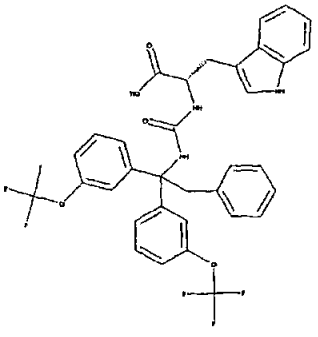
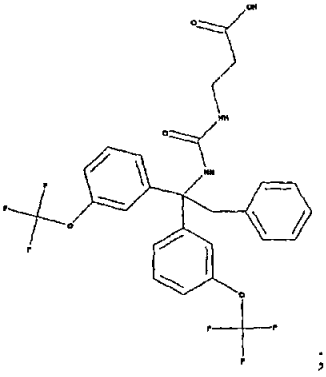

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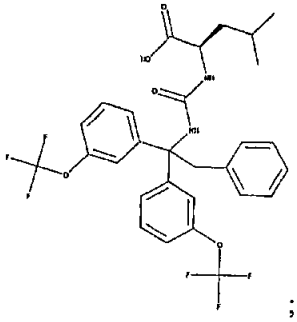

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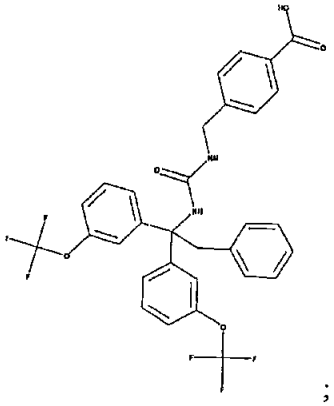

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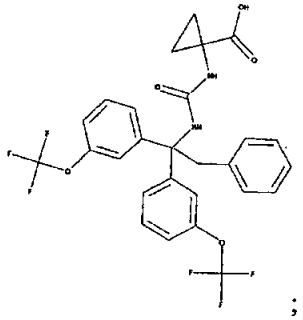

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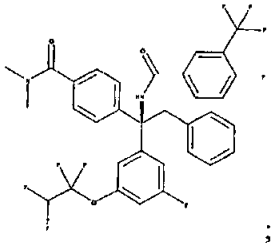

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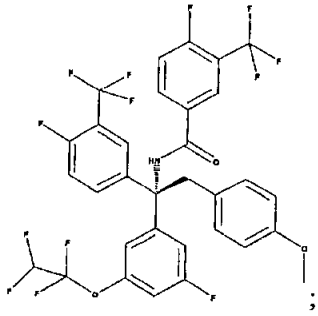

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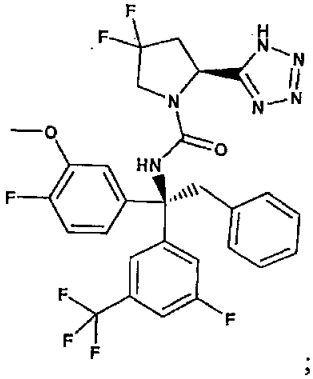

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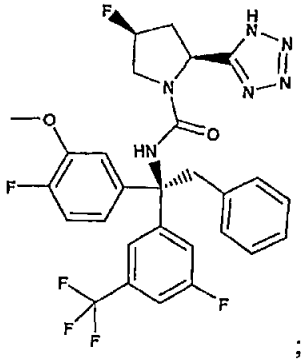
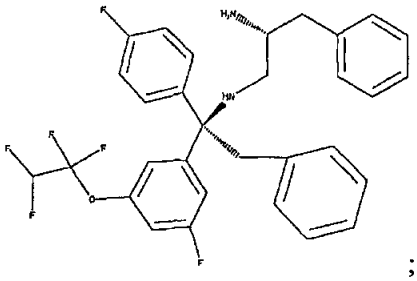
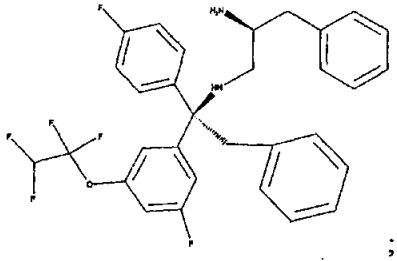
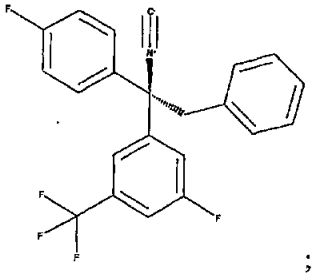
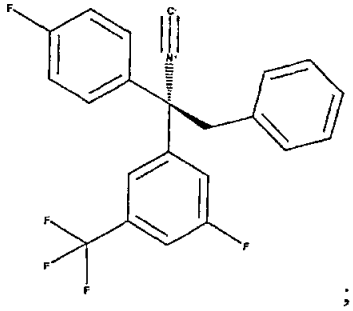
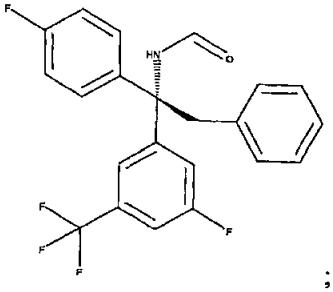

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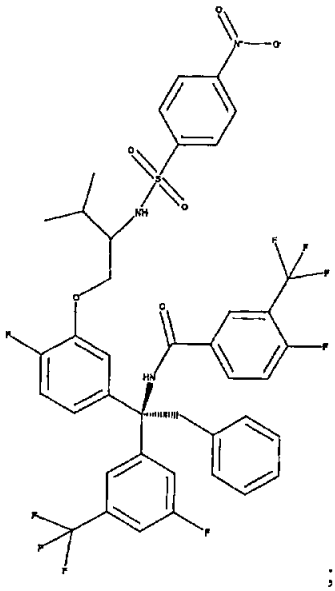

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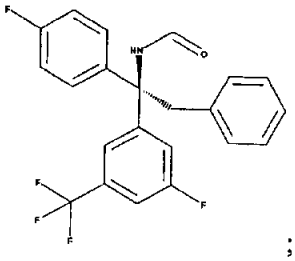

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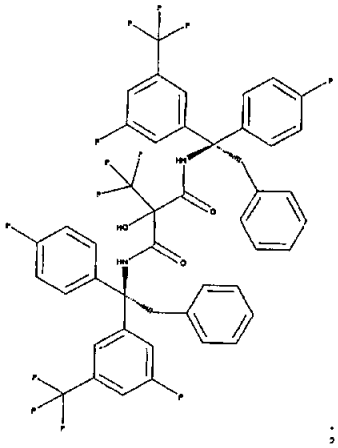

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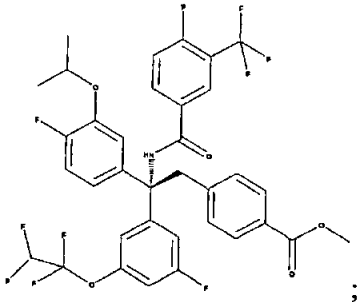

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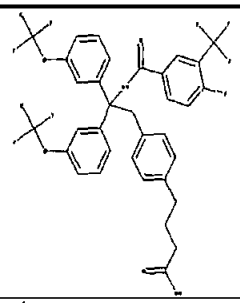
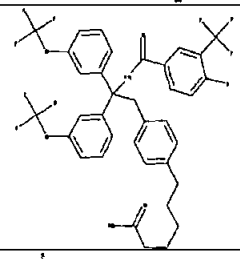
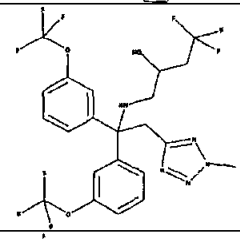
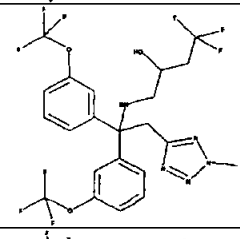
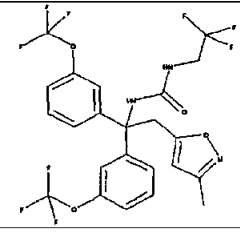
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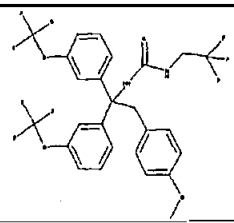
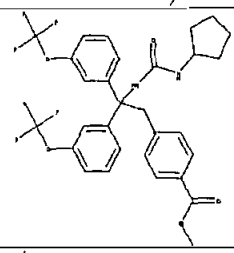
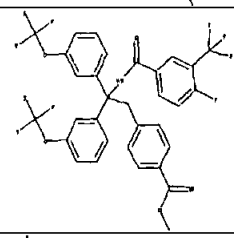
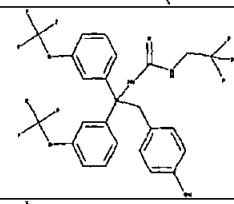
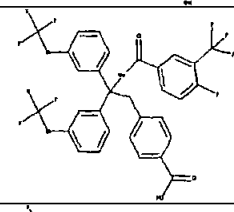
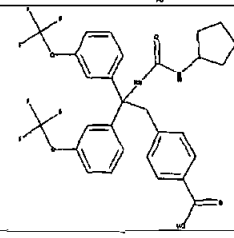

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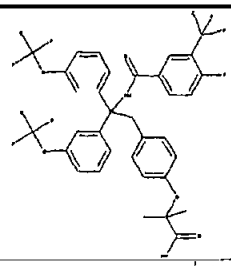
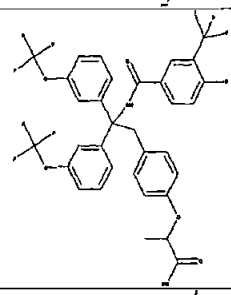
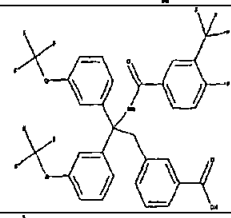
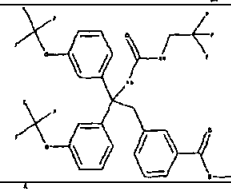
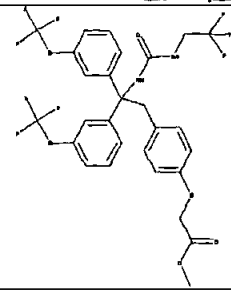

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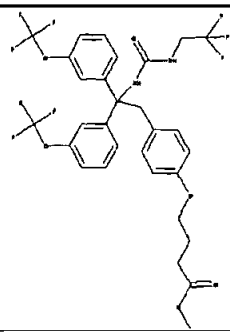
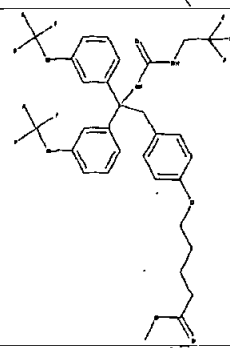
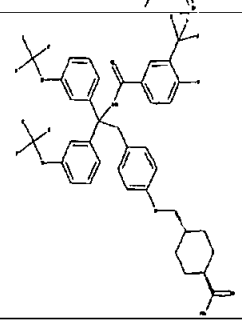
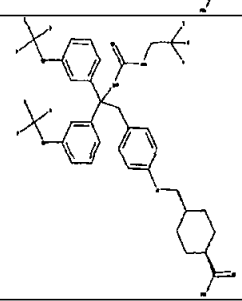
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 883 |  | 4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenyl)butanoic acid | 2.21 LC (2) 718.1 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75 and 76 |
| 884 |  | 6-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenyl)hexanoic acid | 2.28 LC (2) 746.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75 and 76 |
| 885 |  | 4,4,4-trifluoro-1-(2-(2-methyl-2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)butan-2-ol | 3.62 LC (1) 574.04 $[M+H]^+$ | Procedures 11, 18, 6, 8, 79 and 80 |
| 886 |  | 4,4,4-trifluoro-1-(2-(2-methyl-2H-tetrazol-5-yl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethylamino)butan-2-ol | 3.69 LC (1) 574.13 $[M+H]^+$ | Procedures 11, 18, 6, 8, 79 and 80 |
| 887 |  | 1-(2-(3-methylisoxazol-5-yl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.81 LC (1) 572.11 $[M+H]^+$ | Procedures 11, 17, 2 and 9 |

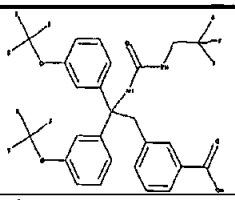
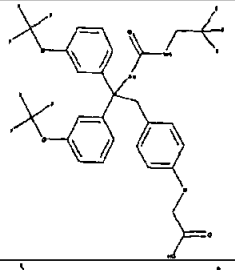
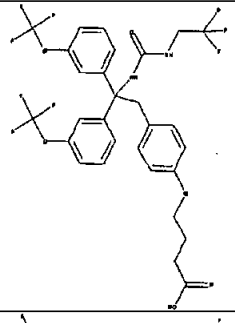
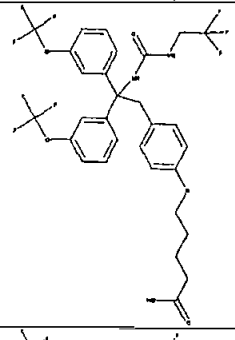
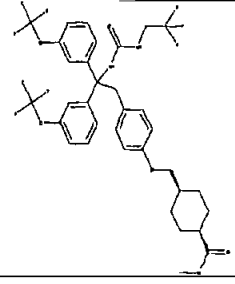
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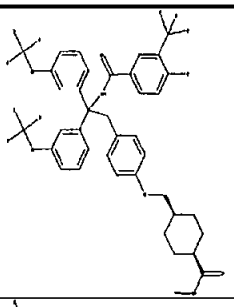
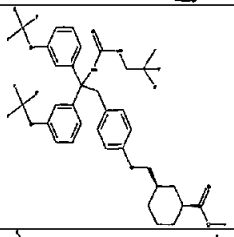
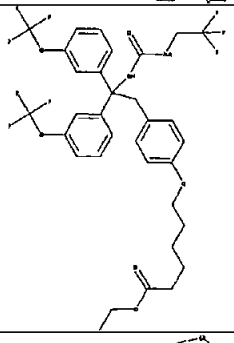
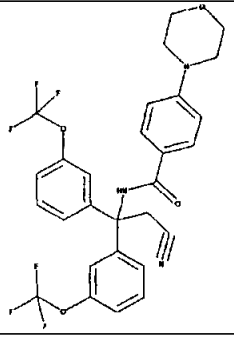
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 888 |  | 1-(2-(4-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 4.291 LC (11) 597.2 $[M+H]^+$ | Procedures 11, 6 and 25 |
| 889 |  | methyl 4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy)phenyl) ethyl)benzoate | 4.345 LC (11) 611.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75 and 2 |
| 890 |  | methyl 4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)benzoate | 4.448 LC (11) 690.1 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75 and 7 |
| 891 |  | 1-(2-(4-hydroxyphenyl)-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 4.101 LC (11) 583.2 $[M+H]^+$ | Procedures 11, 6, 25 and 59 |
| 892 |  | 4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)benzoic acid | 4.286 LC (11) 676.1 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75, 7 and 23 |
| 893 |  | 4-(2-(3-cyclopentylureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)benzoic acid | 4.208 LC (11) 597.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75, 2 and 23 |

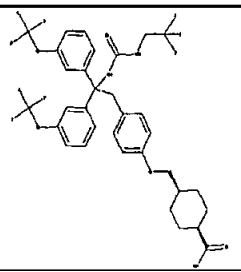
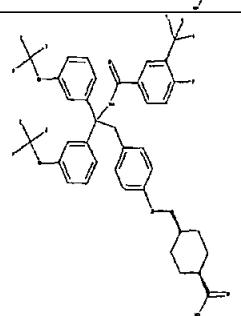
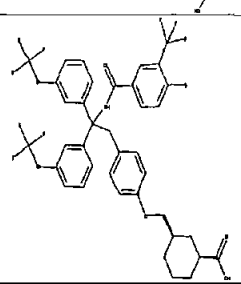
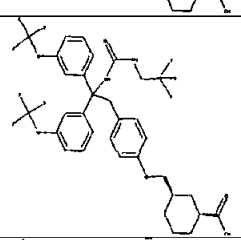
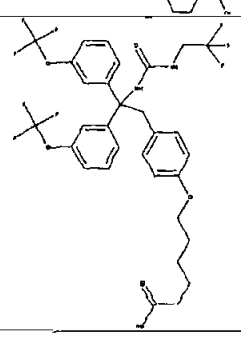
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 894 |  | 2-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)-2-methylpropanoic acid | 4.366 LC (11) 734.1 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |
| 895 |  | 2-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) propanoic acid | 4.388 LC (11) 719.87 $[M+H]^+$ | Procedures 11, 6, 7, 59, 68 and 23 |
| 896 |  | 3-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)benzoic acid | 4.266 LC (11) 675.84 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75, 7 and 23 |
| 897 |  | methyl 3-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)benzoate | 4.246 LC (11) 625.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75 and 25 |
| 898 |  | methyl 2-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetate | 4.196 LC (11) 655.1 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 68 |

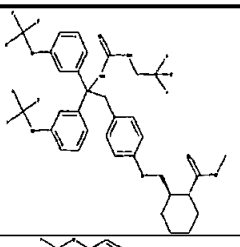
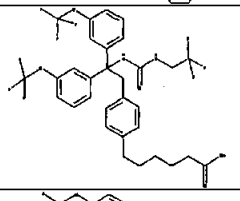
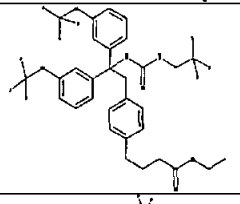
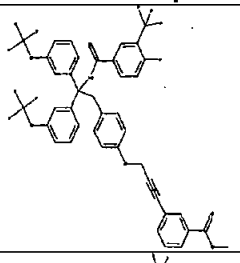
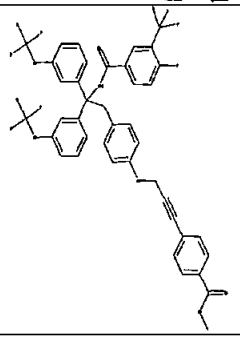
642

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 899 |  | methyl 4-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) butanoate | 4.31 LC (11) 683.1 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 68 |
| 900 |  | methyl 5-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) pentanoate | 4.371 LC (11) 697.2 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 68 |
| 901 |  | (1r,4r)-4-((4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 4.546 LC (11) 788.3 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 129 |
| 902 |  | (1r,4r)-4-((4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 4.35 LC (11) 723.2 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 129 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 903 |  | 3-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)benzoic acid | 4.07 LC (11) 611.1 $[M+H]^+$ | Procedures 11, 72, 73, 74, 75, 25 and 23 |
| 904 |  | 2-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)acetic acid | 4.13 LC (11) 641.1 $[M+H]^+$ | Procedures 11, 6, 25, 59, 68 and 23 |
| 905 |  | 4-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) butanoic acid | 4.188 LC (11) 669.2 $[M+H]^+$ | Procedures 11, 6, 25, 59, 68 and 23 |
| 906 |  | 5-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) pentanoic acid | 4.243 LC (11) 683.2 $[M+H]^+$ | Procedures 11, 6, 25, 59, 68 and 23 |
| 907 |  | (1s,4s)-methyl 4-((4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylate | 4.611 LC (11) 737.2 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 129 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 908 |  | (1s,4s)-methyl 4-((4-(2-(4-fluoro-3-(trifluoromethyl) benzamido)-2,2-bis(3-(trifluoromethoxy)phenyl) ethyl)phenoxy)methyl) cyclohexanecarboxylate | 4.943 LC (11) 802.3 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 129 |
| 909 |  | (1S,3R)-methyl 3-((4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylate | 4.61 LC (11) 737.3 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 129 |
| 910 |  | ethyl 6-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) hexanoate | 4.535 LC (11) 725.3 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 129 |
| 911 |  | N-(2-cyano-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-4-morpholinobenzamide | 3.83 LC (1) 580.15 $[M+H]^+$ | Procedures 11, 18, 6, and 7 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 912 |  | (1s,4s)-4-((4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 4.413 LC (11) 723.2 $[M+H]^+$ | Procedures 11, 6, 25, 59, 129 and 23 |
| 913 |  | (1s,4s)-4-((4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 4.633 LC (11) 788.2 $[M+H]^+$ | Procedures 11, 6, 7, 59, 129 and 23 |
| 914 |  | (1S,3R)-3-((4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 4.625 LC (11) 788.2 $[M+H]^+$ | Procedures 11, 6, 7, 59, 129 and 23 |
| 915 |  | (1S,3R)-3-((4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 4.431 LC (11) 723.2 $[M+H]^+$ | Procedures 11, 6, 25, 59, 129 and 23 |
| 916 |  | 6-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy) hexanoic acid | 4.315 LC (11) 697.2 $[M+H]^+$ | Procedures 11, 6, 25, 59, 129 and 23 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 917 |  | (1R,2R)-methyl 2-((4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) cyclohexanecarboxylate | 4.583 LC (11) 737.3 $[M+H]^+$ | Procedures 11, 6, 25, 59 and 129 |
| 918 |  | 6-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenyl)hexanoic acid | 2.205 LC (2) 681.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 77, 24 and 23 |
| 919 |  | ethyl 4-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenyl)butanoate | 2.233 LC (2) 681.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 77 and 24 |
| 920 |  | methyl 3-(3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)prop-1-ynyl)benzoate | 4.90 LC (11) 820.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 129 |
| 921 |  | methyl 4-(3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)prop-1-ynyl)benzoate | 4.856 LC (11) 820.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 129 |

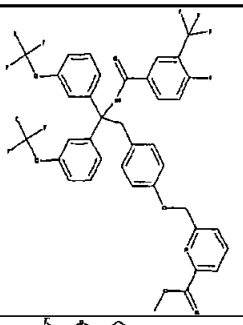
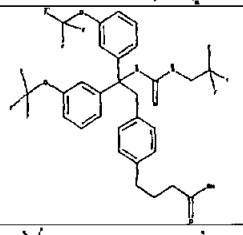
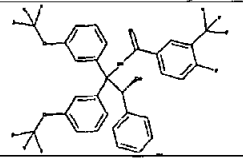
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 922 |  | methyl 6-((4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenoxy)methyl) picolinate | 4.506 LC (11) 797.2 $[M+H]^+$ | Procedures 11, 6, 7, 59 and 129 |
| 923 |  | 4-(4-(2-(3-(2,2,2-trifluoroethyl)ureido)-2,2-bis(3-(trifluoromethoxy) phenyl)ethyl)phenyl)butanoic acid | 2.128 LC (2) 653.2 $[M+H]^+$ | Procedures 11, 72, 73, 74, 77, 24 and 23 |
| 924 |  | (R)-4-fluoro-N-(2-hydroxy-2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 4.128 LC (11) 648.0 $[M+H]^+$ | Procedures 11, 123, 124, 125, 126 and 127 |

**TABLE 15**

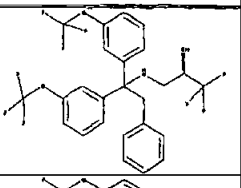
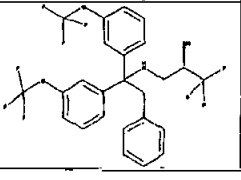
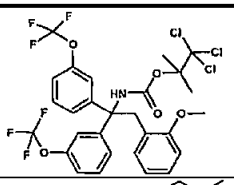
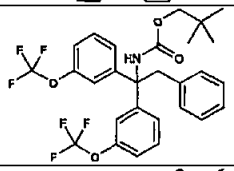
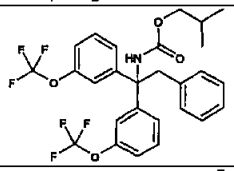
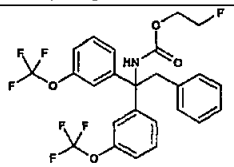
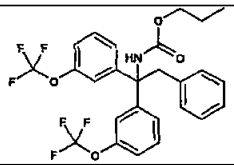
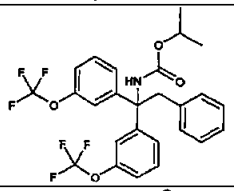
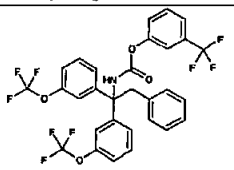
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 925 |  | (R)-1,1,1-trifluoro-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethylamino)propan-2-ol | 2.188 LC (2) 554.2 $[M+H]^+$ | Procedures 11, 6, 27 and 8 |
| 926 |  | (S)-1,1,1-trifluoro-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethylamino)propan-2-ol | 2.193 LC (2) 554.2 $[M+H]^+$ | Procedures 11, 6, 27 and 8 |

**TABLE 16**

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 927 |  | 1,1,1-trichloro-2-methylpropan-2-yl 2-(2-methoxyphenyl)-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamate | 4.266 LC (1) 675.33 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 928 |  | neopentyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamate | 4.45 LC (1) 556.25 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 929 |  | isobutyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamate | 4.38 LC (1) 542.20 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 930 |  | 2-fluoroethyl 2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethylcarbamate | 4.17 LC (1) 532.17 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 931 |  | propyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamate | 4.30 LC (1) 528.20 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 932 |  | isopropyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamate | 4.30 LC (1) 528.20 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 933 |  | 3-(trifluoromethyl)phenyl 2-phenyl-1,1-bis(3-(trifluoromethoxy)phenyl) ethylcarbamate | 4.42 LC (1) 630.26 $[M+H]^+$ | Procedures 11, 6 and 82 |

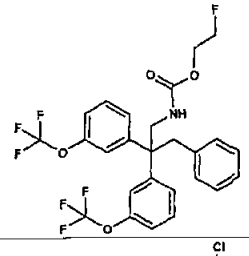
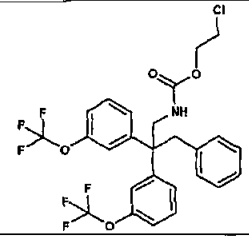
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 934 |  | 2-fluoroethyl 3-phenyl-2,2-bis(3-(trifluoromethoxy) phenyl)propylcarbamate | 4.20 LC (4) 546.14 $[M+H]^+$ | Procedures 11, 6 and 82 |
| 935 |  | 2-chloroethyl 3-phenyl-2,2-bis(3-(trifluoromethoxy) phenyl)propylcarbamate | 4.28 LC (4) 562.08 $[M+H]^+$ | Procedures 11, 6 and 82 |

**TABLE 17**

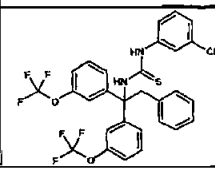
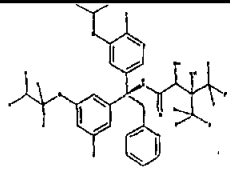
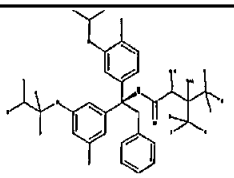
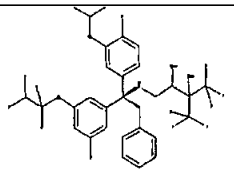
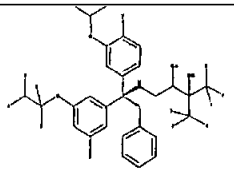
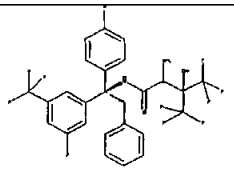
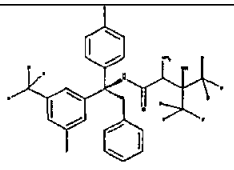
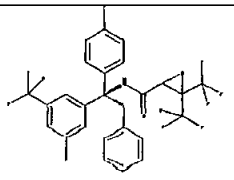
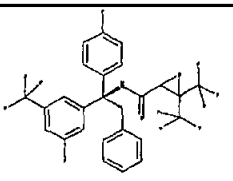
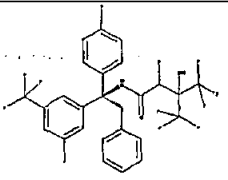
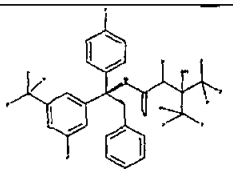
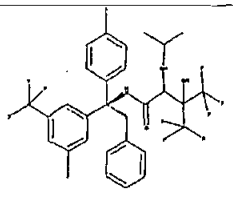
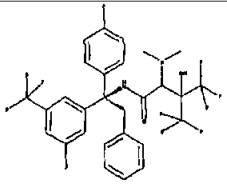
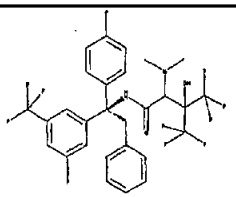
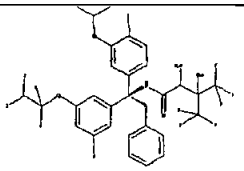
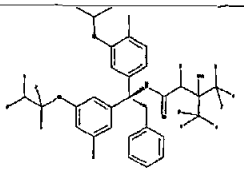
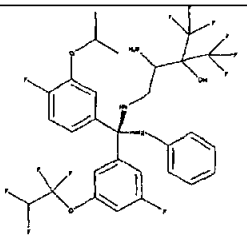
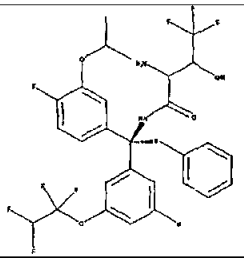
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 936 |  | 1-(3-chlorophenyl)-3-(2-phenyl-1,1-bis(3-(trifluoromethoxy) phenyl)ethyl)thiourea | 4.51 LC (1) 612.5 $[M+H]^+$ | Procedures 11, 6 and 83 |

**Table 18**

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 937 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl) butanamide | 4.181 LC (11) 708.38 $[M+H]^+$ RT = 40 min (AD, EtOH/MeOH/heptane, 4% isocratic, 40 mL/min) | Procedures 3, 109, 110, 111, 112, 113, 114, 84, 85 and 86 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 938 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-2,3-dihydroxy-3-(trifluoromethyl) butanamide | 4.178 LC (11) 708.39 $[M+H]^+$ RT = 50 min (AD, EtOH/MeOH/heptane, 4% isocratic, 40 mL/min) | Procedures 3, 109, 110, 111, 112, 113, 114, 84, 85 and 86 |
| 939 |  | 1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-2-(trifluoromethyl)butane-2,3-diol | 4.12 LC (11) 694.39 $[M+H]^+$ (prepared from precursor Example 937) | Procedures 3, 109, 110, 111, 112, 113, 114, 84, 85, 86 and 89 |
| 940 |  | 1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-2-(trifluoromethyl)butane-2,3-diol | 4.108 LC (11) 694.39 $[M+H]^+$ (prepared from precursor Example 938) | Procedures 3, 109, 110, 111, 112, 113, 114, 84, 85, 86 and 89 |
| 941 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 2.065 LC (2) 601.2 $[M+H]^+$ RT = 11.458 min (PrepHPLC, YMC Sunfire 5μ, C18, 30 X 100 mm, MeOH/$H_2O$/TFA, 30-100% over 12 min) | Procedures 4, 5, 6, 90, 91 and 92 |
| 942 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 2.085 LC (2) 601.3 $[M+H]^+$ RT = 11.619 min (PrepHPLC, YMC Sunfire 5μ, C18, 30 X 100 mm, MeOH/$H_2O$/TFA, 30-100% over 12 min) | Procedures 4, 5, 6, 90, 91 and 92 |
| 943 |  | N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl) oxirane-2-carboxamide | 4.186 LC 582.3 $[M-H]^-$ RT = 28-30 min (AD, IPA/heptane, 5% isocratic, 50 mL/min) | Procedures 4, 5, 6, 90 and 91 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 944 |  | N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3,3-bis(trifluoromethyl) oxirane-2-carboxamide | 4.161 LC 582.3 $[M-H]^-$ RT = 40-45 min (AD, IPA/heptane, 5% isocratic, 50 mL/min) | Procedures 4, 5, 6, 90 and 91 |
| 945 |  | 2,4,4,4-tetrafluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl)phenyl) -1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 3.98 LC (3) 602.3 $[M-H]^-$ RT = 26.94 min (PrepHPLC, YMC Sunfire 5 μ, C18, 30 X 100mm, MeOH/$H_2O$/TFA, 40-100% over 30 min) | Procedures 4, 5, 6, 90, 91 and 93 |
| 946 |  | 2,4,4,4-tetrafluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 4.043 LC (3) 602.3 $[M-H]^-$ RT = 27.40 min (PrepHPLC, YMC Sunfire 5 μ, C18, 30 X 100mm, MeOH/$H_2O$/TFA, 40-100% over 30 min) | Procedures 4, 5, 6, 90, 91 and 93 |
| 947 |  | 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-2-(isopropylamino)-3-(trifluoromethyl) butanamide | 4.258 LC 643.4 $[M+H]^+$ (prepared from precursor Example 944) | Procedures 4, 5, 6, 90, 91 and 95 |
| 948 |  | 2-(dimethylamino)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 4.013 LC 629.2 $[M+H]^+$ (prepared from precursor Example 944) | Procedures 4, 5, 6, 90, 91 and 95 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 949 |  | 2-(dimethylamino)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-1-(4-fluorophenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 4.348 LC 629.3 $[M+H]^+$ (prepared from precursor Example 943) | Procedures 4, 5, 6, 90, 91 and 95 |
| 950 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 2.118 LC (2) 707.4 $[M+H]^+$ (prepared from precursor Example 292B) | Procedures 3, 109, 110, 111, 112, 113, 114, 90, 91 and 92 |
| 951 |  | 2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-hydroxy-3-(trifluoromethyl) butanamide | 2.27 LC (2) 710.8 $[M+H]^+$ (prepared from precursor Example 292B) | Procedures 3, 109, 110, 111, 112, 113, 114, 90, 91 and 92 |
| 952 |  | 3-amino-1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethylamino)-2-(trifluoromethyl)butan-2-ol | 2.06 LC (1) 693.1 $[M+H]^+$ (prepared from precursor Example 950) | Procedures 109, 110, 111, 112, 113, 114, 90, 91, 92 and 145 |
| 953 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-hydroxybutanamide | 3.69 LC (1) 639.1 $[M+H]^+$ Precursor epoxide chiral retention time 12.52 min:Chiralpak AD 4.6 x 250mm 10% heptane/IPA | Procedures 3, 109, 110, 111, 112, 113, 114, 90, 91 and 92 |

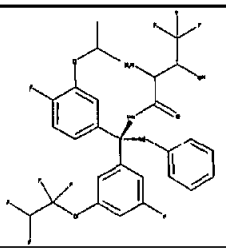
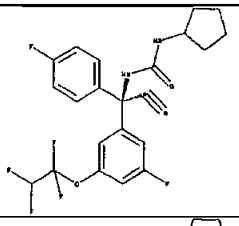
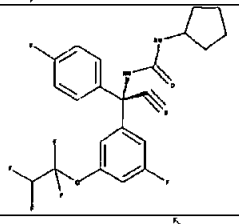
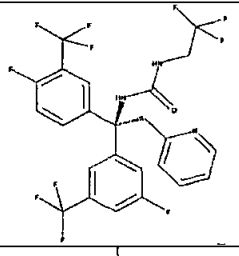
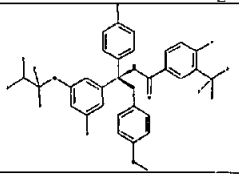
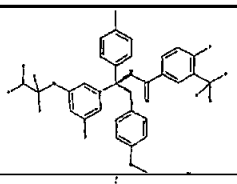
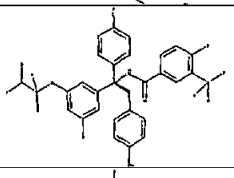
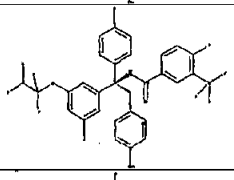
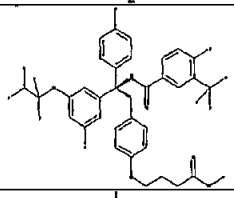
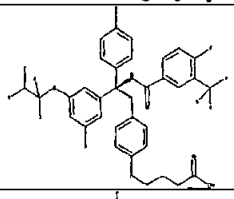
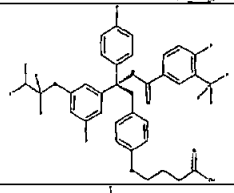
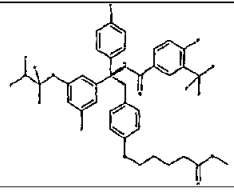
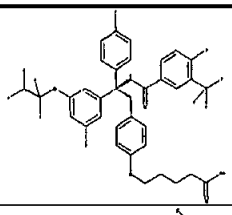
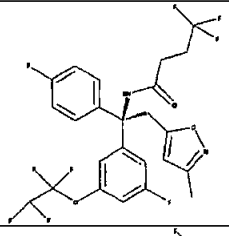
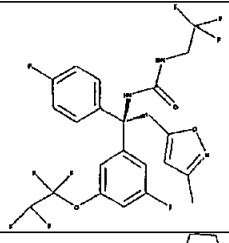
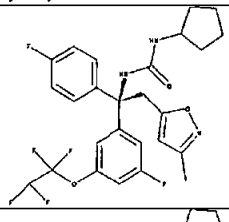
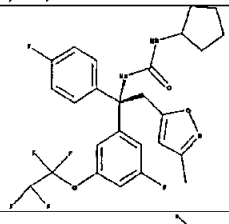
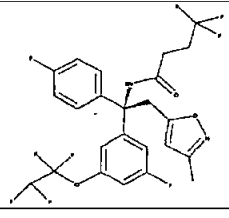
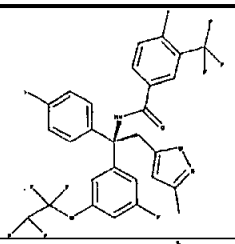
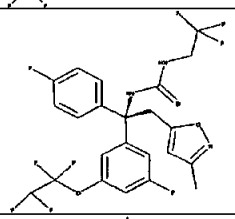
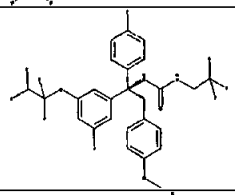
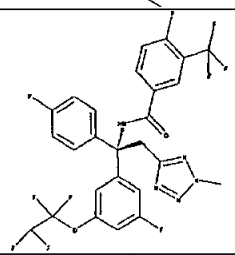
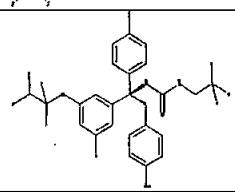
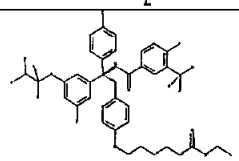
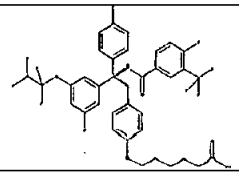
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 954 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-3-hydroxybutanamide | 3.67 LC (1) 639.1 $[M+H]^+$ Precursor epoxide chiral retention time 7.77 min:Chiralpak AD 4.6 x 250mm 10% heptane/IPA | Procedures 3, 109, 110, 111, 112, 113, 114, 90, 91 and 92 |

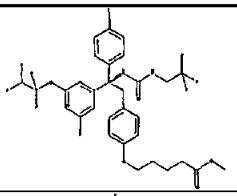
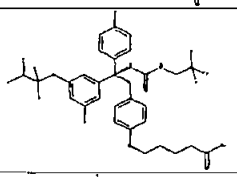
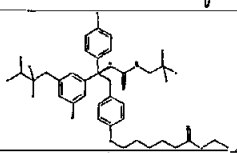
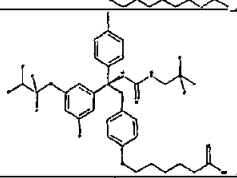
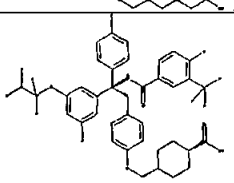
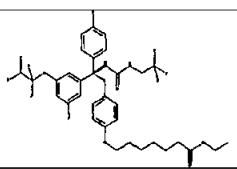
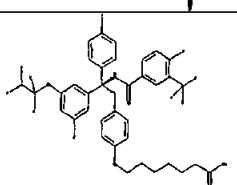
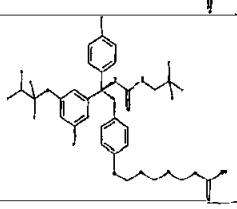
**TABLE 19**

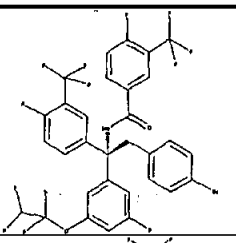
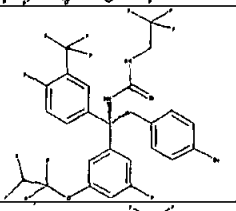
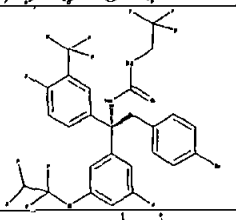
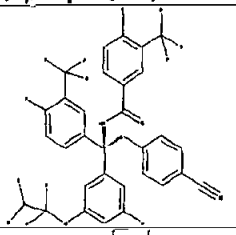
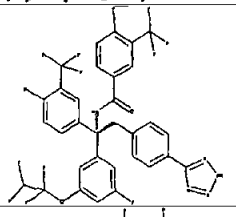
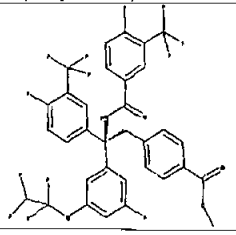
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 955 |  | (R)-1-(cyano(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)(4-fluorophenyl) methyl)-3-cyclopentylurea | 3.71 LC (1) 472.20 $[M+H]^+$ | Procedures 3, 4, 18, 6 and 2 |
| 956 |  | (S)-1-(cyano(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)(4-fluorophenyl) methyl)-3-cyclopentylurea | 3.71 LC (1) 472.20 $[M+H]^+$ | Procedures 3, 4, 18, 6 and 2 |
| 957 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(trifluoromethyl) phenyl)-2-(pyridin-2-yl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.25 LC (1) 572.04 $[M+H]^+$ | Procedures 4, 5, 6, 2 and 9 |
| 958 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.326 LC (11) 646.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |

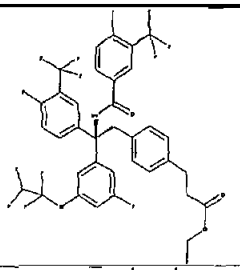
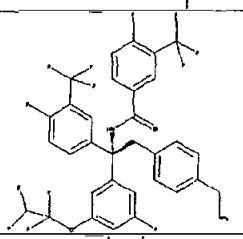
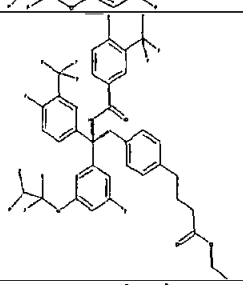
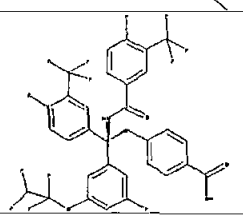
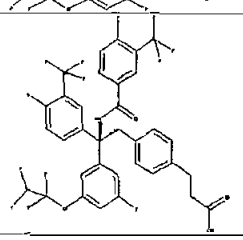
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 959 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.326 LC (11) 646.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 960 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-(4-hydroxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.146 LC (11) 632.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7 and 59 |
| 961 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-(4-hydroxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.146 LC (11) 632.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7 and 59 |
| 962 |  | (R)-methyl 4-(4-(2-(4-fluoro-3-(trifluoromethyl) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl) ethyl)phenoxy)butanoate | 4.326 LC (11) 732.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |
| 963 |  | (R)-4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-fluorophenyl)ethyl) phenoxy)butanoic acid | 4.215 LC (11) 718.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 68 and 23 |
| 964 |  | (S)-4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-fluorophenyl)ethyl) phenoxy)butanoic acid | 4.193 LC (11) 718.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 68 and 23 |
| 965 |  | (R)-methyl 5-(4-(2-(4-fluoro-3-(trifluoromethyl) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl) ethyl)phenoxy)pentanoate | 2.217 LC (2) 746.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 68 |

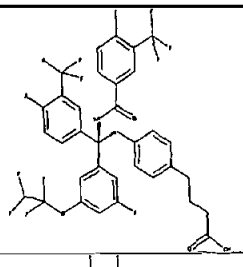
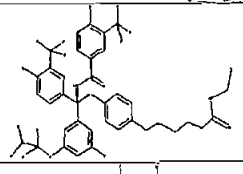
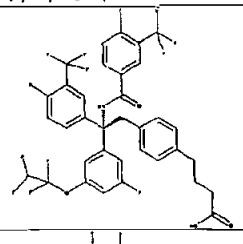
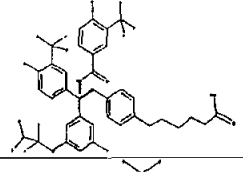
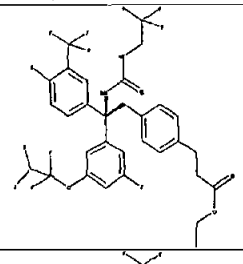
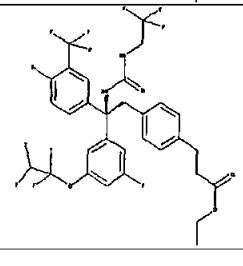
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 966 |  | (R)-5-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-fluorophenyl)ethyl) phenoxy)pentanoic acid | 4.230 LC (11) 732.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 68 and 23 |
| 967 |  | (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl) butanamide | 3.73 LC (1) 555.65 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17 and 128 |
| 968 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.70 LC (1) 556.68 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17, 2 and 9 |
| 969 |  | (R)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl)urea | 3.80 LC (1) 542.74 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17 and 2 |
| 970 |  | (S)-1-cyclopentyl-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl)urea | 3.84 LC (1) 542.79 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17 and 2 |
| 971 |  | (S)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl)butanamide | 3.77 LC (1) 555.73 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17 and 128 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 972 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl)-3-(trifluoromethyl)benzamide | 4.00 LC (1) 621.71 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17 and 7 |
| 973 |  | (S)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(3-methylisoxazol-5-yl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.71 LC (1) 556.68 $[M+H]^+$ | Procedures 3, 4, 5, 6, 17, 2 and 9 |
| 974 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(4-methoxyphenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 4.118 LC 581.1 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 25 |
| 975 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-(2-methyl-2H-tetrazol-5-yl)ethyl)-3-(trifluoromethyl) benzamide | 3.97 LC 622.67 $[M+H]^+$ | Procedures 3, 4, 5, 18, 6, 7, 79 and 80 |
| 976 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-1-(4-fluorophenyl)-2-(4-hydroxyphenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 1.945 LC (2) 567.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25 and 59 |
| 977 |  | (R)-ethyl 6-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-fluorophenyl)ethyl) phenoxy)hexanoate | 2.277 LC (2) 774.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59 and 129 |
| 978 |  | (R)-6-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-fluorophenyl)ethyl) phenoxy)hexanoic acid | 2.172 LC (2) 746.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 129 and 23 |

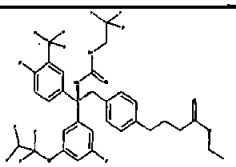
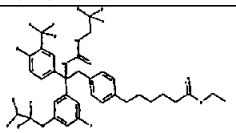
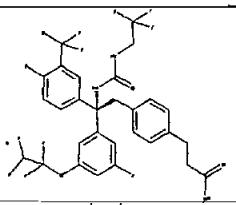
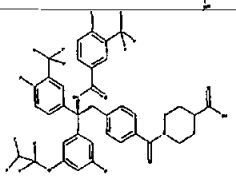
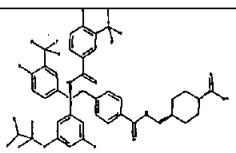
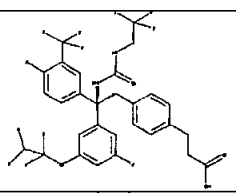
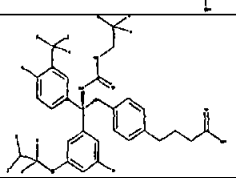
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 979 |  | (R)-methyl 5-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenoxy)pentanoate | 2.092 LC (2) 681.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 59 and 68 |
| 980 |  | (R)-5-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenoxy)pentanoic acid | 2.058 LC (2) 667.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 59, 68 and 23 |
| 981 |  | (R)-ethyl 6-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenoxy)hexanoate | 2.188 LC (2) 709.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 59 and 129 |
| 982 |  | (R)-6-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenoxy)hexanoic acid | 2.097 LC (2) 681.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 59, 129 and 23 |
| 983 |  | (1r,4r)-4-((4-((R)-2-(4-fluoro-3-(trifluoromethyl) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl) ethyl)phenoxy)methyl) cyclohexanecarboxylic acid | 2.207 LC (2) 772.1 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 129 and 23 |
| 984 |  | (R)-ethyl 7-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenoxy)heptanoate | 2.232 LC (2) 723.3 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 59 and 129 |
| 985 |  | (R)-7-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-fluorophenyl)ethyl) phenoxy)heptanoic acid | 2.202 LC (2) 760.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 7, 59, 129 and 23 |
| 986 |  | (R)-7-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-(4-fluorophenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenoxy)heptanoic acid | 2.130 LC (2) 695.2 $[M+H]^+$ | Procedures 3, 4, 5, 6, 25, 59, 129 and 23 |

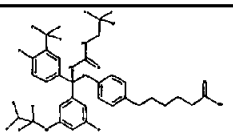
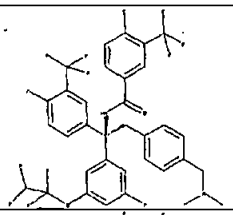
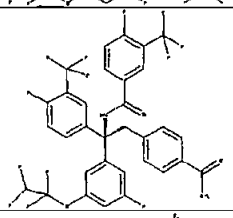
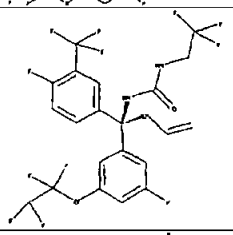
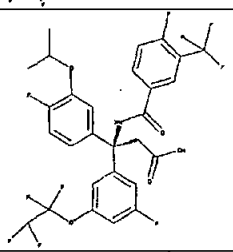
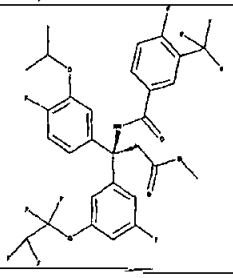
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 987 |  | (S)-N-(2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.30 LC (2) 763.8 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98 and 7 |
| 988 |  | (R)-1-(2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-3-(2,2,2-trifluoroethyl)urea | 4.04 LC (6) 698.0 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98 and 25 |
| 989 |  | (S)-1-(2-(4-bromophenyl)-1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-3-(2,2,2-trifluoroethyl)urea | 4.05 LC (6) 699.0 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98 and 25 |
| 990 |  | (R)-N-(2-(4-cyanophenyl)-1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.130 LC (2) 709.0 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7 and 56 |
| 991 |  | (S)-N-(2-(4-(2H-tetrazol-5-yl)phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.26 LC (6) 752.3 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7 and 99 |
| 992 |  | (R)-methyl 4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)benzoate | 2.17 LC (2) 742.19 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56 and 57 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 993 |  | (R)-ethyl 3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)propanoate | 4.49 LC (6) 784.34 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98 and 24 |
| 994 |  | (S)-N-(2-(4-(aminomethyl) phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.3 LC (6) 713.31 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56 and 101 |
| 995 |  | (R)-ethyl 4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)butanoate | 4.39 LC (6) 798.36 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7 and 25 |
| 996 |  | (R)-4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)benzoic acid | 2.11 LC (2) 728.32 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56, 57 and 23 |
| 997 |  | (R)-3-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)propanoic acid | 4.12 LC (6) 756.3 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 24 and 23 |

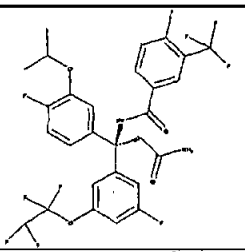
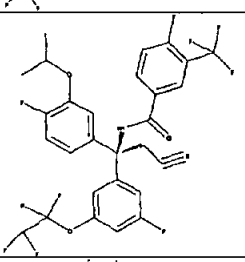
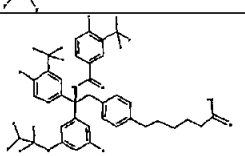
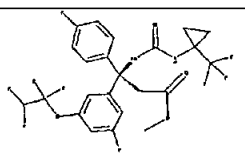
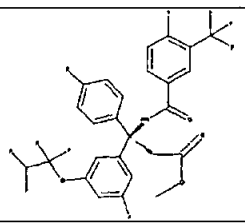
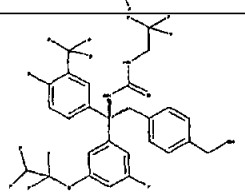
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 998 |  | (R)-4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)butanoic acid | 4.18 LC (6) 770.0 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 24 and 23 |
| 999 |  | (R)-ethyl 6-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)hexanoate | 4.54 LC (6) 826.52 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7 and 24 |
| 1000 |  | (S)-4-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)butanoic acid | 4.16 LC (6) 770.3 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 24 and 23 |
| 1001 |  | (S)-6-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)hexanoic acid | 4.20 LC (6) 798.47 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 24 and 23 |
| 1002 |  | (S)-ethyl 3-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)propanoate | 4.15 LC (6) 719.37 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25 and 24 |
| 1003 |  | (R)-ethyl 3-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)propanoate | 2.20 LC (2) 719.4 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25 and 24 |

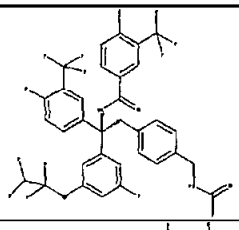
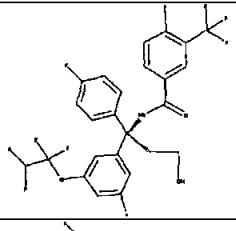
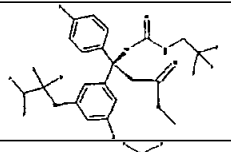
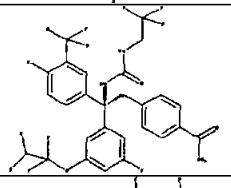
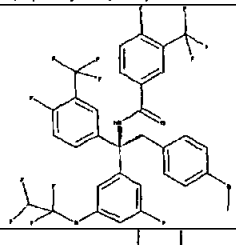
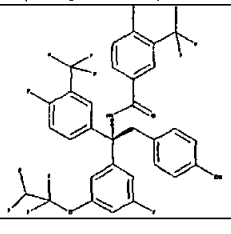
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| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1004 |  | (R)-ethyl 4-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)butanoate | 4.22 LC (6) 733.39 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25 and 24 |
| 1005 |  | (R)-ethyl 6-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)hexanoate | 4.34 LC (6) 761.47 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25 and 24 |
| 1006 |  | (S)-3-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)propanoic acid | 3.97 LC (6) 691.36 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25, 24 and 23 |
| 1007 |  | (R)-1-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl) phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)benzoyl)piperidine-4-carboxylic acid | 4.0 LC (6) 839.5 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56, 57, 23 and 103 |
| 1008 |  | (1r,4r)-4-((4-((R)-2-(4-fluoro-3-(trifluoromethyl) benzamido)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)benzamido)methyl) cyclohexanecarboxylic acid | 4.0 LC (6) 867.5 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56, 57, 23 and 103 |
| 1009 |  | (R)-3-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)propanoic acid | 4.0 LC (6) 691.37 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25, 24 and 23 |
| 1010 |  | (R)-4-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)butanoic acid | 4.02 LC (6) 705.4 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25, 24 and 23 |

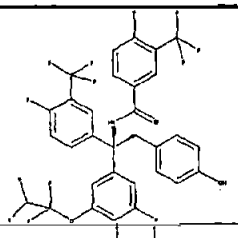
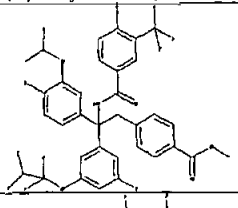
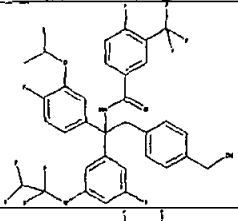
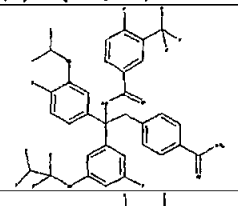
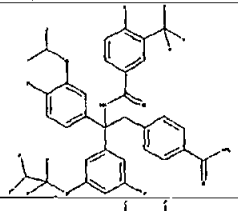
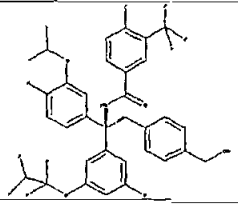
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1011 |  | (R)-6-(4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)phenyl)hexanoic acid | 4.2 LC (6) 733.5 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 25, 24 and 23 |
| 1012 |  | (R)-N-(2-(4-((dimethylamino) methyl)phenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 3.45 LC (6) 741.5 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56, 57, 100 and 102 |
| 1013 |  | (R)-N-(2-(4-carbamoylphenyl)-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 3.97 LC (6) 727.41 $[M+H]^+$ | Procedures 3, 4, 72, 96, 97, 98, 7, 56, 57, 23 and 103 |
| 1014 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)but-3-enyl)-3-(2,2,2-trifluoroethyl) urea | 568.355 | Procedures 3, 4, 5, 6 and 10 |
| 1015 |  | (R)-3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(4-fluoro-3-isopropoxyphenyl)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) propanoic acid | 641.454 | Procedures 3, 4, 5, 14, 6, 7, 59, 68 and 23 |
| 1016 |  | (R)-methyl 3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(4-fluoro-3-isopropoxyphenyl)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) propanoate | 655.481 | Procedures 3, 4, 5, 14, 6, 7, 59 and 68 |

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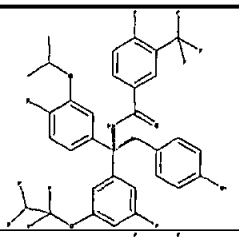
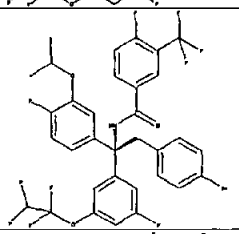
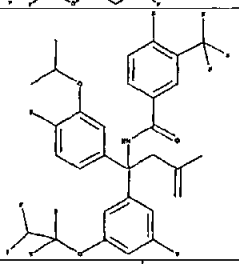
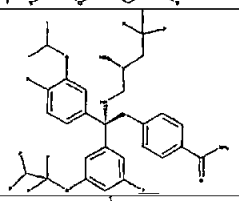
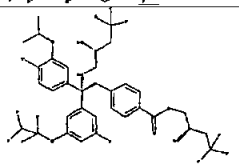
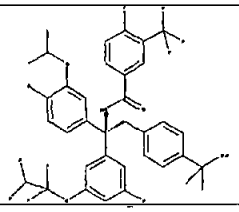
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1017 |  | (R)-N-(3-amino-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-oxopropyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.0 LC (2) 641.2 $[M+H]^+$ | Procedures 3, 4, 5, 14, 6, 7, 59, 68, 23 and 103 |
| 1018 |  | (R)-N-(2-cyano-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.0 LC (2) 623.5 $[M+H]^+$ | Procedures 3, 4, 5, 18, 6, 7, 59 and 68 |
| 1019 |  | (R)-6-(4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)phenyl)hexanoic acid | 4.3 LC (6) 798.4 $[M+H]^+$ | Procedures 3, 4, 96, 97, 98, 24 and 23 |
| 1020 |  | (R)-methyl 3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-3-(4-fluorophenyl)-3-(3-(1-(trifluoromethyl) cyclopropyl)ureido)propanoat e | 1.94 LC (2) 559.4 $[M+H]^+$ | Procedures 3, 4, 5, 14, 6 and 30 |
| 1021 |  | (R)-methyl 3-(4-fluoro-3-(trifluoromethyl)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(4-fluorophenyl)propanoate | 3.95 LC (1) 598.2 $[M+H]^+$ | Procedures 3, 4, 5, 14, 6 and 7 |
| 1022 |  | (R)-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl) phenyl)ethyl)-3-(2,2,2-trifluoroethyl)urea | 3.8 LC (6) 649.3 $[M+H]^+$ | Procedures 3, 4, 96, 97, 98, 56, and 100 |

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1023 |  | (R)-N-(2-(4-(acetamidomethyl)phenyl)-1-(4-fluoro-3-(trifluoromethyl) phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 4.0 LC (6) 755.38 $[M+H]^+$ | Procedures 3, 4, 96, 97, 98, 56, 101 and 65 |
| 1024 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-3-hydroxypropyl)-3-(trifluoromethyl)benzamide | 2.05 LC (2) 570.5 $[M+H]^+$ | Procedures 3, 4, 5, 14, 6, 7 and 100 |
| 1025 |  | (R)-methyl 3-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-3-(4-fluorophenyl)-3-(3-(2,2,2-trifluoroethyl)ureido) propanoate | 3.39 LC (1) 533.2 $[M+H]^+$ | Procedures 3, 4, 5, 14, 6 and 25 |
| 1026 |  | (R)-4-(2-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(3-(2,2,2-trifluoroethyl)ureido) ethyl)benzamide | 3.74 LC (6) 662.3 $[M+H]^+$ | Procedures 3, 4, 96, 97, 98, 56, 57, 23 and 103 |
| 1027 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-methoxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 4.3 LC (6) 714.0 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 7 |
| 1028 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-hydroxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 2.2 LC (2) 700.0 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 and 59 |

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| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1029 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-hydroxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 2.2 LC (2) 700.0 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 and 59 |
| 1030 |  | methyl 4-(2-(4-fluoro-3-(trifluoromethyl)benzamido)-2-(4-fluoro-3-isopropoxyphenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)benzoate | 2.3 LC (2) 731.9 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56 and 57 |
| 1031 |  | 4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 2.17 LC (2) 704.0 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57 and 100 |
| 1032 |  | N-(2-(4-carbamoylphenyl)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.13 LC (2) 716.9 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57, 23 and 103 |
| 1033 |  | N-(2-(4-carbamoylphenyl)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.13 LC (2) 716.9 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57, 23 and 103 |
| 1034 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(hydroxymethyl)phenyl) ethyl)-3-(trifluoromethyl) benzamide | 2.17 LC (2) 704.1 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57 and 100 |

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| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1035 |  | (R)-N-(2-(4-bromophenyl)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.17 LC (2) 753.8 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176 and 7 |
| 1036 |  | (S)-N-(2-(4-bromophenyl)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl) ethyl)-4-fluoro-3-(trifluoromethyl)benzamide | 2.17 LC (2) 753.8 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176 and 7 |
| 1037 |  | 4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-methylbut-3-enyl)-3-(trifluoromethyl)benzamide | 2.19 LC (2) 638.9 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176 and 7 |
| 1038 |  | 4-((S)-2-(4-fluoro-3-isopropoxyphenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-((R)-4,4,4-trifluoro-2-hydroxybutylamino)ethyl) benzamide | 1.93 LC (2) 653.0 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 56, 57, 23, 136, 27 and 8 |
| 1039 |  | (R)-4,4,4-trifluoro-2-hydroxybutyl 4-((S)-2-(4-fluoro-3-isopropoxyphenyl)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-((R)-4,4,4-trifluoro-2-hydroxybutylamino)ethyl) benzoate | 2.08 LC (2) 780.0 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 56, 57, 23, 136, 27 and 8 |
| 1040 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-(2-hydroxypropan-2-yl)phenyl)ethyl)-3-(trifluoromethyl)benzamide | 2.2 LC (2) 714.0 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 52 and 53 |

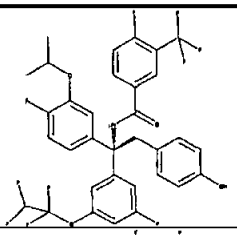
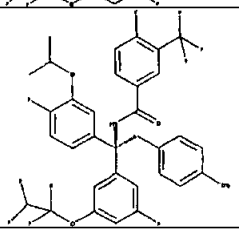
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1041 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-hydroxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 2.15 LC (2) 689.9 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 and 59 |
| 1042 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy)phenyl)-2-(4-hydroxyphenyl)ethyl)-3-(trifluoromethyl)benzamide | 2.15 LC (2) 689.9 $[M+H]^+$ | Procedures 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 and 59 |

**TABLE 20**

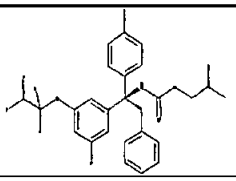
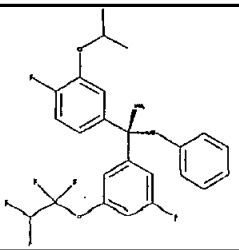
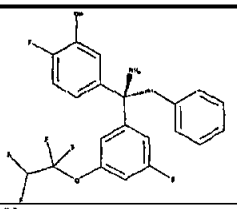
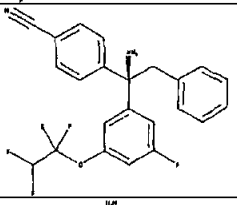
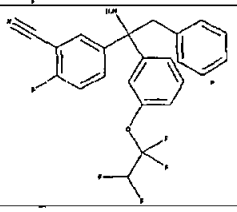
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1043 |  | (R)-isobutyl 1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-1-(4-fluorophenyl)-2-phenylethylcarbamate | 2.165 LC (2) 526.02 $[M+H]^+$ | Procedures 3, 4, 5, 6 and 82 |

**TABLE 21**

| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1044 |  | (R)-1-(4-fluoro-3-isopropoxyphenyl)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethanamine | 1.89 LC (2) 467.46 $[M-NH_2]$ | Procedure 109, 110, 111, 112, 113 and 114 |

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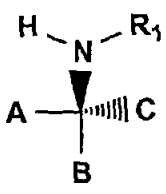
| Ex. No. | Structure | Name | Retention Time Min./ Molecular Mass | Prepared in the manner described in: |
|---|---|---|---|---|
| 1045 |  | (R)-5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-2-fluorophenol | 1.70 LC (2) 425.1 [M-$NH_2$] | Procedure 109, 110, 111, 112, 113 and 114 |
| 1046 |  | (R)-4-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl) benzonitrile | 1.02 LC (12) 433 $[M+H]^+$ | Procedures 3, 4, 5, 6, and 56 |
| 1047 |  | 5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroethoxy) phenyl)-2-phenylethyl)-2-fluorobenzonitrile | 3.281 LC (11) 451 $[M+H]^+$ | Procedures 3, 62, 5, 6 and 56 |

**[00538]** It is noted that the proceeding examples, while illustrative of the present invention, are not in sequential order and some example numbers may be missing.

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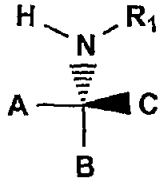
**WHAT IS CLAIMED IS:**

1. A compound of formula Ia or Ib




Ia

or




Ib

or stereoisomers or prodrugs or pharmaceutically acceptable salt forms thereof, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) –$S(O)_pR_6$, 18) –$SO_2NHR_6$, 19) –$COOR_6$, 20) –$NHC(CN)NHR_6$, 21) –$CONR_6R_6$, 22) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 23) ($C_2$-$C_6$)-alkenyl, which may be optionally substituted with one or more $R_{20}$'s, 24) –$OCOR_6$, 25) –$OCOOR_6$, 26) -$OCONR_6R_6$, or 27) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl,

which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$, 20) –$CONR_6R_6$; and 21) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(b) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$, 20) –$CONR_6R_6$; and 21) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

C is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be

optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, 17) –NHC(CN)$NHR_6$; and 18) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl; and 15) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, 17) –NHC(CN)$NHR_6$; and 18) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(d) heterocyclo, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be

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optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) –$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, 17) –$NHC(CN)NHR_6$; and 18) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is H, –$C(O)R_3$, -$C(O)NR_2R_3$, -$C(O)OR_4$, -$SO_2R_5$, -$C(S)NHR_7$, -$CR_8R_8R_8$, or -$C(S)R_3$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$; and 20) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$,

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19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, 22) $-NHC(CN)NHR_6$; and 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;or

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1-C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo$(C_1-C_6)$alkyl, 15) $-CO(C_1-C_6)$-alkyl, 16) -COOH, 17) $-CO_2(C_1-C_6)$-alkyl, 18) $-CONR_6R_6$, 19) $(C_2-C_6)$-alkenyl, 20) $(C_2-C_6)$-alkynyl; and 21) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1-C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo$(C_1-C_6)$alkyl, 12) $-CONR_6R_6$, 13) $(C_2-C_6)$-alkenyl, 14) $(C_2-C_6)$-alkynyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$; and 20) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1-C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$,

20) –S(O)$_p$R$_6$, 21) –SO$_2$NHR$_6$, 22) –COOR$_6$, 23) –NHC(CN)NHR$_6$; and 24) cycloalkyl, which may be optionally substituted with one or more R$_{20}$'s;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) (C$_1$-C$_6$)-alkyl, which may be optionally substituted with one or more R$_{20}$'s, 3) -OR$_6$, 4) (C$_1$-C$_6$)-alkylthio, 5) cyano, 6) nitro, 7) -NR$_9$R$_{10}$, 8) aryl, which may be optionally substituted with one or more R$_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more R$_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more R$_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 14) halo(C$_1$-C$_6$)alkyl, 15) -CONR$_6$R$_6$, 16) (C$_2$-C$_6$)-alkenyl, 17) =O, 18) (C$_2$-C$_6$)-alkynyl, 19) –COR$_6$, 20) –S(O)$_p$R$_6$, 21) –SO$_2$NHR$_6$, 22) –COOR$_6$, 23) –NHC(CN)NHR$_6$; and 24) cycloalkyl, which may be optionally substituted with one or more R$_{20}$'s;or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) (C$_1$-C$_6$)-alkyl, which may be optionally substituted with one or more R$_{20}$'s, 3) -OR$_6$, 4) (C$_1$-C$_6$)-alkylthio, 5) cyano, 6) nitro, 7) -NR$_9$R$_{10}$, 8) aryl, which may be optionally substituted with one or more R$_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more R$_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more R$_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 14) halo(C$_1$-C$_6$)alkyl, 15)-CONR$_6$R$_6$, 16) (C$_2$-C$_6$)-alkenyl, 17) (C$_2$-C$_6$)-alkynyl, 18) –COR$_6$, 19) –S(O)$_p$R$_6$, 20) –SO$_2$NHR$_6$, 21) –COOR$_6$, 22) –NHC(CN)NHR$_6$; and 23) cycloalkyl, which may be optionally substituted with one or more R$_{20}$'s;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_4$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) ($C_2$-$C_6$)-alkenyl; or

(e) ($C_2$-$C_6$)-alkynyl;

$R_5$ is arylalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, 23) –$NHC(CN)NHR_6$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH,

3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, 24) –$NHC(CN)NHR_{36}$; and 25) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(*d*) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$,

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23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) $-OR_{36}$, 5) $(C_1-C_6)$-alkylthio, 6) cyano, 7) nitro, 8) $-NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo$(C_1-C_6)$alkyl, 13) $(C_2-C_6)$-alkenyl, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) $(C_2-C_6)$-alkynyl, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) $-OR_{36}$, 5) $(C_1-C_6)$-alkylthio, 6) cyano, 7) nitro, 8) $-NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo$(C_1-C_6)$alkyl, 13) $(C_2-C_6)$-alkenyl, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) $(C_2-C_6)$-alkynyl, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_7$ is aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1-C_6)$-alkyl, which may be

optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, 23) –$NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

$R_8$ can independently be:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, 18) –$S(O)_pR_{26}$, 19) –$SO_2NHR_{26}$, 20) –$COOR_{26}$, 21) –$NHC(CN)NHR_{26}$; and 22) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(c) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may

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be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, 23) – $NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, 23) – $NHC(CN)NHR_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(e) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, 23) –

NHC(CN)NHR$_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more R$_{20}$'s;or

(f) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) (C$_1$-C$_6$)-alkyl, which may be optionally substituted with one or more R$_{20}$'s, 3) -OR$_{26}$, 4) (C$_1$-C$_6$)-alkylthio, 5) cyano, 6) nitro, 7) -NR$_9$R$_{10}$, 8) aryl, which may be optionally substituted with one or more R$_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more R$_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more R$_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 14) halo(C$_1$-C$_6$)alkyl, 15) (C$_2$-C$_6$)-alkenyl, 16) -CONR$_{26}$R$_{26}$, 17) =O, 18) (C$_2$-C$_6$)-alkynyl, 19) –COR$_{26}$, 20) –S(O)$_p$R$_{26}$, 21) –SO$_2$NHR$_{26}$, 22) –COOR$_{26}$, 23) –NHC(CN)NHR$_{26}$; and 24) cycloalkyl, which may be optionally substituted with one or more R$_{20}$'s;

or two R$_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more R$_{20}$'s;

R$_9$ and R$_{10}$ are independently: (a) hydrogen; (b) –[(C=O)O$_r$]$_s$aryl, wherein the aryl may be optionally substituted with one or more R$_{20}$'s; (c) –[(C=O)O$_r$]$_s$(C$_2$-C$_8$)-alkenyl, wherein the alkenyl may be optionally substituted with one or more R$_{20}$'s; (d) –[(C=O)O$_r$]$_s$(C$_1$-C$_8$)alkyl, wherein the alkyl may be optionally substituted with one or more R$_{20}$'s; (e) heterocyclyl optionally substituted with one or more R$_{20}$'s; (f) –CONR$_{26}$R$_{26}$; (g) -(C$_2$-C$_6$)-alkynyl; (h) –COR$_{26}$; (i) –S(O)$_p$R$_{26}$; (j) –SO$_2$NHR$_{26}$; (k) –COOR$_{26}$; (l) –NHC(CN)NHR$_{26}$; or m) –[(C=O)O$_r$]$_s$cycloalkyl, which may be optionally substituted with one or more R$_{20}$'s;

or R$_9$ and R$_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more R$_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) =O; (q) -($C_2$-$C_6$)-alkynyl; (r) –$COR_{26}$; (s) –$S(O)_pR_{26}$; (t) –$SO_2NHR_{26}$; (u) –$COOR_{26}$; (v) –$NHC(CN)NHR_{26}$; (w) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (x) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (y) –$CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) –$CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) =O; (r) ($C_2$-$C_6$)-alkynyl; (s) cycloalkyl; (t) cycloalkylalkyl; (u) –$COR_{26}$; (v) –$S(O)_pR_{26}$; (w) –$SO_2NHR_{26}$; (x) –$COOR_{26}$; or (y) –$NHC(CN)NHR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$; and 23) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, 24) –$NHC(CN)NHR_{36}$; and 25) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –$NHC(CN)NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which

may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –NHC(CN)$NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, 25) –NHC(CN)$NHR_{36}$; and 26) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl,

13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

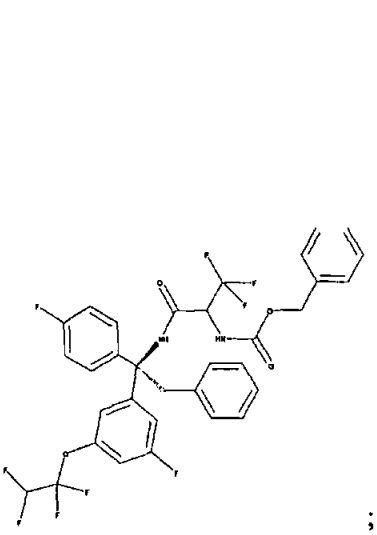
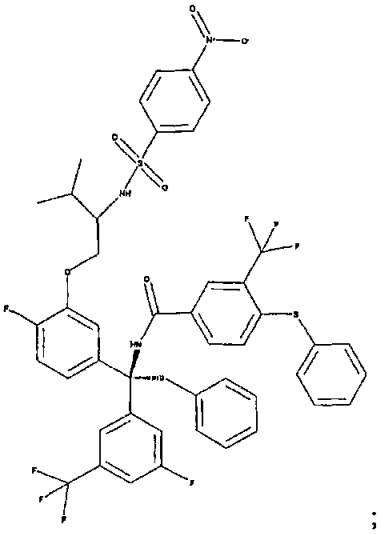
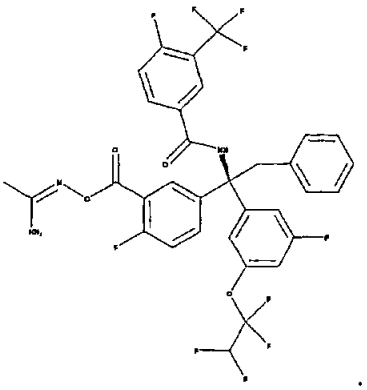
or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, –$[(C=O)O_r]_s$aryl, –$[(C=O)O_r]_s$alkenyl, –$[(C=O)O_r]_s$alkyl, heterocyclyl, –$CONR_{46}R_{46}$, alkynyl, –$COR_{36}$, –$S(O)_pR_{36}$, –$SO_2NHR_{36}$, –$COOR_{36}$, –$C(CN)NHR_{36}$, or cycloalkyl, wherein the aryl, alkyl, alkenyl, cycloalkyl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

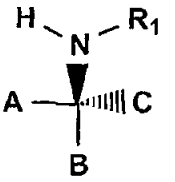
or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

713 710 712


;

;


2. A compound of claim 1, wherein the compound is a compound of formula Ia




Ia

3. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) –$S(O)_pR_6$, 18) –$SO_2NHR_6$, 19) –$COOR_6$, 20) –$NHC(CN)NHR_6$, 21) –$CONR_6R_6$, 22) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 23) ($C_2$-$C_6$)-alkenyl, which may be optionally substituted with one or more $R_{20}$'s, 24) –$OCOR_6$, 25) –$OCOOR_6$, or 26) -$OCONR_6R_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$, and 20) –$CONR_6R_6$; or

(b) heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be

optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$;

C is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, and 17) $-NHC(CN)NHR_6$;

(b) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl; or

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) –$S(O)_pR_6$, 15) –$SO_2NHR_6$, 16) –$COOR_6$, and 17) –$NHC(CN)NHR_6$;

$R_1$ is H, –$C(O)R_3$, -$C(O)NR_2R_3$, -$C(O)OR_4$, -$SO_2R_5$, -$C(S)NHR_7$, -$CR_8R_8R_8$, or -$C(S)R_3$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, and 19) –$NHC(CN)NHR_6$;

(c) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may

be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) $-COR_6$, 19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, and 22) $-NHC(CN)NHR_6$; or

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-CO(C_1$-$C_6)$-alkyl, 16) -COOH, 17) $-CO_2(C_1$-$C_6)$-alkyl, 18) $-CONR_6R_6$, 19) ($C_2$-$C_6$)-alkenyl, and 20) ($C_2$-$C_6$)-alkynyl;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) $-CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, and 19) $-NHC(CN)NHR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be

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optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$; or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, 19) –$S(O)_pR_6$, 20) –$SO_2NHR_6$, 21) –$COOR_6$, and 22) –$NHC(CN)NHR_6$;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_4$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may

be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

(d) ($C_2$-$C_6$)-alkenyl; or

(e) ($C_2$-$C_6$)-alkynyl;

$R_5$ is arylalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_6$, 21) –$SO_2NHR_6$, 22) –$COOR_6$, and 23) –$NHC(CN)NHR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –NHC(CN)$NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

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(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –NHC(CN)$NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_7$ is aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –NHC(CN)$NHR_{26}$;

$R_8$ can independently be:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, 18) –$S(O)_pR_{26}$, 19) –$SO_2NHR_{26}$, 20) –$COOR_{26}$, and 21) –$NHC(CN)NHR_{26}$;

(c) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

(e) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$; or

(f) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, 20) –$S(O)_pR_{26}$, 21) –$SO_2NHR_{26}$, 22) –$COOR_{26}$, and 23) –$NHC(CN)NHR_{26}$;

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or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; (b) $-[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s; (c) $-[(C=O)O_r]_s(C_2-C_8)$-alkenyl, wherein the alkenyl may be optionally substituted with one or more $R_{20}$'s; (d) $-[(C=O)O_r]_s(C_1-C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s; (e) heterocyclyl optionally substituted with one or more $R_{20}$'s; (f) $-CONR_{26}R_{26}$; (g) $-(C_2-C_6)$-alkynyl; (h) $-COR_{26}$; (i) $-S(O)_pR_{26}$; (j) $-SO_2NHR_{26}$; (k) $-COOR_{26}$; or (l) $-NHC(CN)NHR_{26}$;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1-C_6)$alkyl; (o) $(C_2-C_6)$-alkenyl; (p) =O; (q) $-(C_2-C_6)$-alkynyl; (r) $-COR_{26}$; (s) $-S(O)_pR_{26}$; (t) $-SO_2NHR_{26}$; (u) $-COOR_{26}$; (v) $-NHC(CN)NHR_{26}$; (w) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (x) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (y) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1-C_6)$alkyl; (o) $-CONR_{26}R_{26}$;

(p) ($C_2$-$C_6$)-alkenyl; (q) =O; (r) ($C_2$-$C_6$)-alkynyl; (s) cycloalkyl; (t) cycloalkylalkyl; (u) $-COR_{26}$; (v) $-S(O)_pR_{26}$; (w) $-SO_2NHR_{26}$; (x) $-COOR_{26}$; or (y) $-NHC(CN)NHR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, and 22) $-NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, and 24) $-NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which

may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, and 25) $-NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, and 25) $-NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18)

-$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(f) hydrogen;

(g) alkynyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{20}$'s; or

(h) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, 22) –$NHC(CN)NHR_{36}$, or 23) cycloalkyl, which may be optionally substituted with one or more $R_{40}$'s;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, –$[(C=O)O_r]_s$aryl, –$[(C=O)O_r]_s$alkenyl, –$[(C=O)O_r]_s$alkyl, heterocyclyl, –$CONR_{46}R_{46}$, alkynyl, –$COR_{36}$,

$-S(O)_pR_{36}$, $-SO_2NHR_{36}$, $-COOR_{36}$, or $-C(CN)NHR_{36}$, wherein the aryl, alkyl, alkenyl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, $-NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, or $-NHC(CN)NHR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl;

r is 0 to 5;

s is 0 to 4; and

p is 1 or 2.

4. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) –$COOR_6$, 18) –$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 20) ($C_2$-$C_6$)-alkenyl, which may be optionally substituted with one or more $R_{20}$'s, 21) –$OCOR_6$, 22) –$OCOOR_6$, or 23) -$OCONR_6R_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$COOR_6$, and 17) –$CONR_6R_6$; or

(b) a nitrogen containing heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$COOR_6$, and 17) –$CONR_6R_6$;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) -$OR_6$, 3) -$NR_9R_{10}$, 4) aryl, which may be optionally substituted with one or more $R_{20}$'s, 5) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 6) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 7) -$CONR_6R_6$, and 8) –$COOR_6$;

$R_1$ is –$C(O)R_3$, -$C(O)NR_2R_3$, -$C(O)OR_4$ or –$CH_2R_8$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, and 16) –$COOR_6$;

(c) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, and 19) –$COOR_6$; or

(d) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -CO($C_1$-$C_6$)-alkyl, 16) -COOH, 17) -$CO_2$($C_1$-$C_6$)-alkyl, 18) -$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkenyl, and 20) ($C_2$-$C_6$)-alkynyl;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more

$R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, and 19) –$COOR_6$;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_4$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may

be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH,

3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-

alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; (b) $-[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s; (c) $-[(C=O)O_r]_s(C_1-C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s; or (d) heterocyclyl optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1-C_6)$alkyl; (o) $(C_2-C_6)$-alkenyl; (p) $-(C_2-C_6)$-alkynyl; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1-C_6)$alkyl; (o) $-CONR_{26}R_{26}$; (p) $(C_2-C_6)$-alkenyl; (q) $(C_2-C_6)$-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) $-COR_{26}$; or (u) $-COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –NHC(CN)$NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –NHC(CN)$NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14)

heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, and 25) $-NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, and 25) $-NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, and 25) $-NHC(CN)NHR_{36}$; or

(f) hydrogen;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, $-[(C=O)O_r]_s$aryl, $-[(C=O)O_r]_s$alkyl, or heterocyclyl, wherein the aryl, alkyl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, $-NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$ or $-COOR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl, heteroaryl or heterocyclyl, other than heteroaryl;

r is 0 to 3;

s is 0 to 2; and

p is 1 or 2.

5. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro,

7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) –$COOR_6$, 18) –$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 20) –$OCOR_6$, 21) –$OCOOR_6$, or 22) -$OCONR_6R_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COOR_6$, and 16) –$CONR_6R_6$; or

(b) a 6- to 10-membered nitrogen containing heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s,

13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) $-COOR_6$, and 16) $-CONR_6R_6$;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $-OR_6$, 3) $-NR_9R_{10}$, 4) aryl, which may be optionally substituted with one or more $R_{20}$'s, 5) a nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 6) $-CONR_6R_6$, and 7) $-COOR_6$;

$R_1$ is $-C(O)R_3$, $-C(O)NR_2R_3$, or $-CH_2R_8$;

$R_2$ is:

(a) H;

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, and 16) $-COOR_6$; or

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl,

15) -CO($C_1$-$C_6$)-alkyl, 16) -COOH, 17) -$CO_2$($C_1$-$C_6$)-alkyl, 18) -$CONR_6R_6$, 19) ($C_2$-$C_6$)-alkenyl, and 20) ($C_2$-$C_6$)-alkynyl;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(f) alkenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$,

4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15)-$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_6$, and 19) –$COOR_6$;

or $R_2$ and $R_3$ are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl,

which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

or two $R_6$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$,

4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl,

15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen, (b) –$[(C=O)O_r]_s$aryl, wherein the aryl may be optionally substituted with one or more $R_{20}$'s, or (c) –$[(C=O)O_r]_s$($C_1$-$C_8$)alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may

be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) -($C_2$-$C_6$)-alkynyl; (q) –$COR_{26}$; (r) –$COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) –$CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) –$CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) ($C_2$-$C_6$)-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) –$COR_{26}$; or (u) –$COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl,

which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$; or

(f) hydrogen;

or two $R_{26}$'s are taken together to form a 3- to 9-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{29}$ and $R_{30}$ are independently hydrogen, –$[(C=O)O_r]_s$aryl, or –$[(C=O)O_r]_s$alkyl, wherein the aryl or alkyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, -$NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl,

haloalkyloxy, $-CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, $-COR_{49}$ or $-COOR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl or heteroaryl;

r is 0 to 2;
s is 0 to 1; and
p is 1 or 2.

6. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo$(C_1$-$C_6)$alkyl, 15) $-COR_6$, 16) =O, 17) $-COOR_6$, 18) $(C_2$-$C_6)$-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, 19) $-OCOR_6$, and 20) $-OCOOR_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is:

(a) phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with

one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, and 15) $-COOR_6$; or

(b) a 6-membered nitrogen containing heteroaryl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, and 15) $-COOR_6$;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) phenyl, which may be optionally substituted with one or more $R_{20}$'s, or 3) a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is $-C(O)R_3$, $-C(O)NR_2R_3$, or $-CH_2R_8$;

$R_2$ is:

(a) H; or

(b) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) –$COR_6$, 13) -$CONR_6R_6$, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, and 16) –$COOR_6$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be

optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –NHC(CN)$NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –NHC(CN)$NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may

be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which

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may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

or two $R_8$'s are taken together to form a 3- to 9-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and may be optionally substituted with one or more $R_{20}$'s;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; or (b) $-[(C=O)O_r]_s(C_1-C_8)$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

or $R_9$ and $R_{10}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo$(C_1-C_6)$alkyl; (o) $(C_2-C_6)$-alkenyl; (p) $-(C_2-C_6)$-alkynyl; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) $-CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) $(C_1-C_6)$-alkyl; (c) $-OR_{26}$; (d) $(C_1-C_6)$-alkylthio; (e) cyano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo$(C_1-C_6)$alkyl; (o) $-CONR_{26}R_{26}$; (p) $(C_2-C_6)$-alkenyl; (q) $(C_2-C_6)$-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) $-COR_{26}$; or (u) $-COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) $(C_1-C_6)$-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) $-OR_{36}$, 5) $(C_1-C_6)$-alkylthio, 6) cyano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo$(C_1-C_6)$alkyl,

13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4)

-$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –NHC(CN)$NHR_{36}$; or

(f) hydrogen;

$R_{29}$ and $R_{30}$ are independently hydrogen or –$[(C=O)O_r]_s$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{40}$'s;

or $R_{29}$ and $R_{30}$ are taken together with the nitrogen to which both are attached to form a 3- to 8-membered ring, which may optionally contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, cycloalkyl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, -$NR_{49}R_{50}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, –$CONR_{49}R_{50}$, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl, cycloalkylalkyl, –$COR_{49}$ or –$COOR_{49}$;

$R_{49}$ and $R_{50}$, at each occurrence, are independently hydrogen, alkyl, aryl or heteroaryl;

r is 0 to 2;

s is 0 to 1; and

p is 1 or 2.

7. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, which may be optionally substituted with one or more $R_{20}$'s, and 18) –$OCOR_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl;

C is alkyl, which is substituted with one or more substituents selected from the group consisting of: 1) phenyl, which may be optionally substituted with one or more $R_{20}$'s, or 2) a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is –C(O)$R_3$, -C(O)NH$R_3$ or –$CH_2R_8$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be

optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl,

which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or

more $R_{20}$'s, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; or (b) –$[(C=O)O_r]_s$($C_1$-$C_8$)alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{21}$'s; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) -($C_2$-$C_6$)-alkynyl; (q) –$COR_{26}$; (r) –$COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) –$CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) –$CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) ($C_2$-$C_6$)-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) –$COR_{26}$; or (u) –$COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$S(O)_pR_{36}$, 20) –$SO_2NHR_{36}$, 21) –$COOR_{36}$, and 22) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$S(O)_pR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14)

heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$;

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{40}$'s, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$S(O)_pR_{36}$, 23) –$SO_2NHR_{36}$, 24) –$COOR_{36}$, and 25) –$NHC(CN)NHR_{36}$; or

(f) hydrogen;

$R_{29}$ and $R_{30}$ are independently hydrogen or $-[(C=O)O_r]_s$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl, heteroaryl or heterocyclyl, other than heteroaryl, wherein the alkyl, aryl, heteroaryl or heterocyclyl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl or cycloalkylalkyl;

r is 0 to 2;

s is 0 to 1; and

p is 1 or 2.

8. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) $(C_1$-$C_6)$-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) $-OR_6$, 4) $(C_1$-$C_6)$-alkylthio, 5) cyano, 6) nitro, 7) $-NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo$(C_1$-$C_6)$alkyl, 15) $-COR_6$, 16) =O, and 17) $-OCOR_6$; or any two adjacent substituents may join together to form a 4- to 8-membered ring, which optionally may contain 1-4 heteroatoms selected from N, O, and S and be optionally substituted with one or more $R_{20}$'s;

B is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl;

C is methyl, which is substituted with one or more substituents selected from the group consisting of: 1) phenyl, which may be optionally substituted with one or more $R_{20}$'s, or 2) a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is –C(O)$R_3$, -C(O)N$HR_3$ or –$CH_2R_8$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) -$CONR_6R_6$, 13) ($C_2$-$C_6$)-alkenyl, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_6$, and 16) –$COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may

be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more

$R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) -$CONR_6R_6$, 16) ($C_2$-$C_6$)-alkenyl, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_6$, and 20) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$SO_2NHR_{36}$, 20) –$COOR_{36}$, and 21) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$, 9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$SO_2NHR_{36}$, 22) –$COOR_{36}$, and 23) –$NHC(CN)NHR_{36}$;

(c) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_9R_{10}$,

9) aryl, which may be optionally substituted with one or more $R_{20}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$; or

(d) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) aryl($C_2$-$C_6$)-alkynyl, 14) -$CONR_{26}R_{26}$, 15) =O, 16) ($C_2$-$C_6$)-alkynyl, 17) –$COR_{26}$, and 18) –$COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with

one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, 15) ($C_2$-$C_6$)-alkenyl, 16) -$CONR_{26}R_{26}$, 17) =O, 18) ($C_2$-$C_6$)-alkynyl, 19) –$COR_{26}$, and 20) –$COOR_{26}$;

$R_9$ and $R_{10}$ are independently: (a) hydrogen; or (b) –$[(C=O)O_r]_s$($C_1$-$C_8$)alkyl, wherein the alkyl may be optionally substituted with one or more $R_{20}$'s;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl, which may be optionally substituted with one or more $R_{21}$'s; (i) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (k) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (m) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (n) halo($C_1$-$C_6$)alkyl; (o) ($C_2$-$C_6$)-alkenyl; (p) -($C_2$-$C_6$)-alkynyl; (q) –$COR_{26}$; (r) –$COOR_{26}$; (s) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; (t) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (u) –$CONR_{26}R_{26}$;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) –$NR_{29}R_{30}$; (h) aryl; (i) arylalkyl; (j) heteroaryl; (k) heteroarylalkyl; (l) heterocyclyl; (m) heterocyclylalkyl; (n) halo($C_1$-$C_6$)alkyl; (o) –$CONR_{26}R_{26}$; (p) ($C_2$-$C_6$)-alkenyl; (q) ($C_2$-$C_6$)-alkynyl; (r) cycloalkyl; (s) cycloalkylalkyl; (t) –$COR_{26}$; or (u) –$COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 12) halo($C_1$-$C_6$)alkyl, 13) ($C_2$-$C_6$)-alkenyl, 14) -COOH,

15) -$CONR_{36}R_{36}$, 16) =O, 17) ($C_2$-$C_6$)-alkynyl, 18) –$COR_{36}$, 19) –$SO_2NHR_{36}$, 20) –$COOR_{36}$, and 21) –$NHC(CN)NHR_{36}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) ($C_2$-$C_6$)-alkynyl, 20) –$COR_{36}$, 21) –$SO_2NHR_{36}$, 22) –$COOR_{36}$, and 23) –$NHC(CN)NHR_{36}$;

(c) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) aryl, which may be optionally substituted with one or more $R_{40}$'s, 10) arylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 11) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 12) heteroarylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 13) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 14) heterocyclylalkyl, which may be optionally substituted with one or more $R_{40}$'s, 15) halo($C_1$-$C_6$)alkyl, 16) ($C_2$-$C_6$)-alkenyl, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) ($C_2$-$C_6$)-alkynyl, 21) –$COR_{36}$, 22) –$SO_2NHR_{36}$, 23) –$COOR_{36}$, and 24) –$NHC(CN)NHR_{36}$; or

(d) hydrogen;

$R_{29}$ and $R_{30}$ are independently hydrogen or –$[(C=O)O_r]_s$alkyl, wherein the alkyl may be optionally substituted with one or more $R_{40}$'s;

$R_{36}$, at each occurrence, is independently alkyl, aryl or heteroaryl, wherein the alkyl, aryl or heteroaryl may be optionally substituted with one or more $R_{40}$'s;

$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, alkenyl, arylalkyloxy, =O, alkynyl, cycloalkyl or cycloalkylalkyl;

r is 0 to 2; and

s is 0 to 1.

9. A compound of claim 1, wherein:

A is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 14) halo($C_1$-$C_6$)alkyl, and 15) –$COR_6$;

B is phenyl, which is substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl;

C is methyl, which is substituted with a 5- or 6-membered nitrogen containing heteroaryl, which may be optionally substituted with one or more $R_{20}$'s;

$R_1$ is $-C(O)R_3$, $-C(O)NHR_3$ or $-CH_2R_8$;

$R_3$ is:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 10) halo($C_1$-$C_6$)alkyl, 11) ($C_2$-$C_6$)-alkenyl, 12) ($C_2$-$C_6$)-alkynyl, 13) $-COR_6$, and 14) $-COOR_6$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_6$, and 17) $-COOR_6$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which

may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_6$, and 17) –$COOR_6$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_6$, and 17) –$COOR_6$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5)cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_6$, and 17) –$COOR_6$;

$R_6$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s,

11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) -COOH, 14) ($C_2$-$C_6$)-alkynyl, 15) $-COR_{36}$, and 16) $-COOR_{36}$; or

(b) hydrogen;

$R_8$ can independently be:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 9) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 10) halo($C_1$-$C_6$)alkyl, 11) ($C_2$-$C_6$)-alkenyl, 12) ($C_2$-$C_6$)-alkynyl, 13) $-COR_{26}$, and 14) $-COOR_{26}$;

(b) aryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_{26}$, and 17) $-COOR_{26}$;

(c) cycloalkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) $-OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) $-COR_{26}$, and 17) $-COOR_{26}$;

(d) heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_{26}$, and 17) –$COOR_{26}$; or

(e) heterocyclyl, other than heteroaryl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, 3) -$OR_{26}$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) aryl, which may be optionally substituted with one or more $R_{20}$'s, 8) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 11) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 13) halo($C_1$-$C_6$)alkyl, 14) ($C_2$-$C_6$)-alkenyl, 15) ($C_2$-$C_6$)-alkynyl, 16) –$COR_{26}$, and 17) –$COOR_{26}$;

$R_{20}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) aryl, which may be optionally substituted with one or more $R_{21}$'s; (h) arylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (i) heteroaryl, which may be optionally substituted with one or more $R_{21}$'s; (j) heteroarylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (k) heterocyclyl, which may be optionally substituted with one or more $R_{21}$'s; (l) heterocyclylalkyl, which may be optionally substituted with one or more $R_{21}$'s; (m) halo($C_1$-$C_6$)alkyl; (n) ($C_2$-$C_6$)-alkenyl; (o) -($C_2$-$C_6$)-alkynyl; (p) –$COR_{26}$; (q) –$COOR_{26}$; (r) cycloalkyl, which may be optionally substituted with one or more $R_{21}$'s; or (s) cycloalkylalkyl, which may be optionally substituted with one or more $R_{21}$'s;

$R_{21}$ is: (a) halo; (b) ($C_1$-$C_6$)-alkyl; (c) -$OR_{26}$; (d) ($C_1$-$C_6$)-alkylthio; (e) cyano; (f) nitro; (g) aryl; (h) arylalkyl; (i) heteroaryl; (j) heteroarylalkyl; (k) heterocyclyl; (l) heterocyclylalkyl; (m) halo($C_1$-$C_6$)alkyl; (n) ($C_2$-$C_6$)-alkenyl; (o) ($C_2$-$C_6$)-alkynyl; (p) cycloalkyl; (q) cycloalkylalkyl; (r) –$COR_{26}$; or (s) –$COOR_{26}$;

$R_{26}$, at each occurrence, is independently:

(a) alkyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) –OH, 3) ($C_1$-$C_6$)-alkyl, 4) -$OR_{36}$, 5) ($C_1$-$C_6$)-alkylthio, 6) cyano, 7) nitro, 8) aryl, which may be optionally substituted with one or more $R_{40}$'s, 9) heteroaryl, which may be optionally substituted with one or more $R_{40}$'s, 10) heterocyclyl, which may be optionally substituted with one or more $R_{40}$'s, 11) halo($C_1$-$C_6$)alkyl, 12) ($C_2$-$C_6$)-alkenyl, 13) -COOH, 14) ($C_2$-$C_6$)-alkynyl, 15) –$COR_{36}$, or 16) –$COOR_{36}$; or

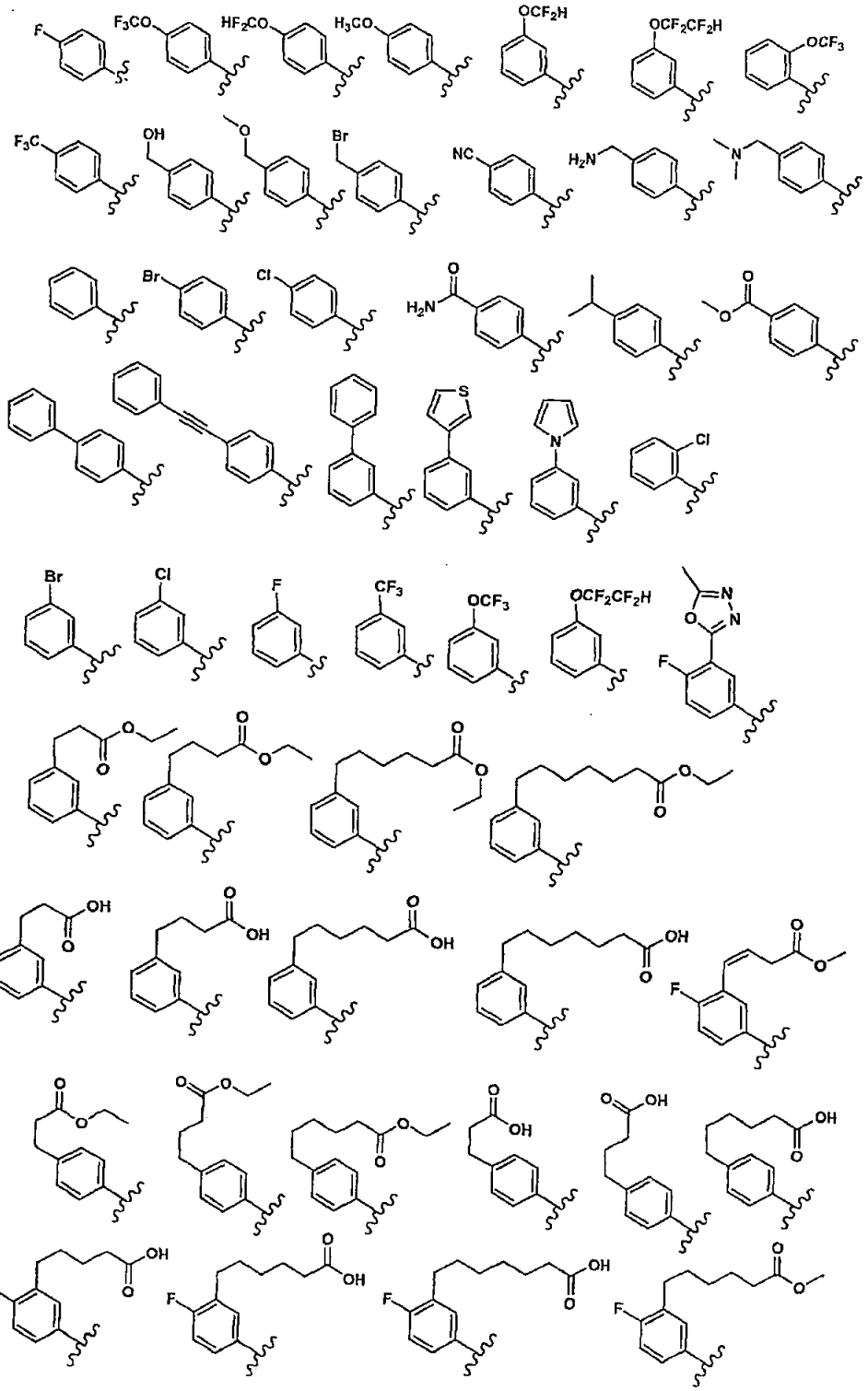
(b) hydrogen;

$R_{36}$, at each occurrence, is independently alkyl, aryl or heteroaryl, wherein the alkyl, aryl or heteroaryl may be optionally substituted with one or more $R_{40}$'s; and

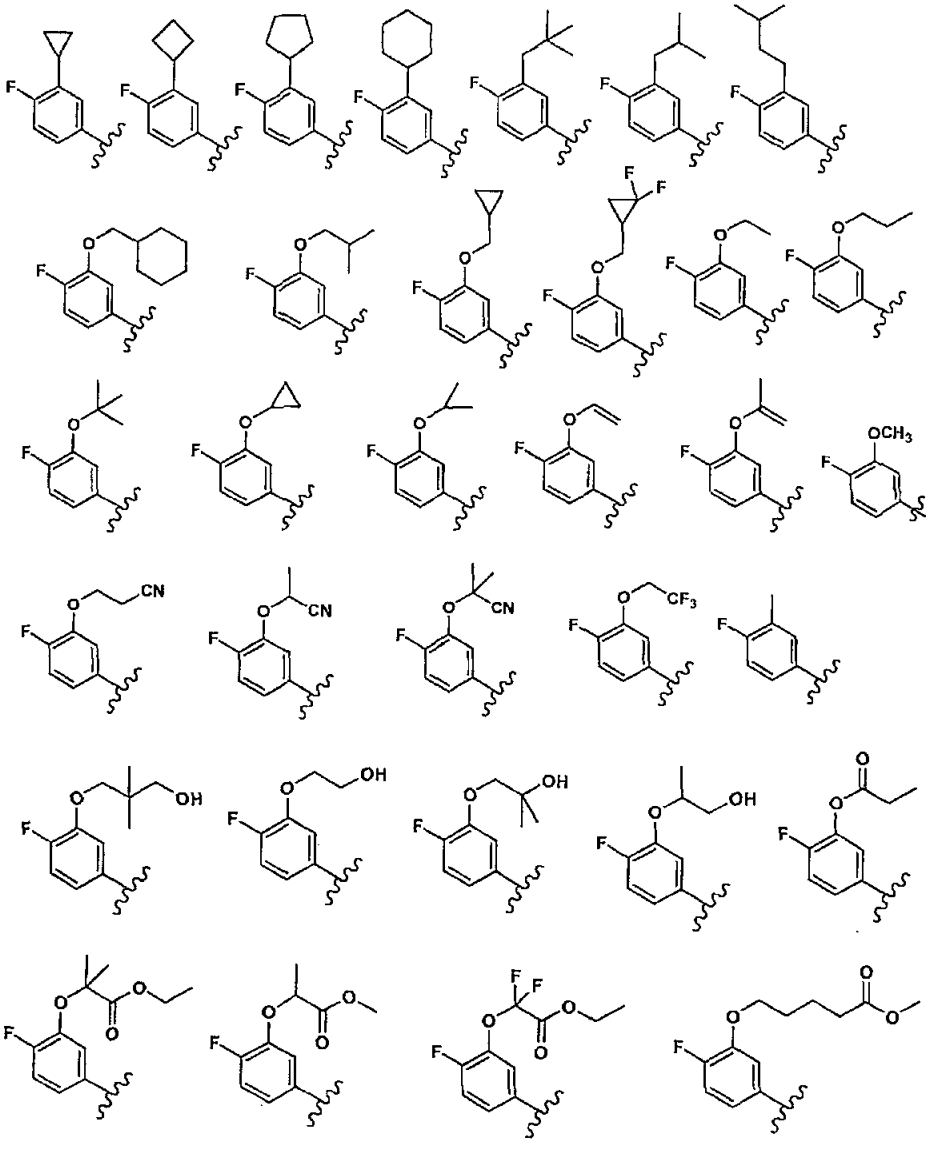
$R_{40}$ is halo, –OH, alkyl, alkyloxy, alkylthio, cyano, nitro, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, haloalkyloxy, alkenyl, arylalkyloxy, alkynyl, cycloalkyl or cycloalkylalkyl.

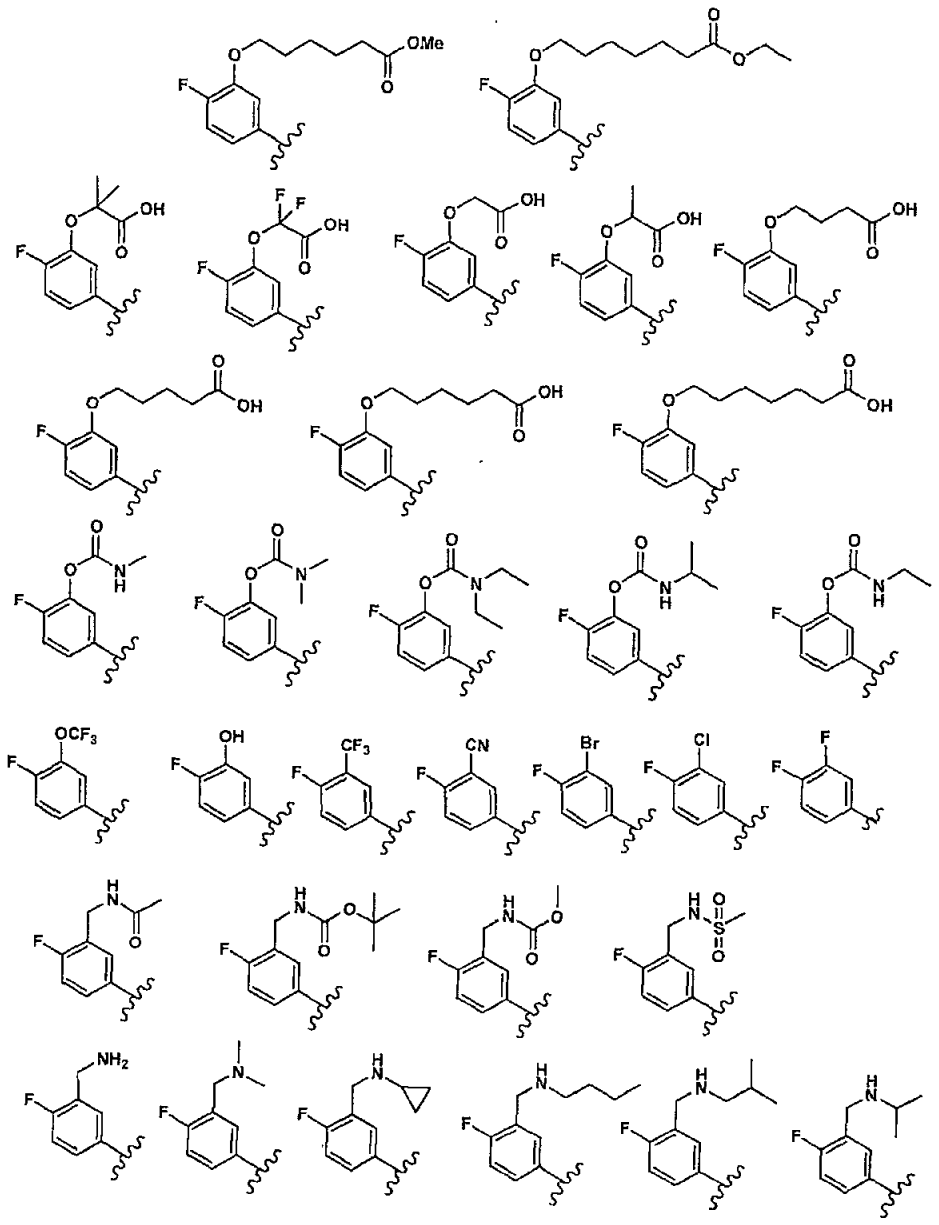
10. A compound of claim 1, wherein:

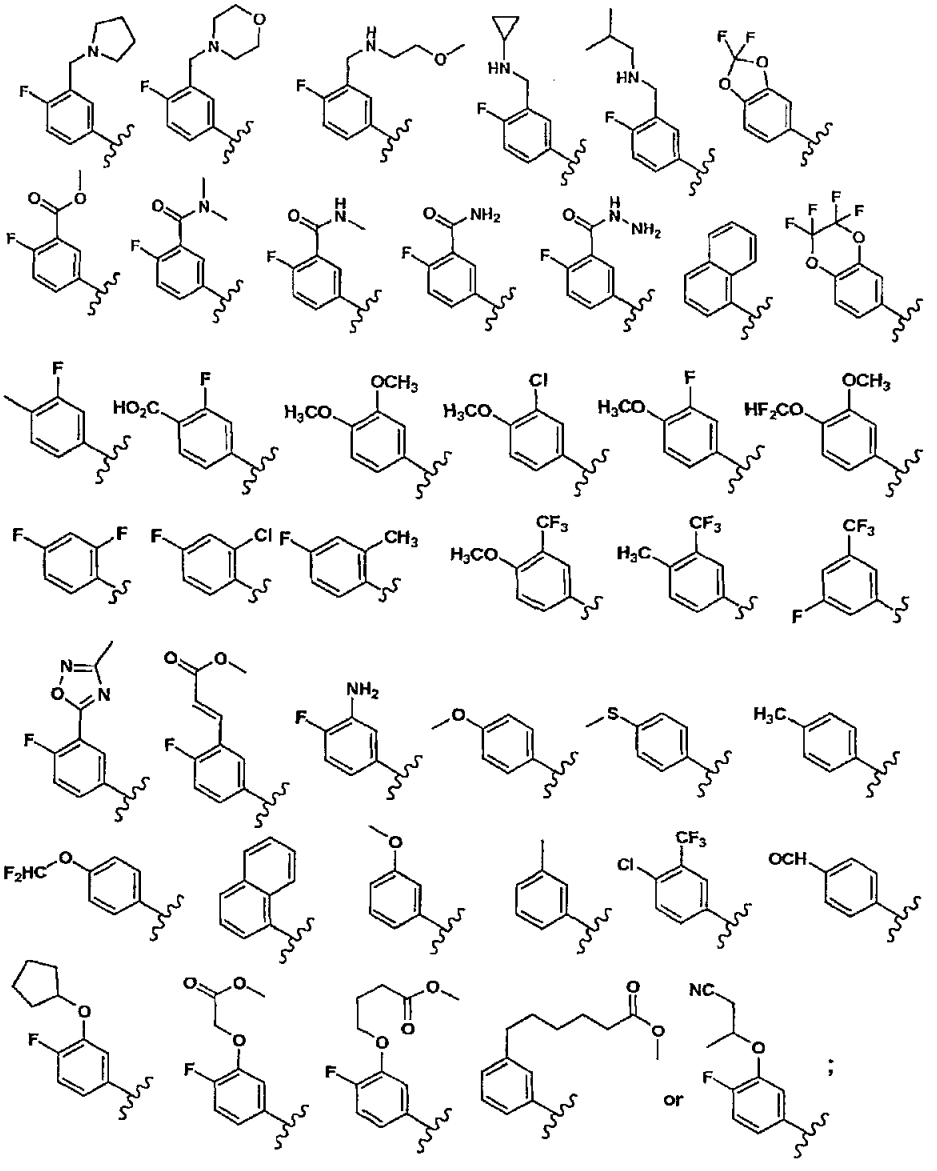
A is:



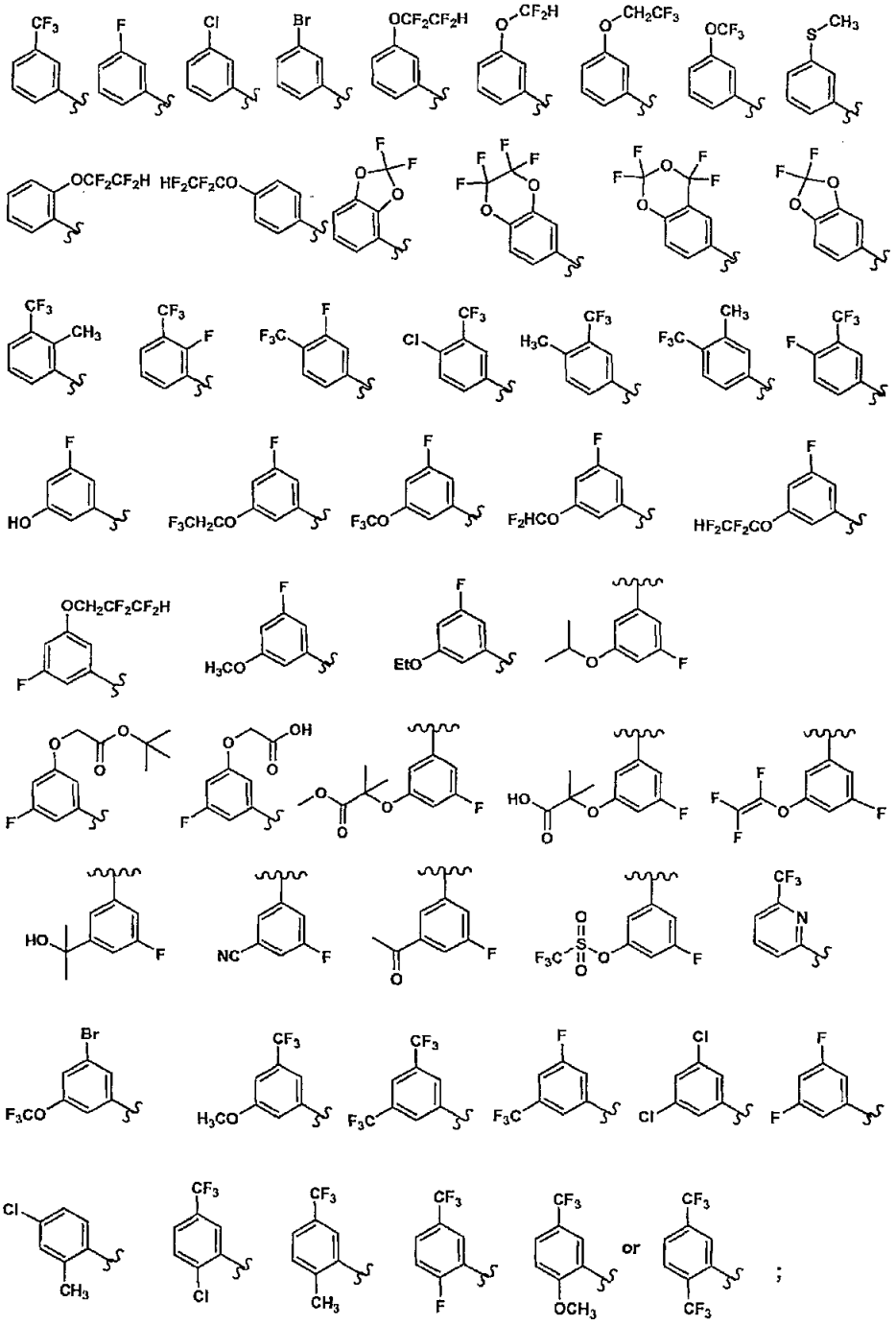
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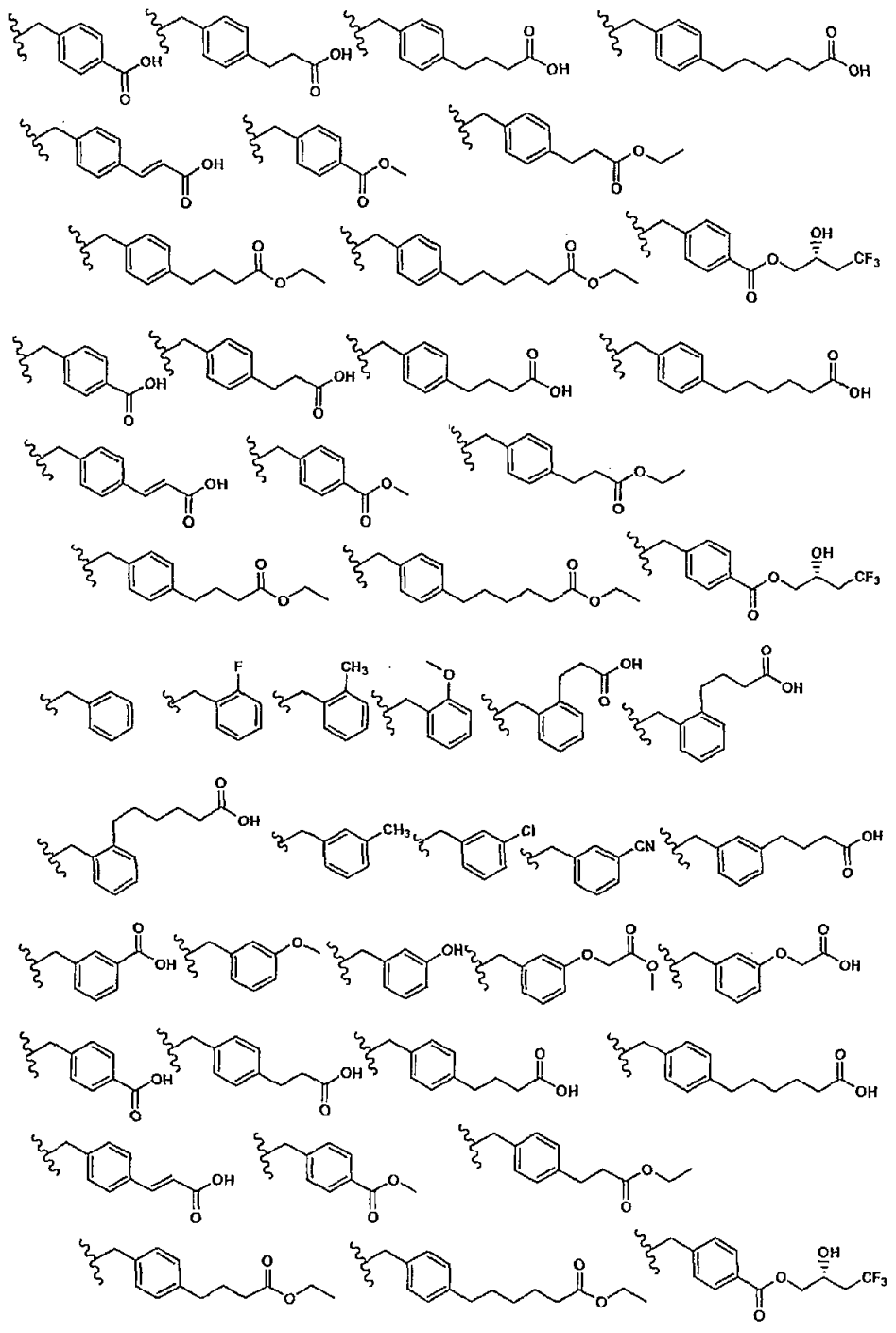


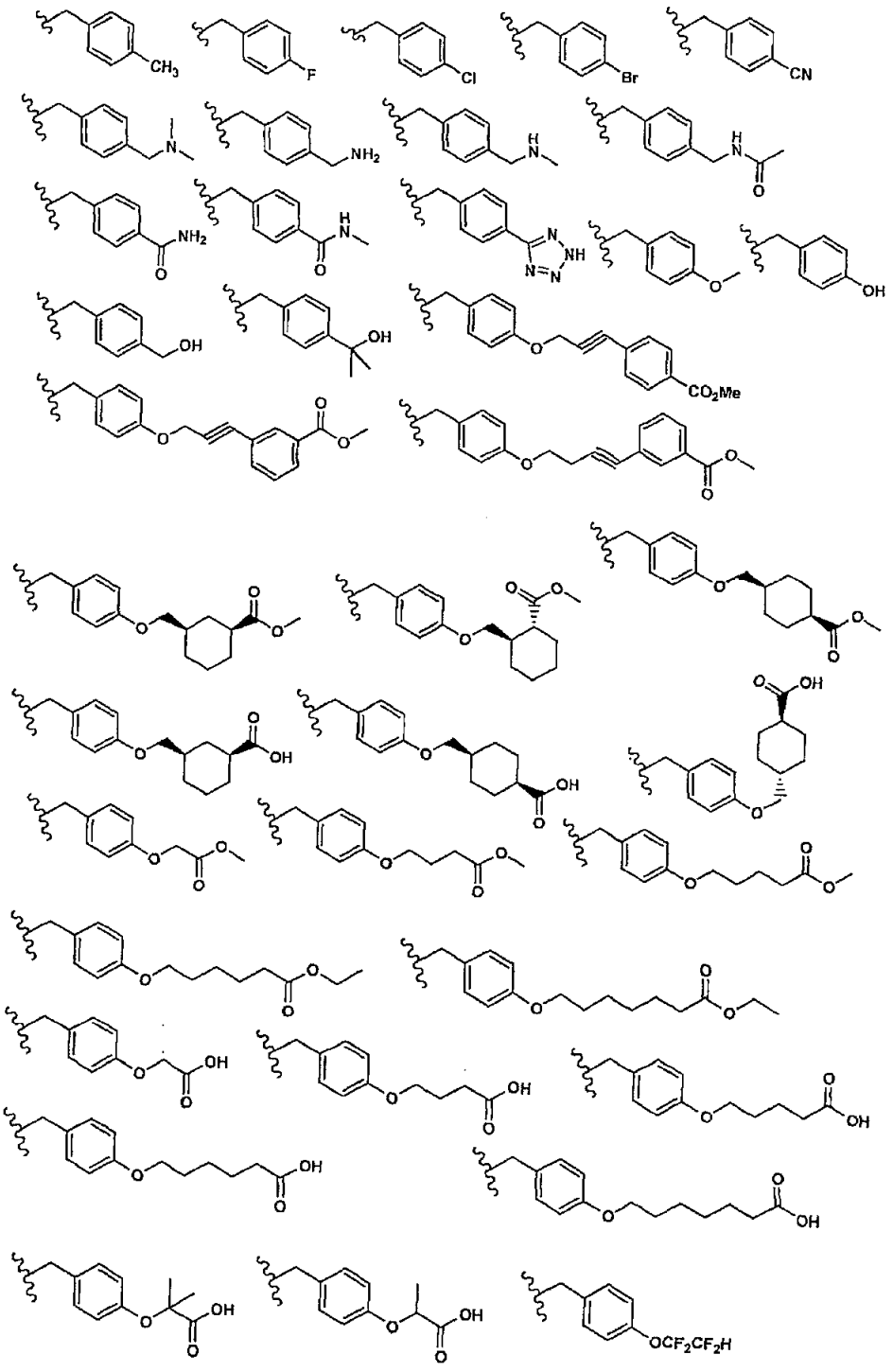
B is:

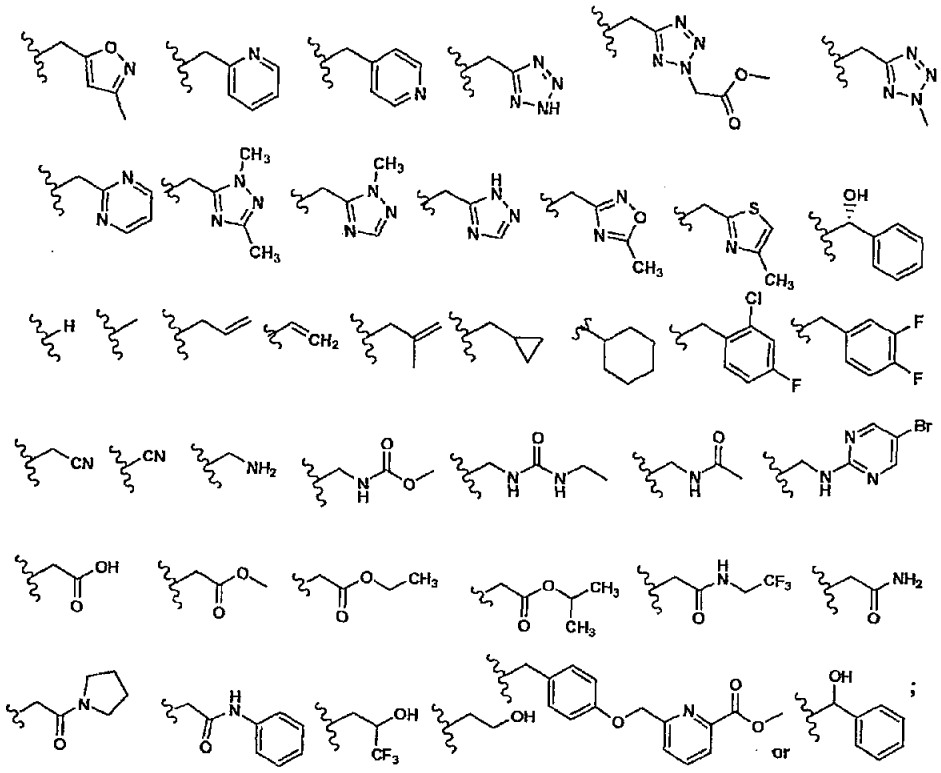


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C is:

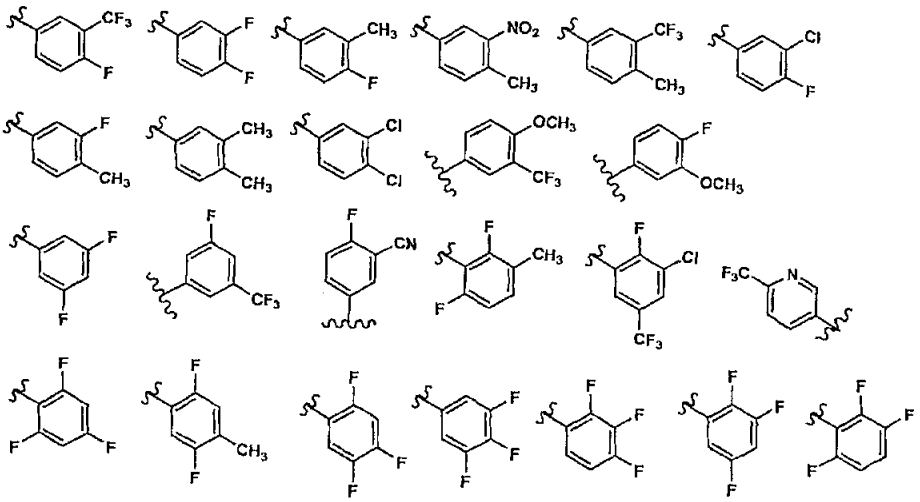


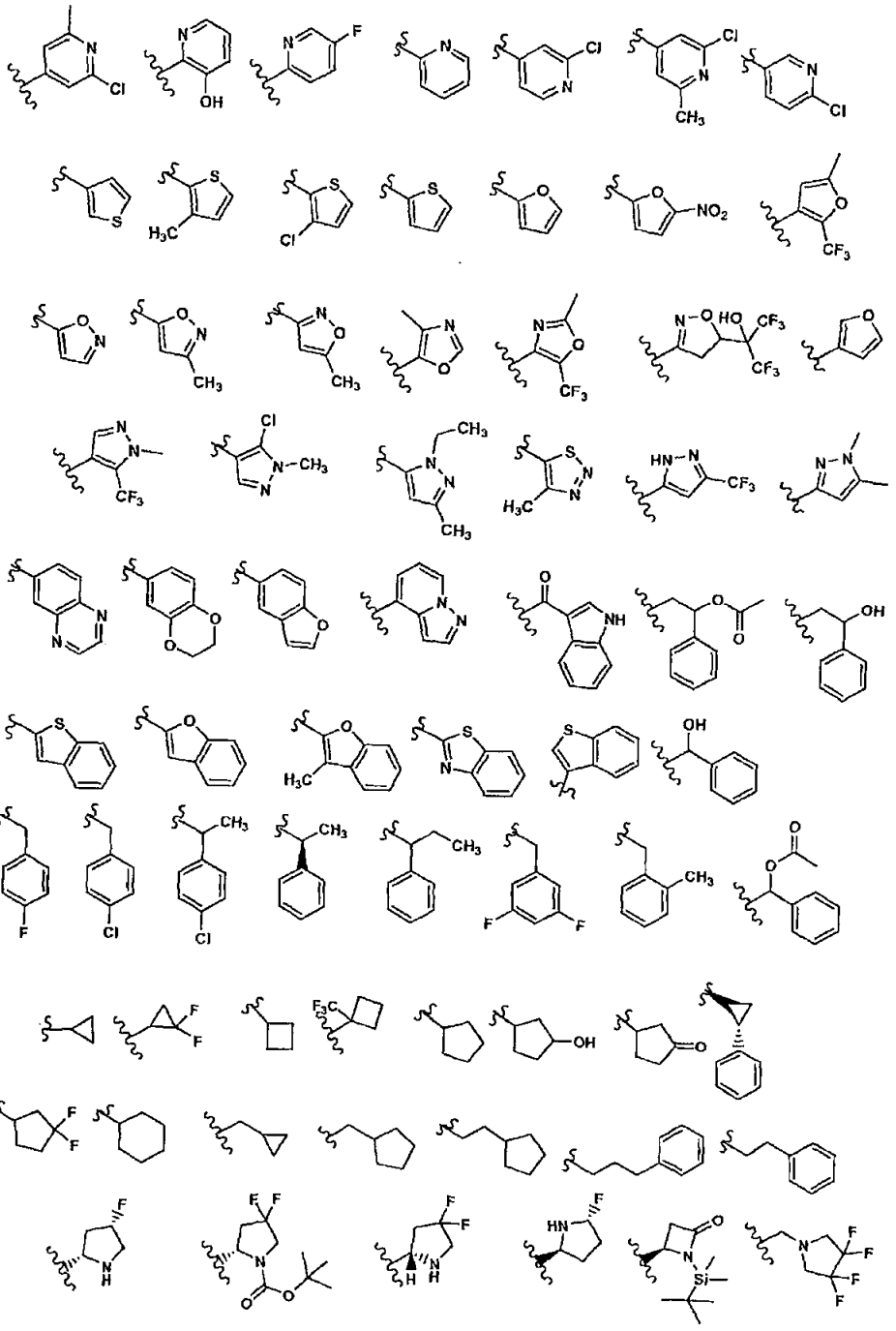


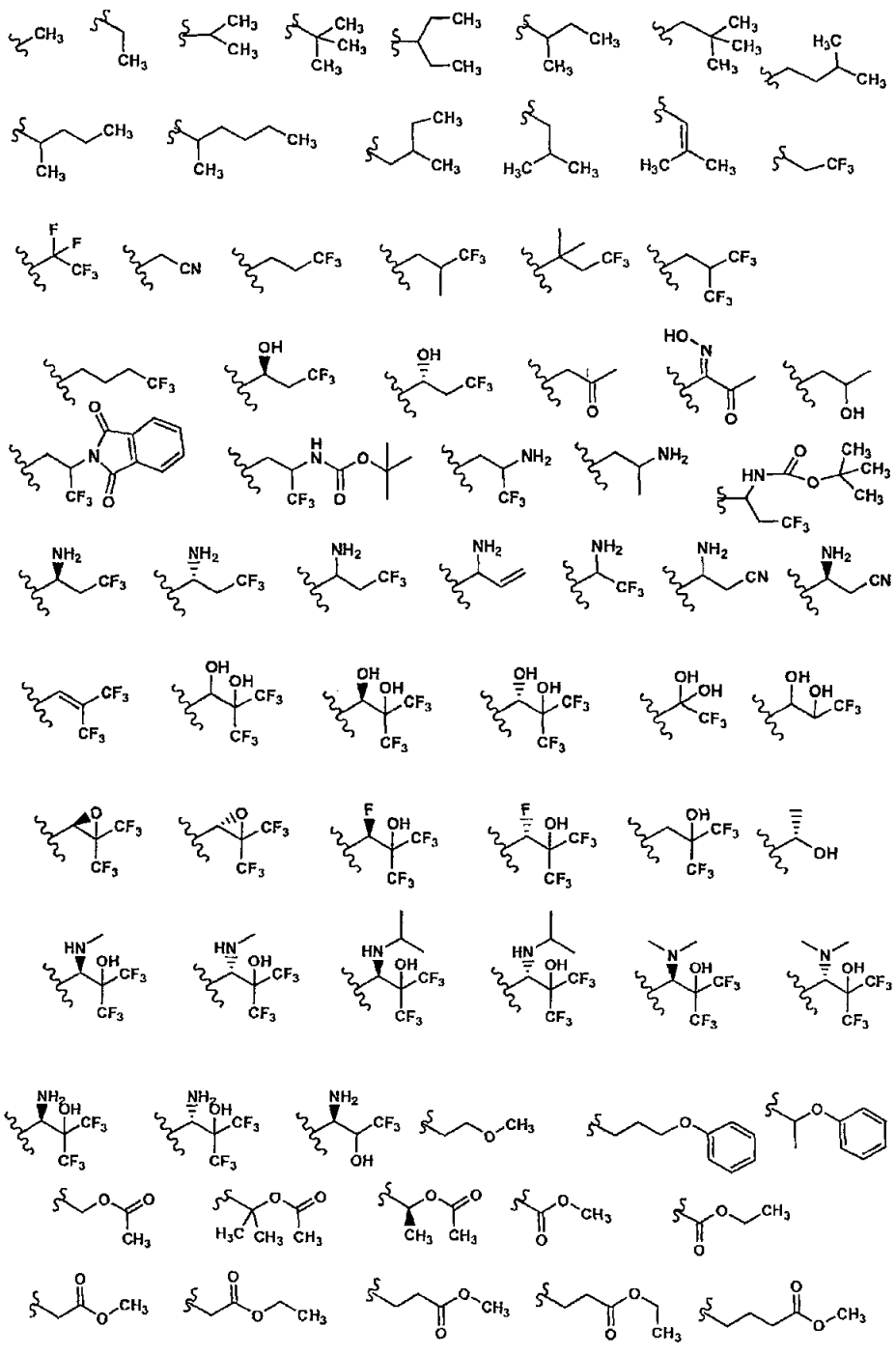


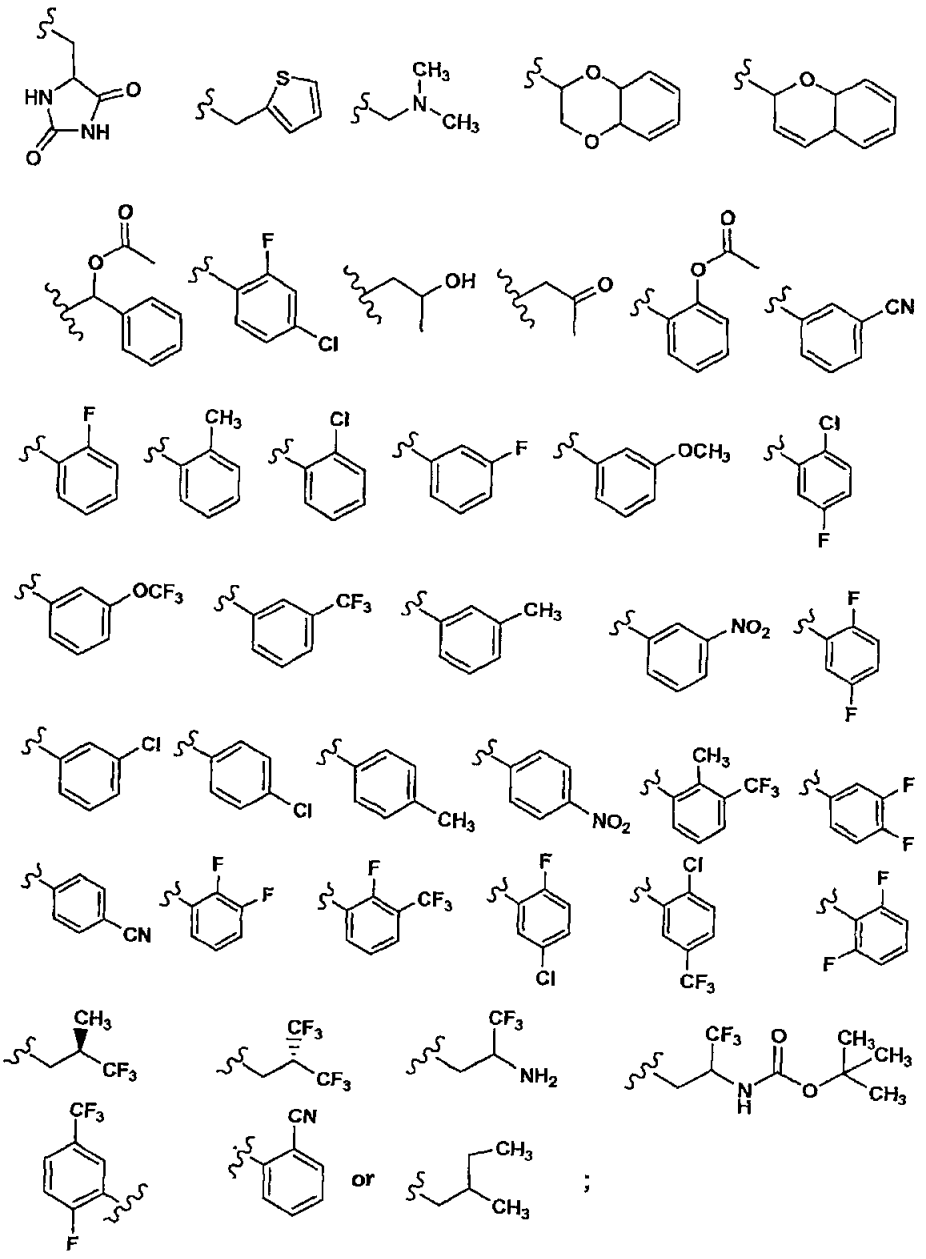
$R_1$ is:

(a) $-C(O)R_3$, wherein $R_3$:



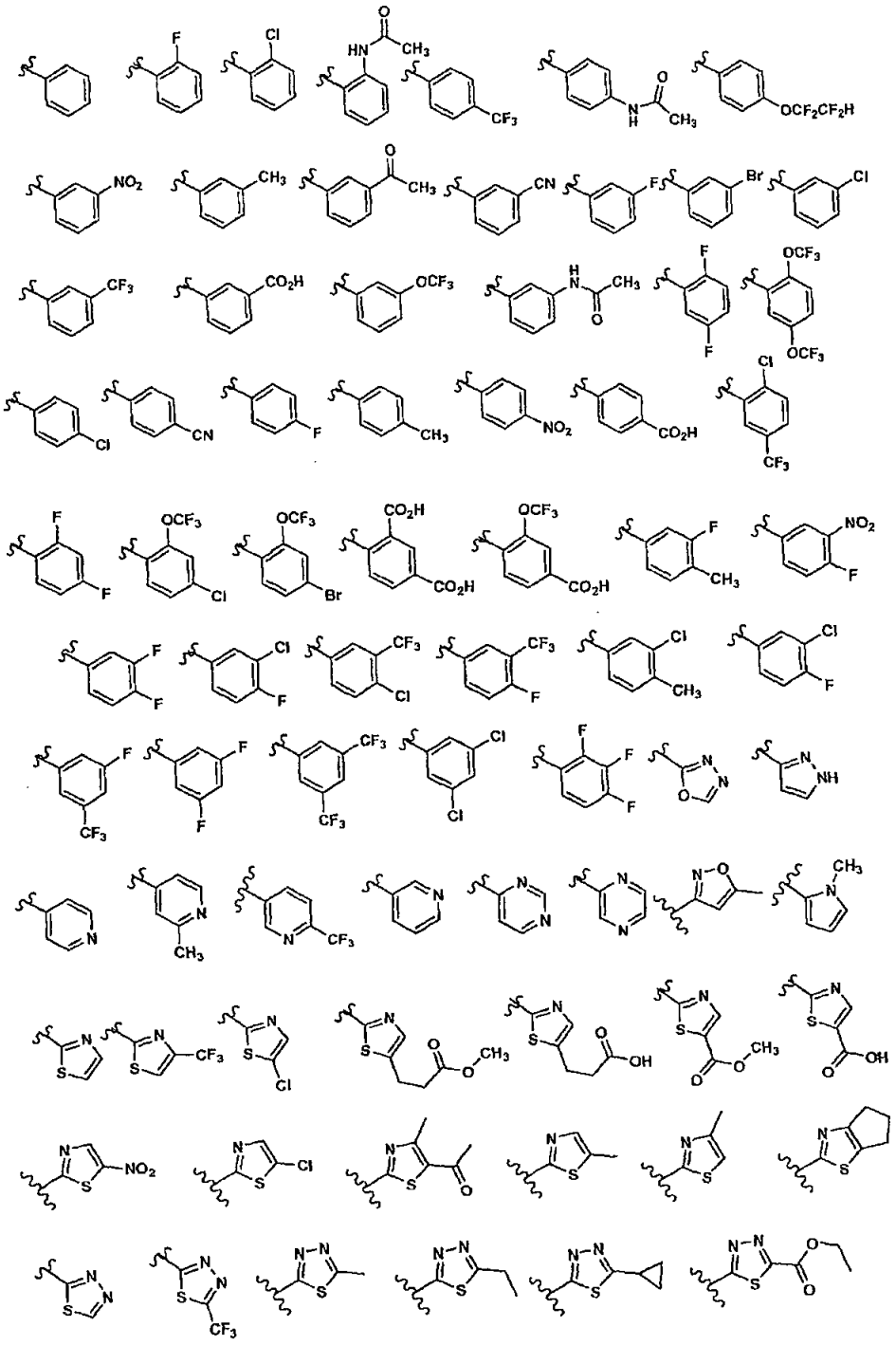


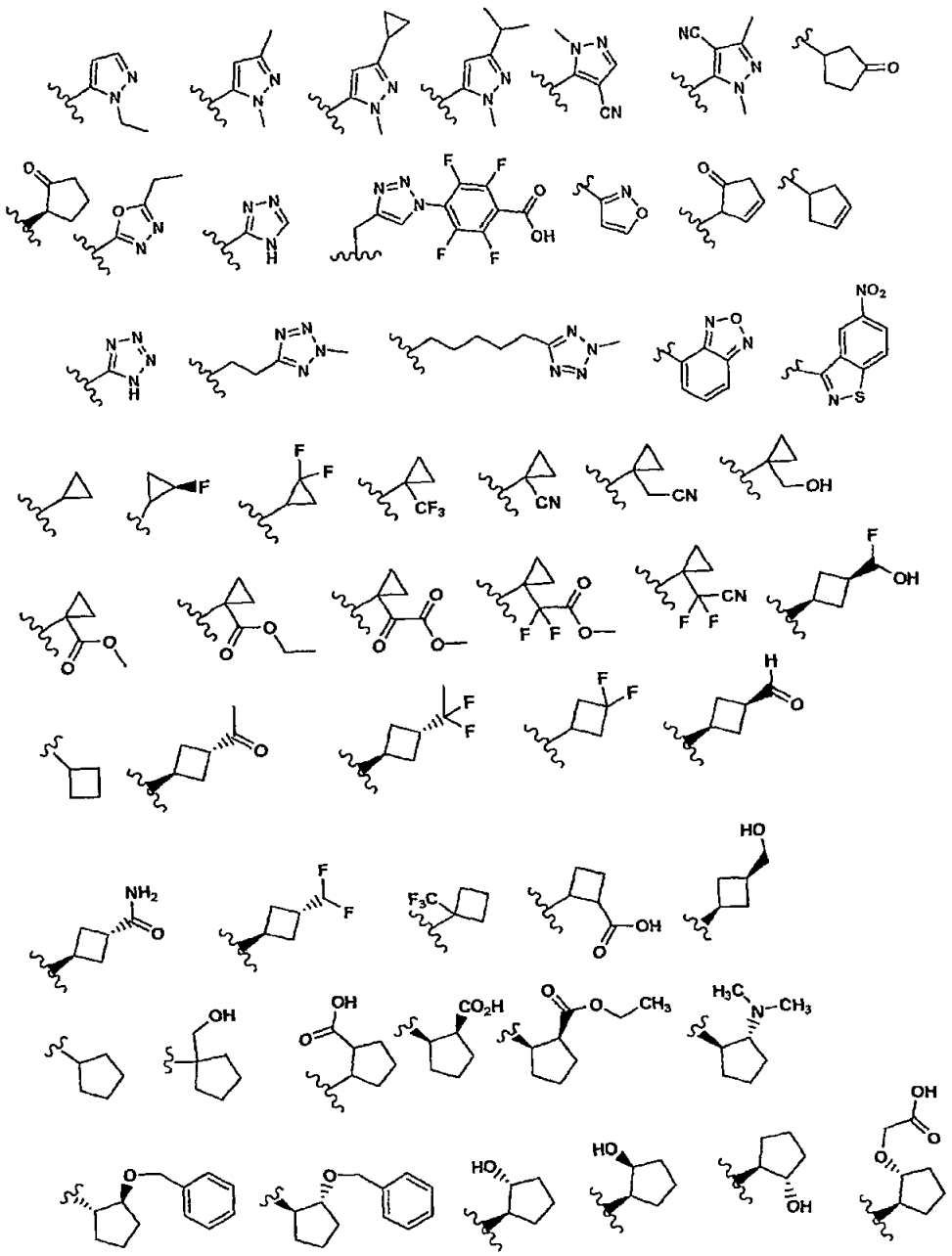


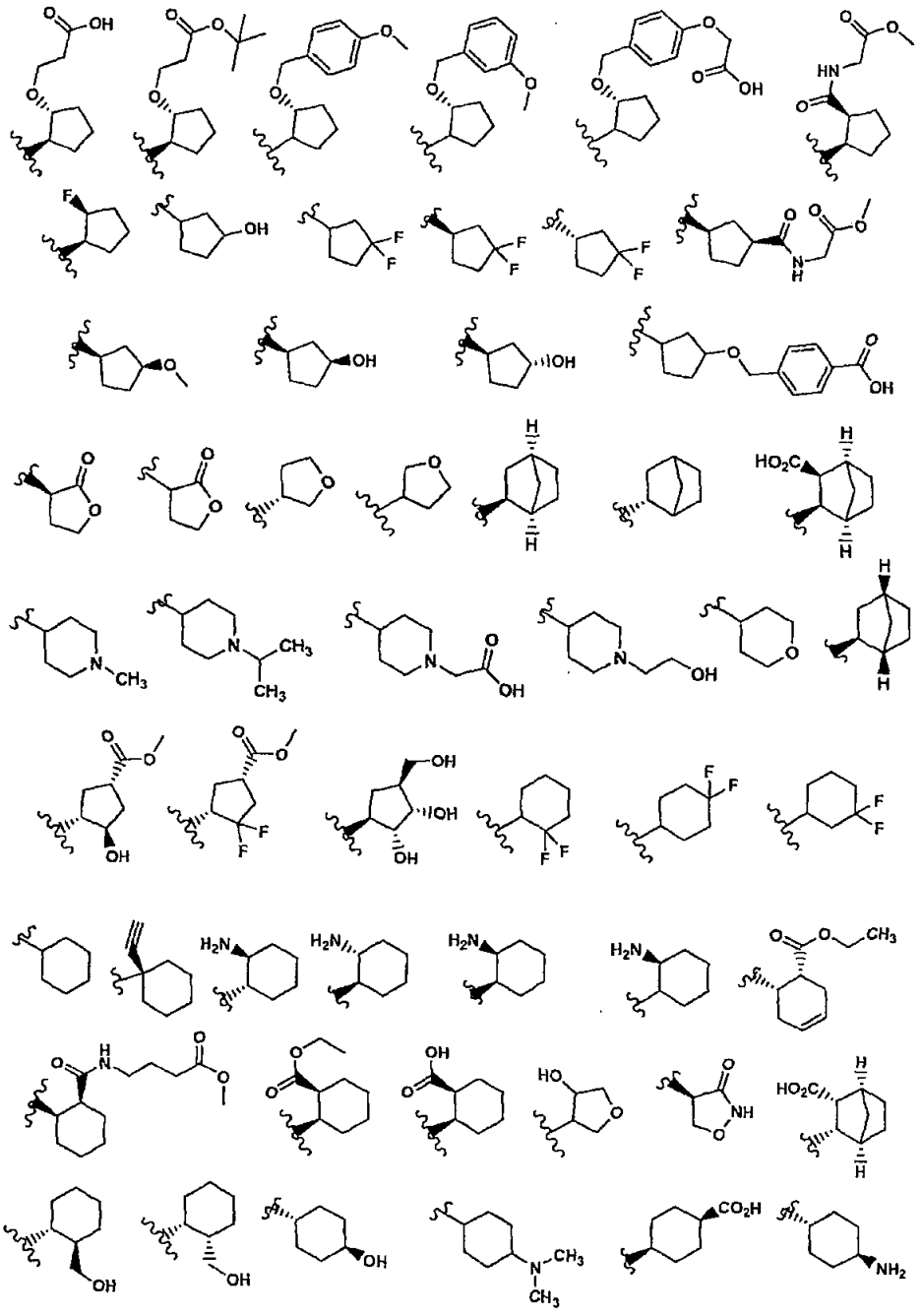


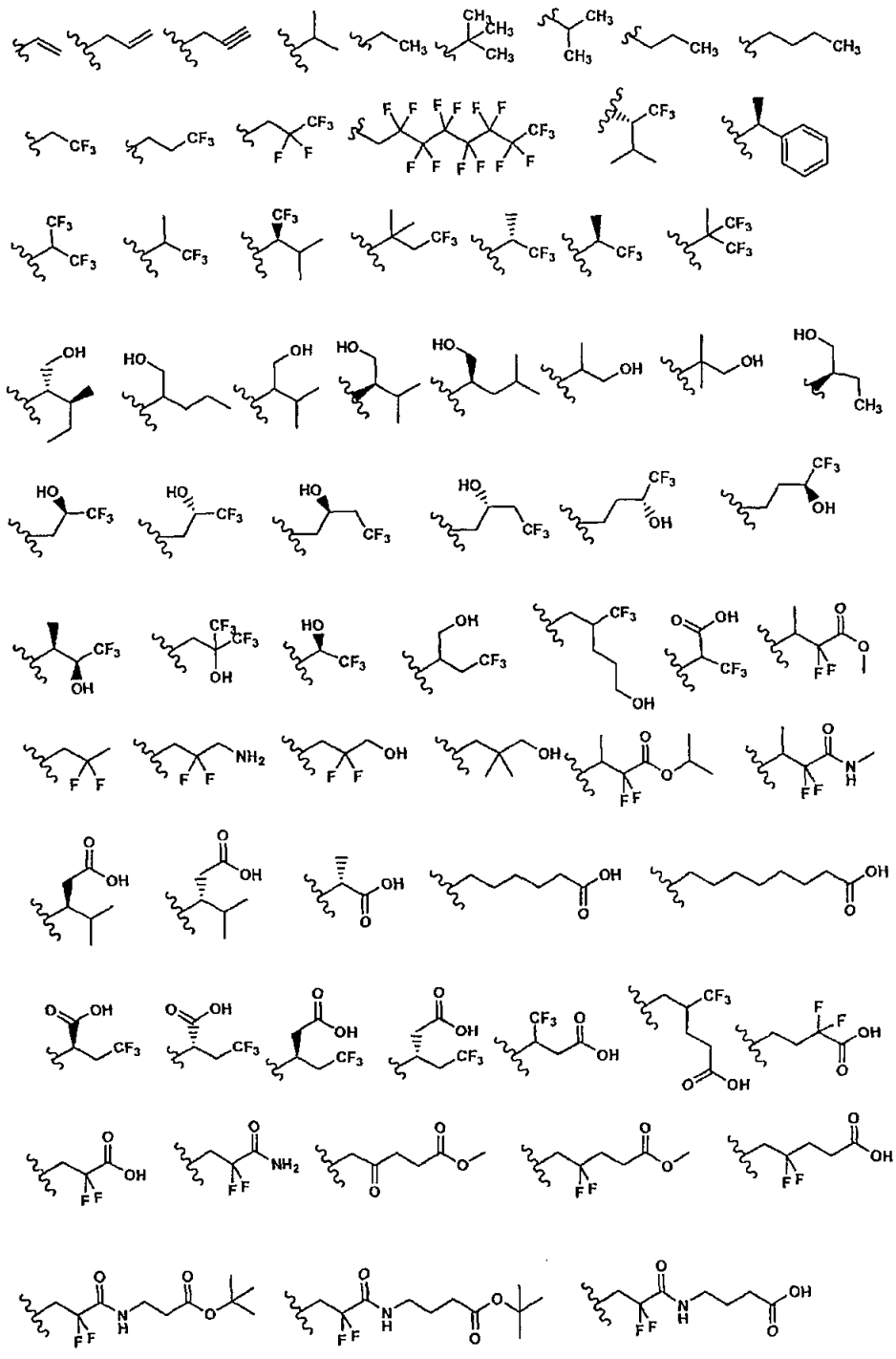
(b) -C(O)NHR$_3$, wherein the R$_3$ is:

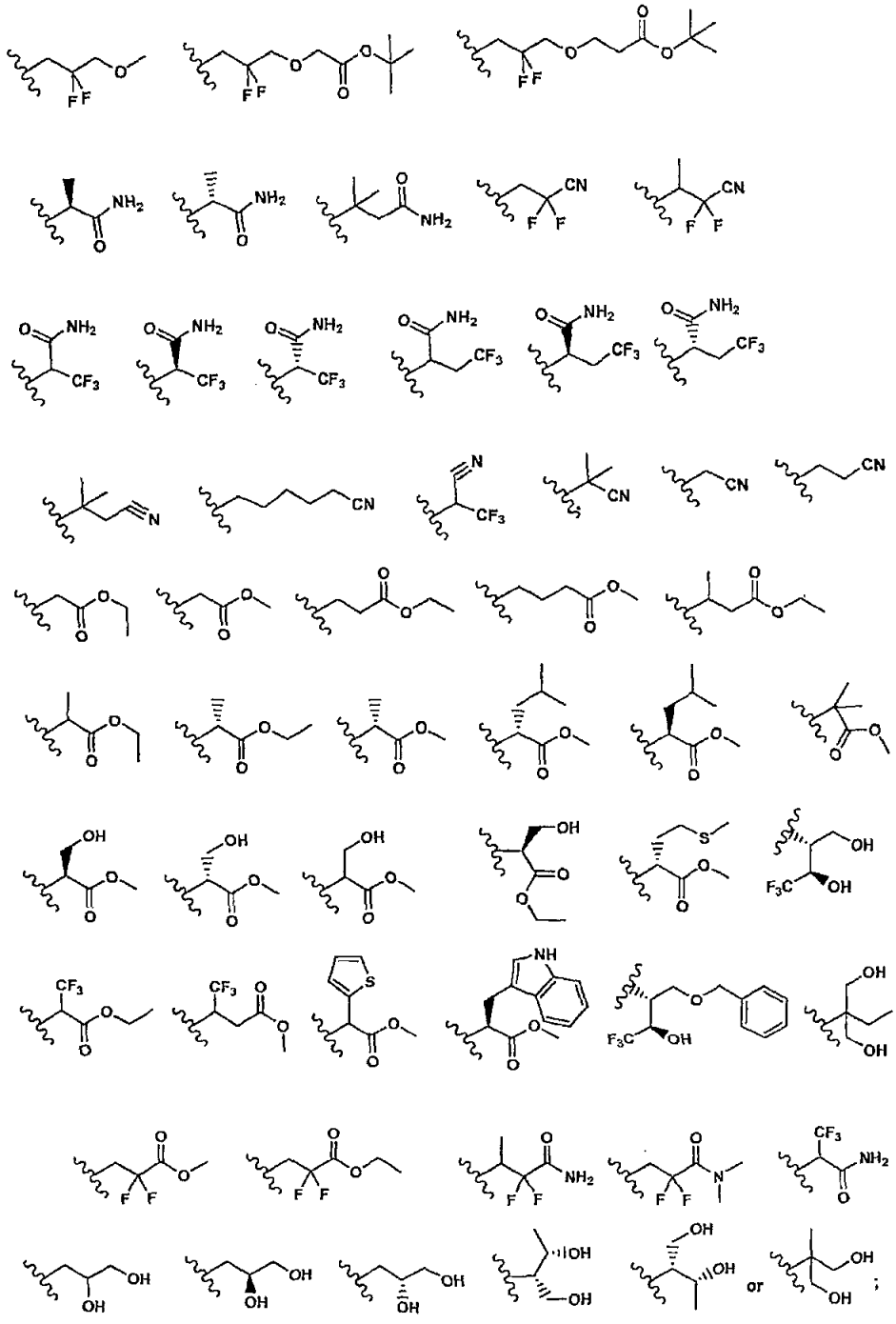
804



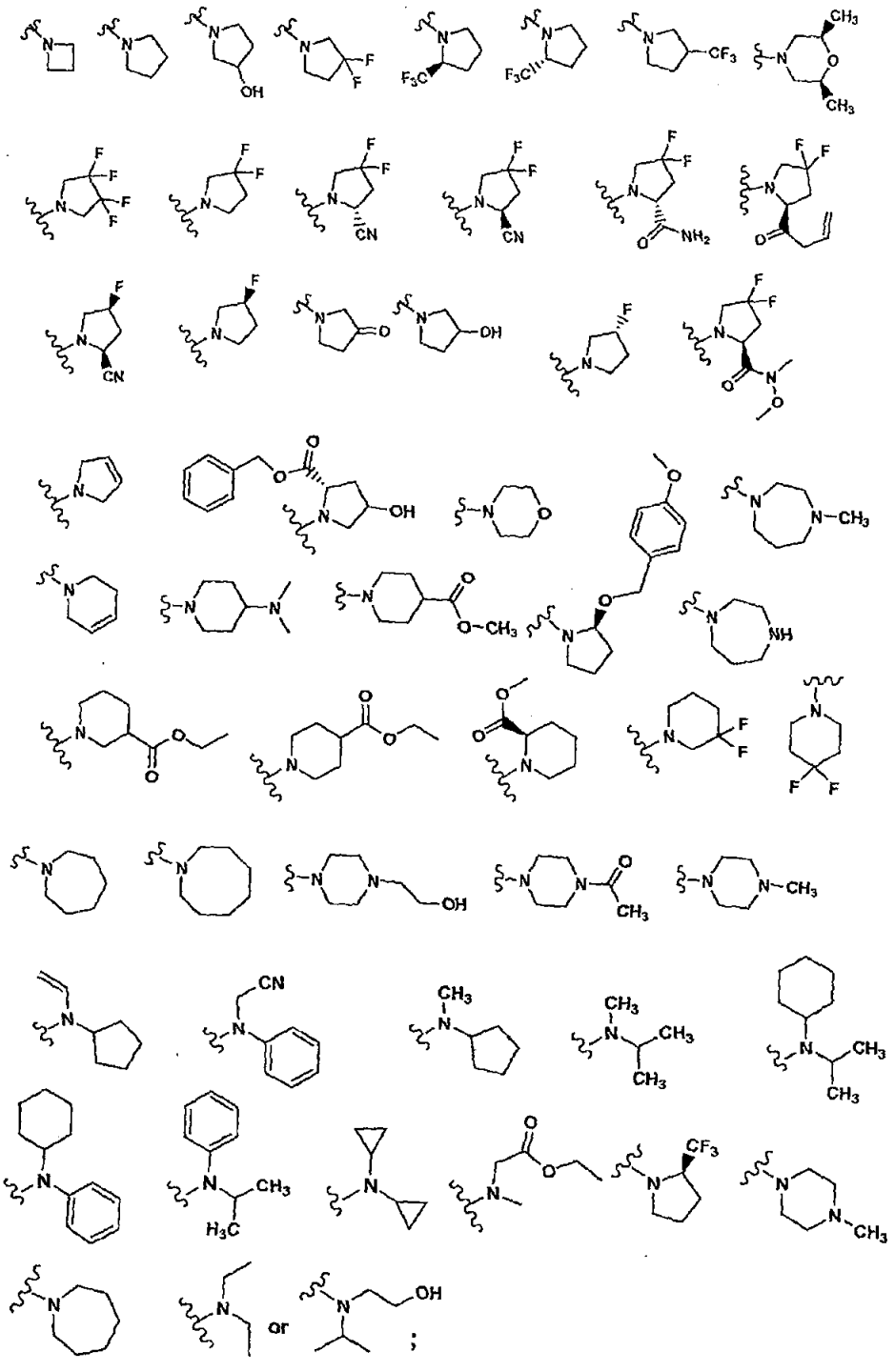




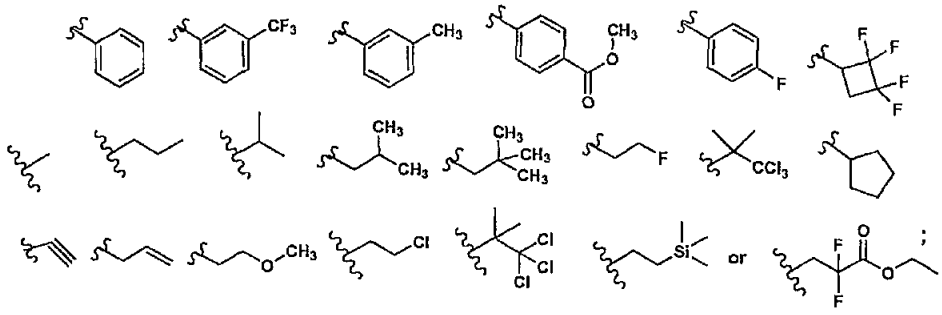




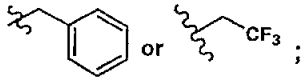
(c) -C(O)$NR_2R_3$, wherein the $NR_2R_3$ is:



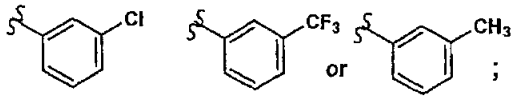
(d) -C(O)$OR_4$ wherein the $R_4$ is:



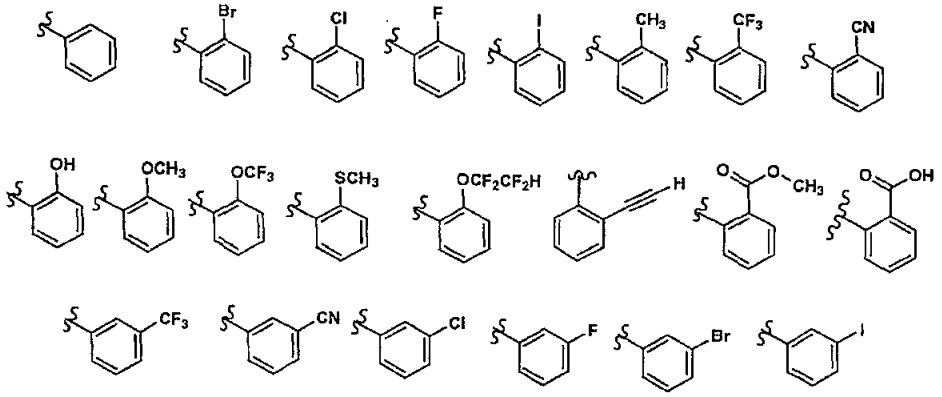
(e) $-SO_2R_5$ wherein the $R_5$ is:

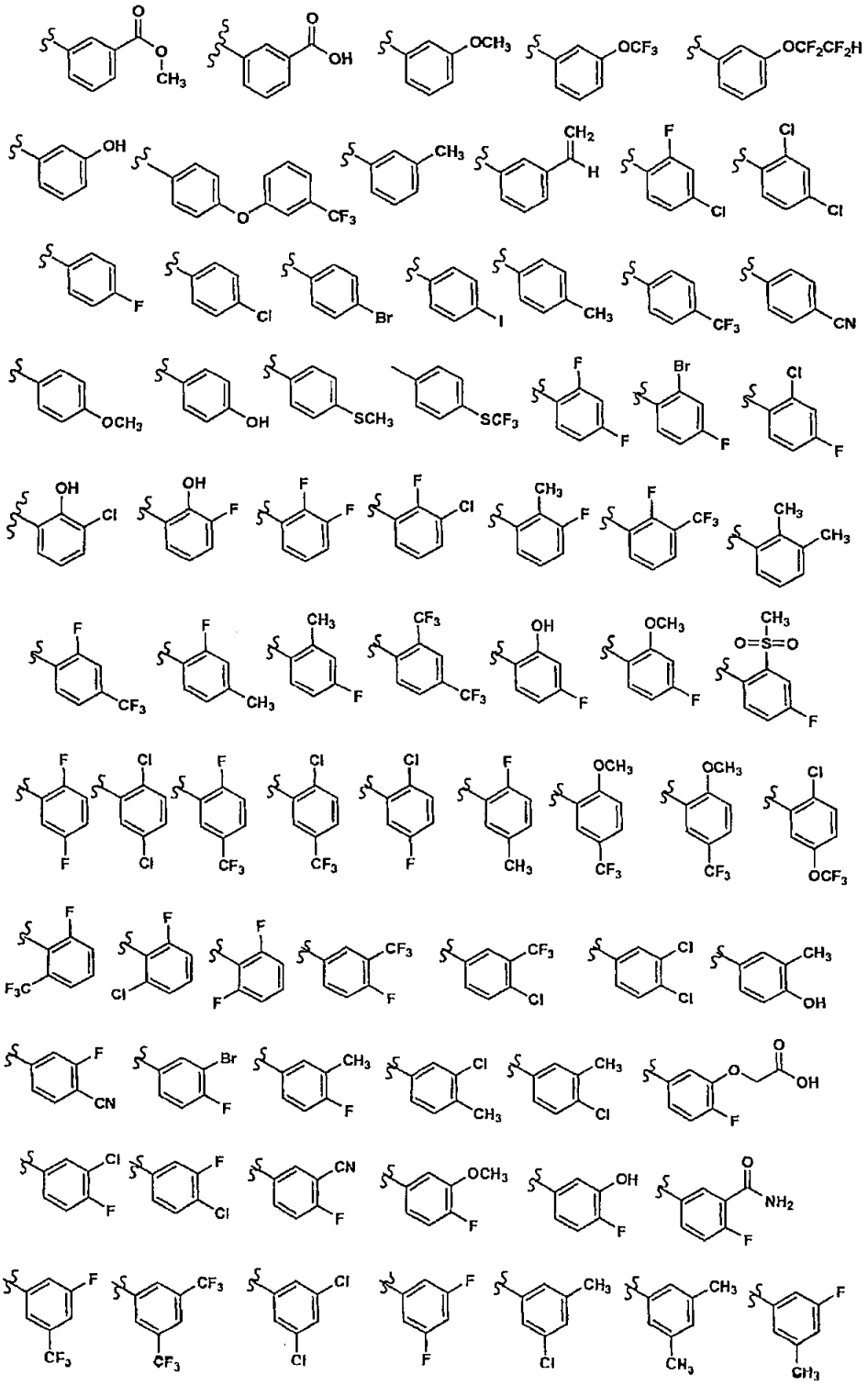


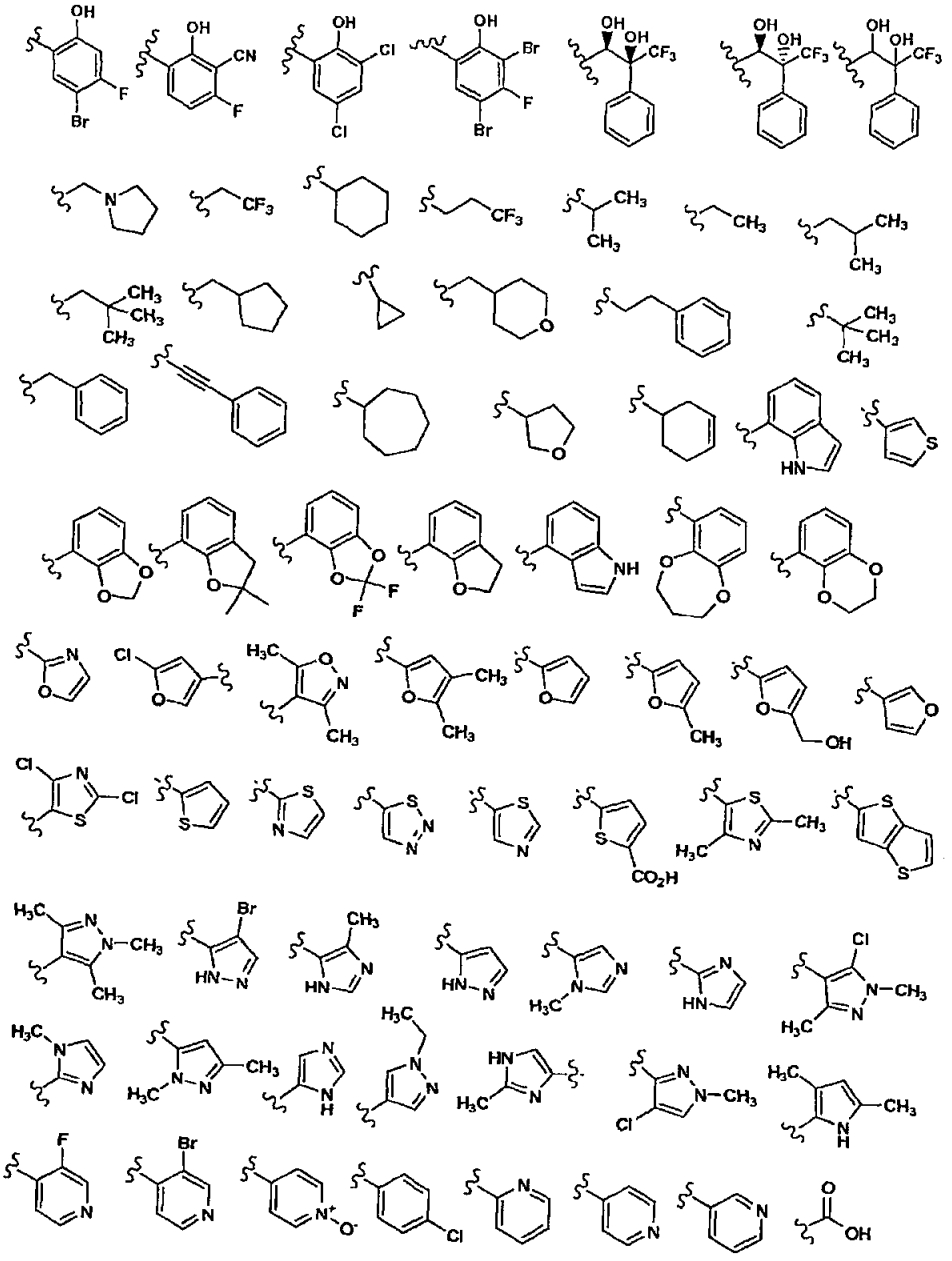
(f) -CSN$HR_7$ wherein the $R_7$ is:

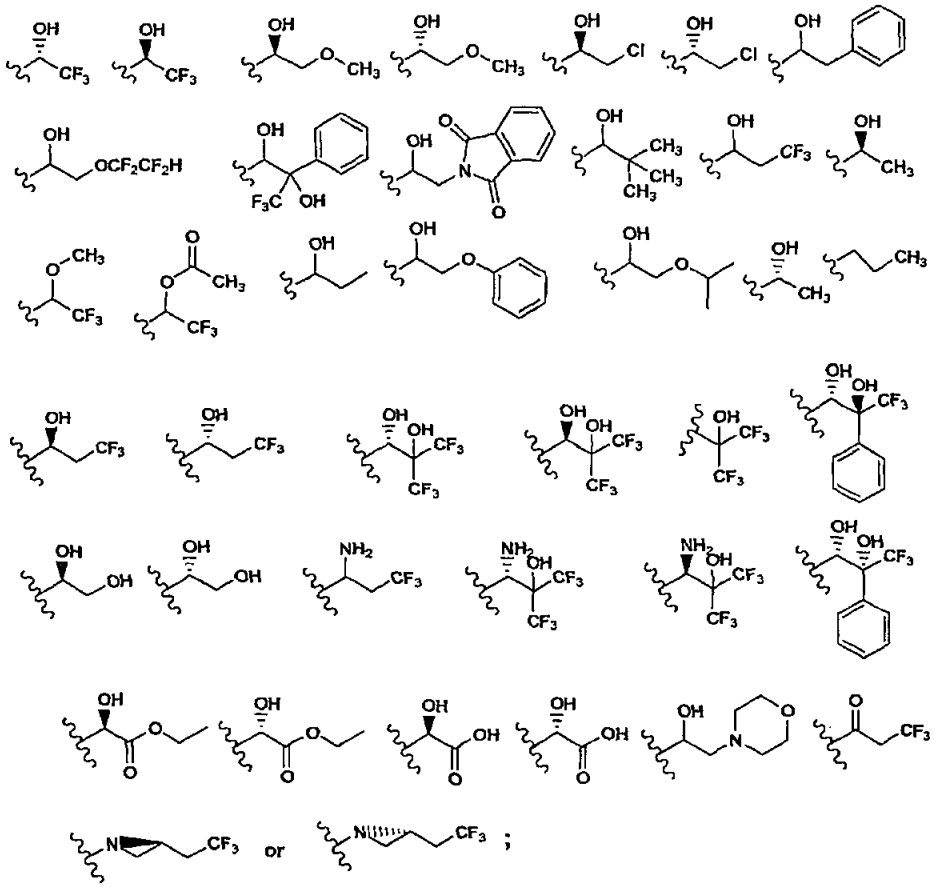


(g) $-CH_2R_8$ wherein the $R_8$ is:

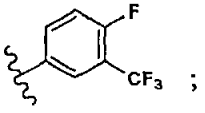






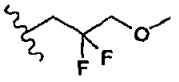


(h) -C(S)$R_3$ wherein the $R_3$ is:



;

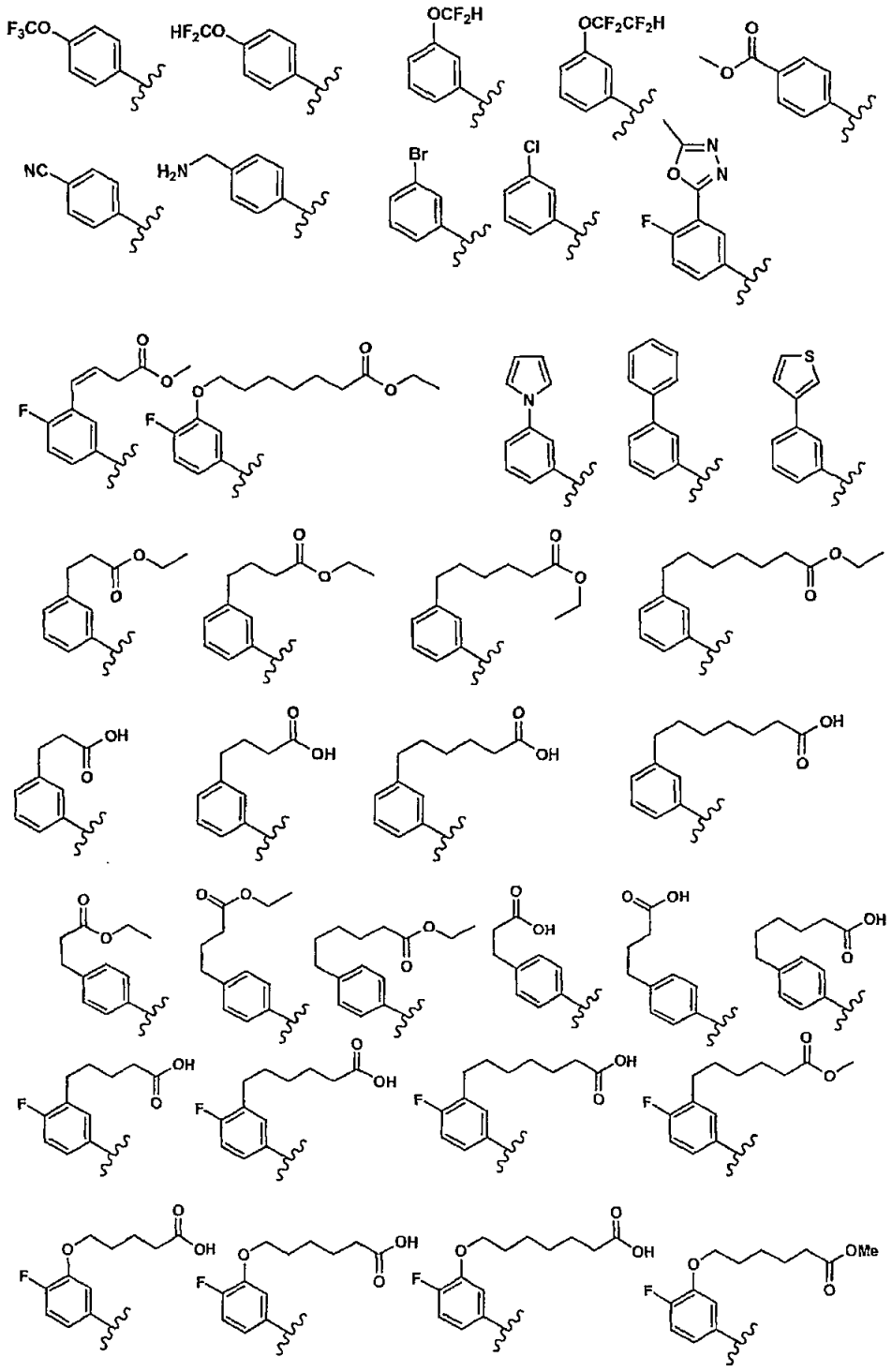
(i) –C(=N$R_3$)Oalkyl wherein the $R_3$ is:

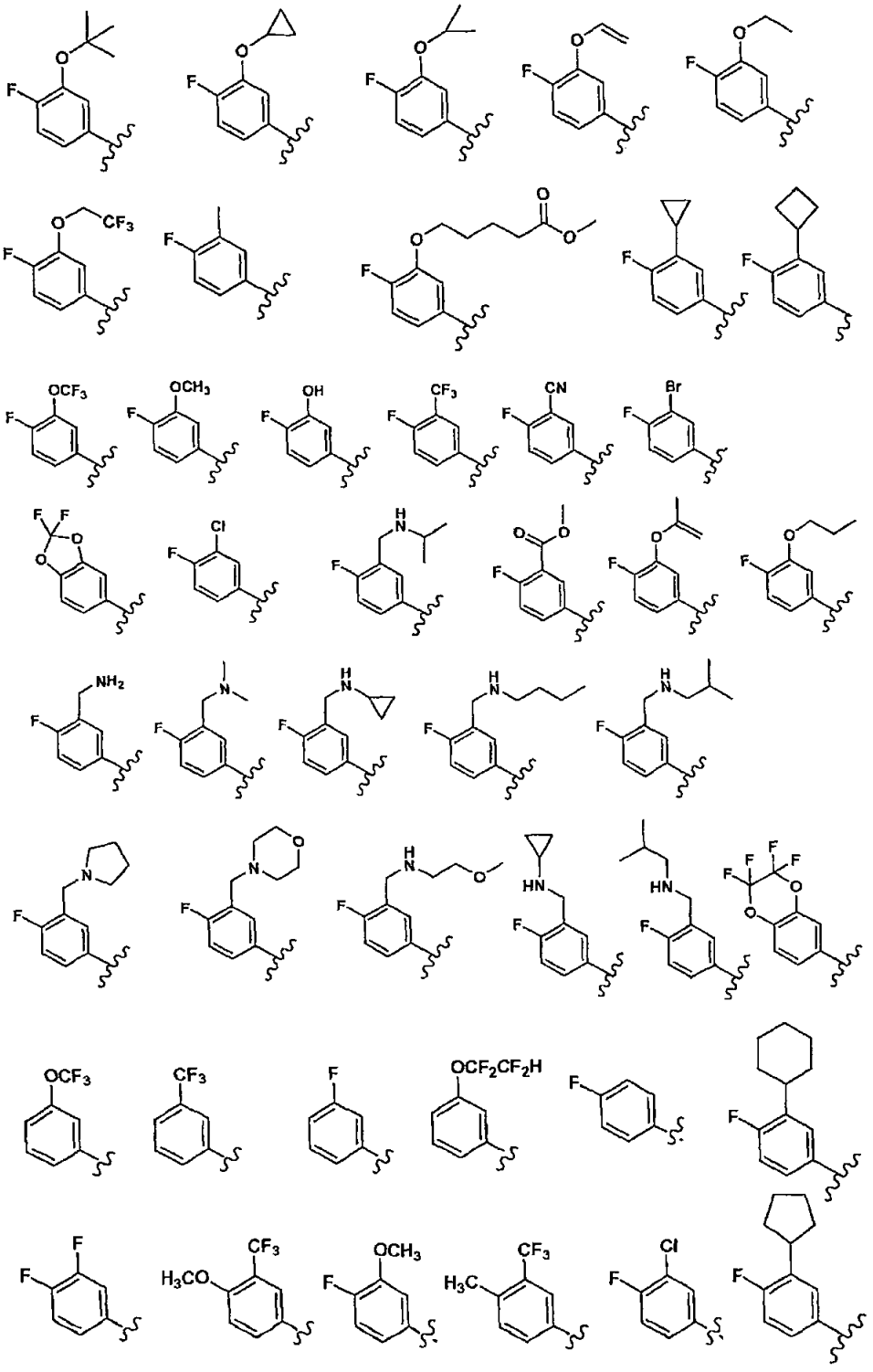


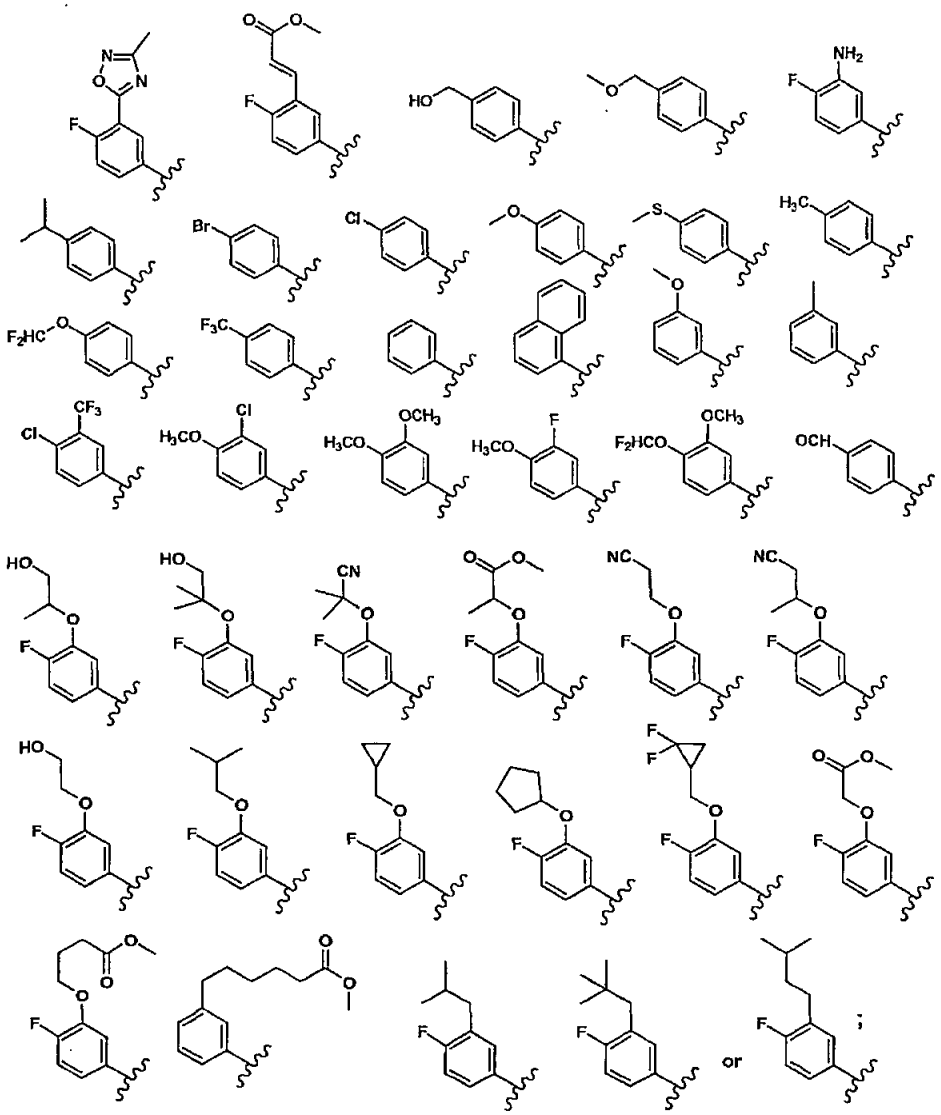
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11. A compound of claim 2, wherein:

A is:

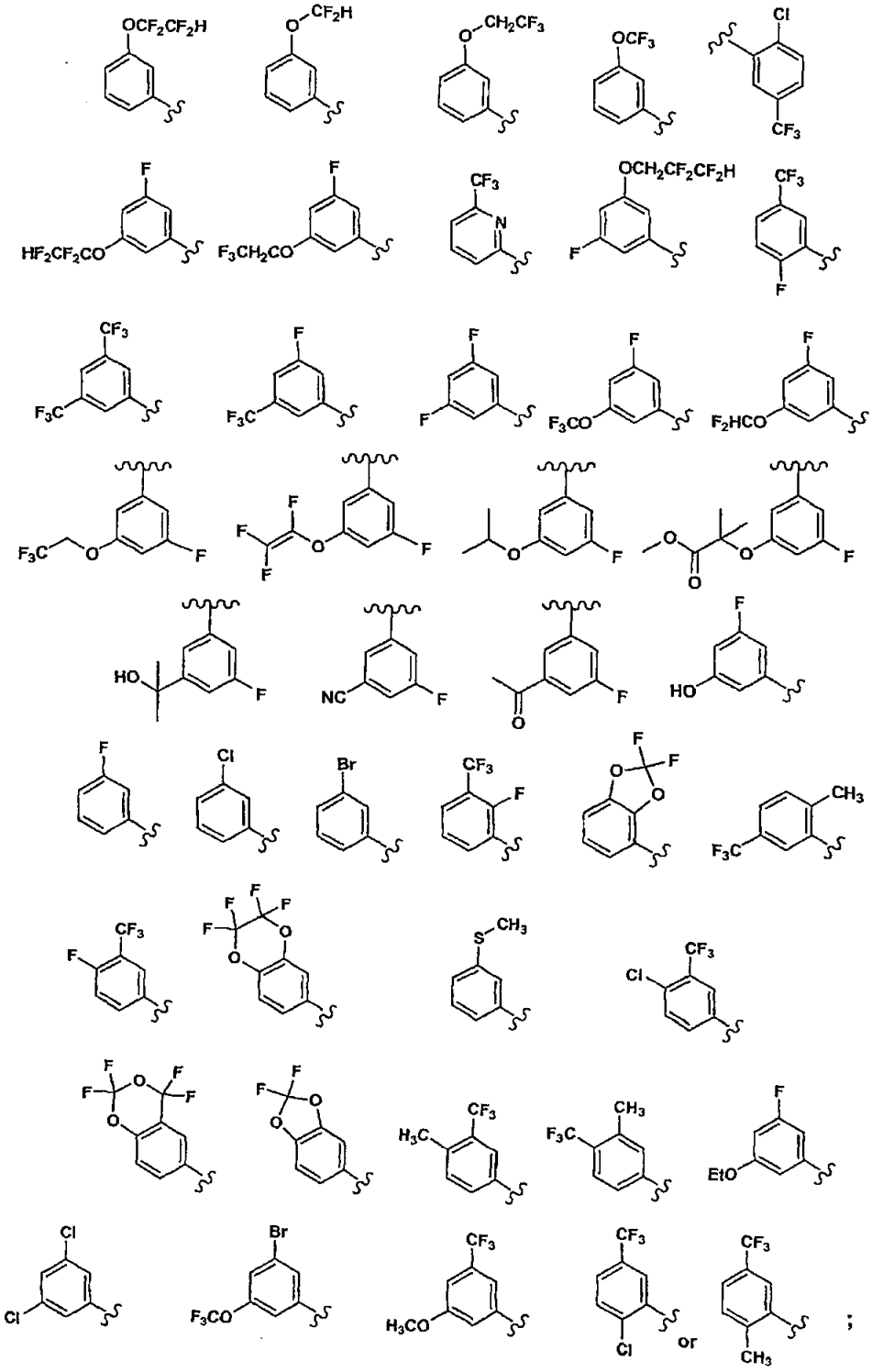






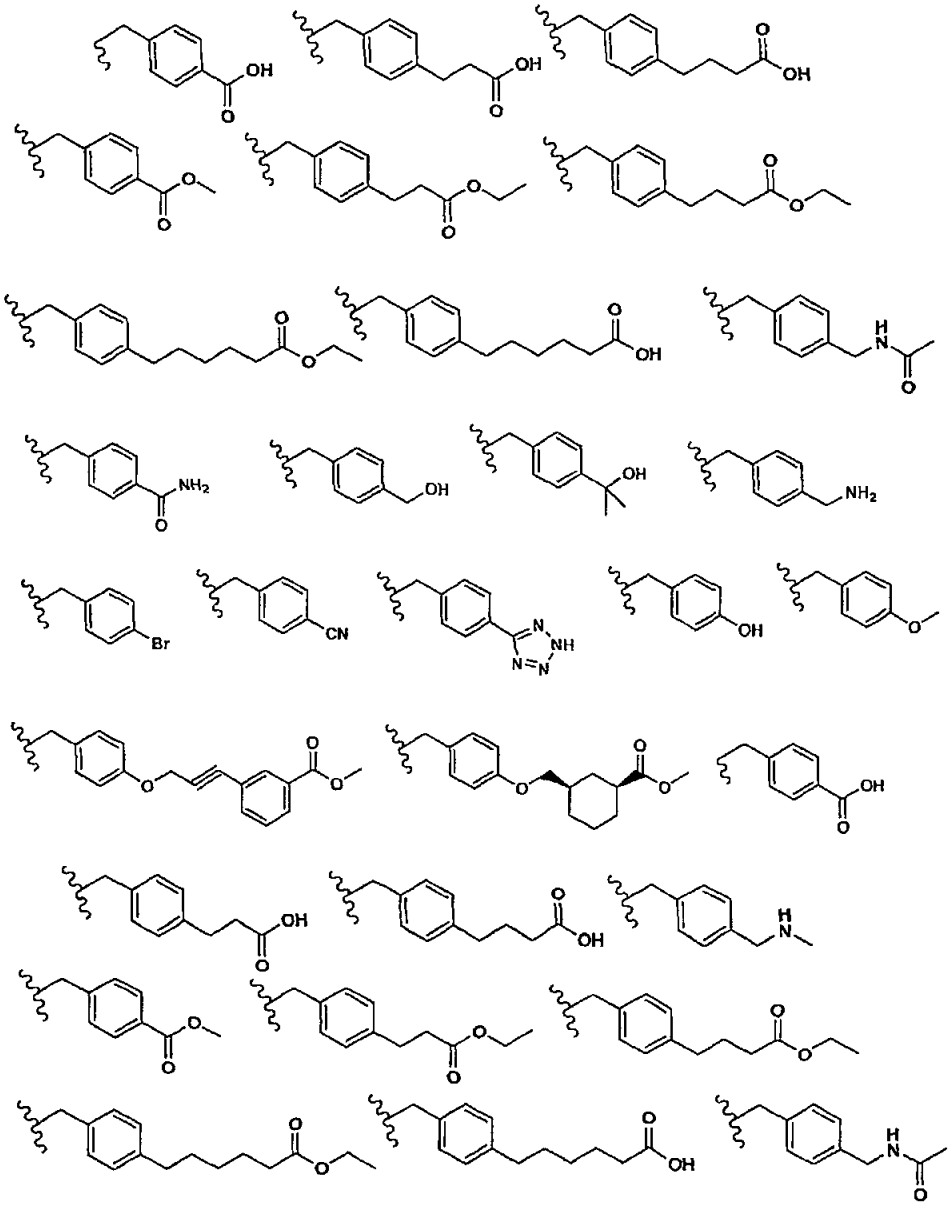
B is:

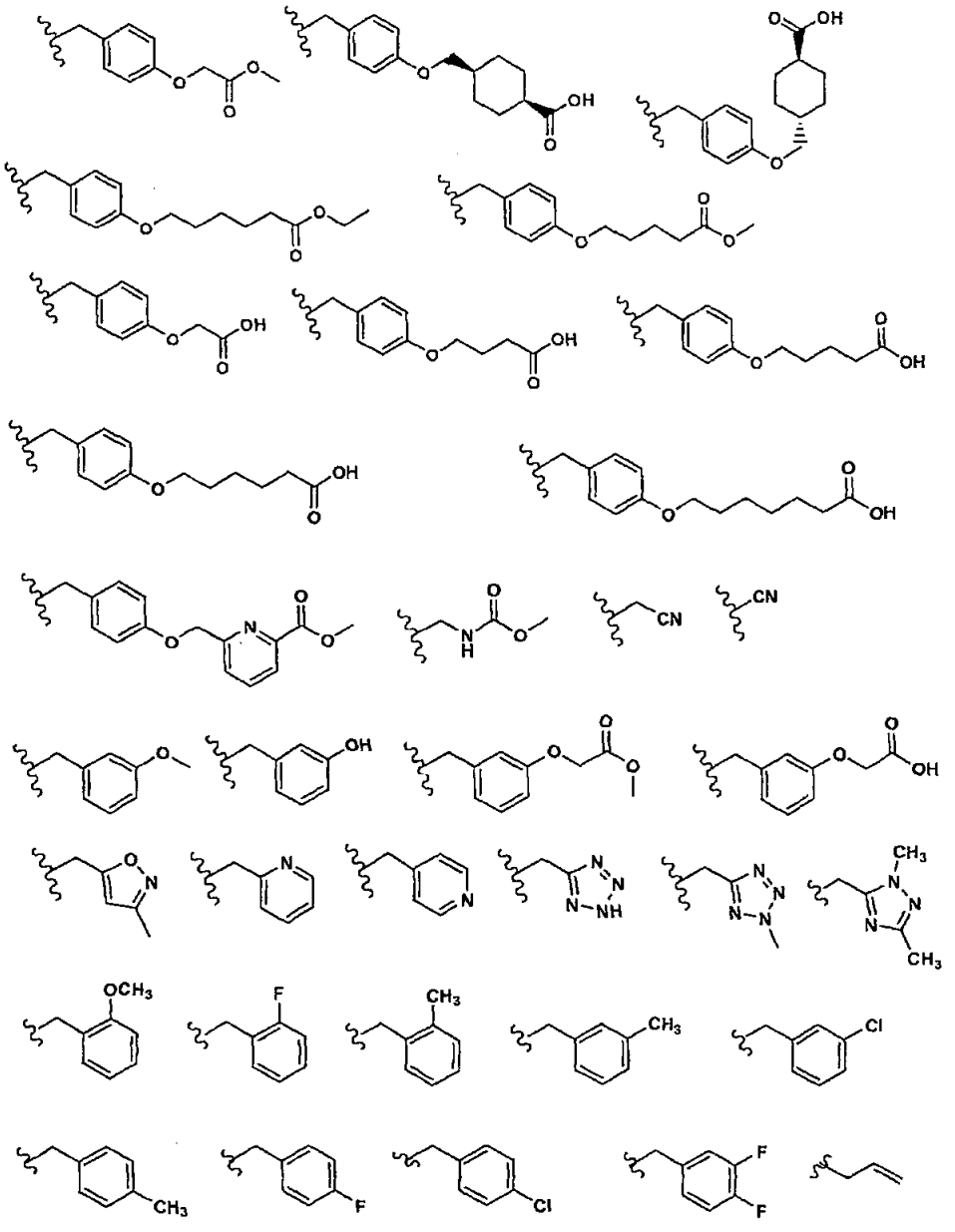
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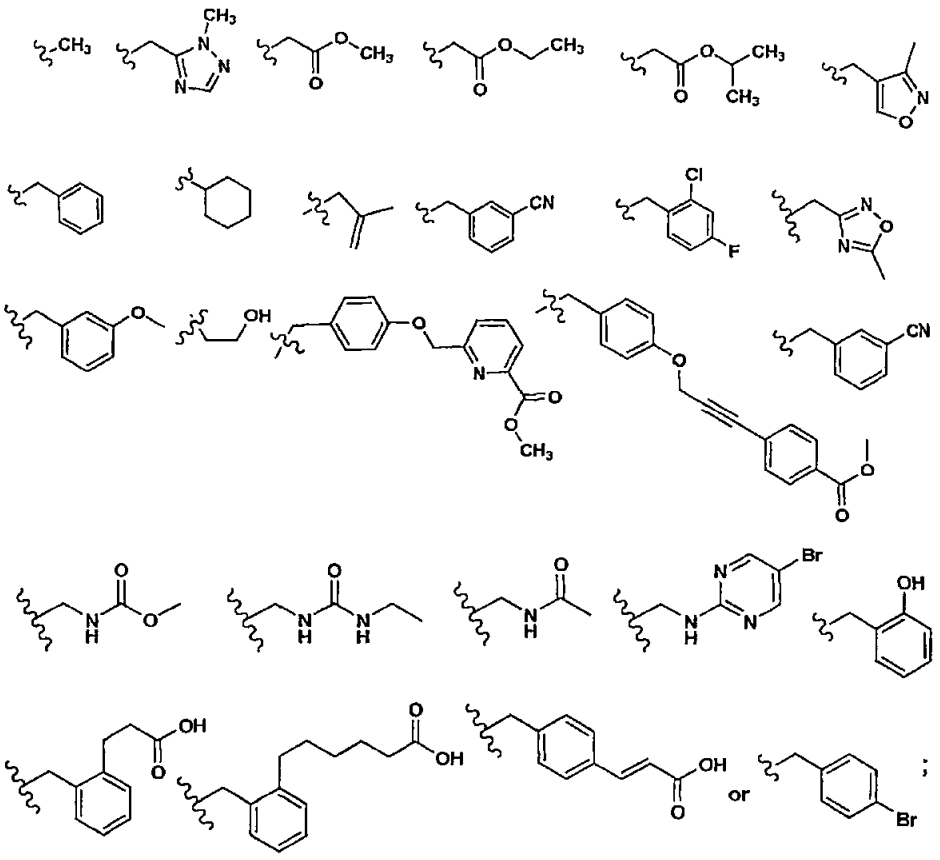


;

C is:

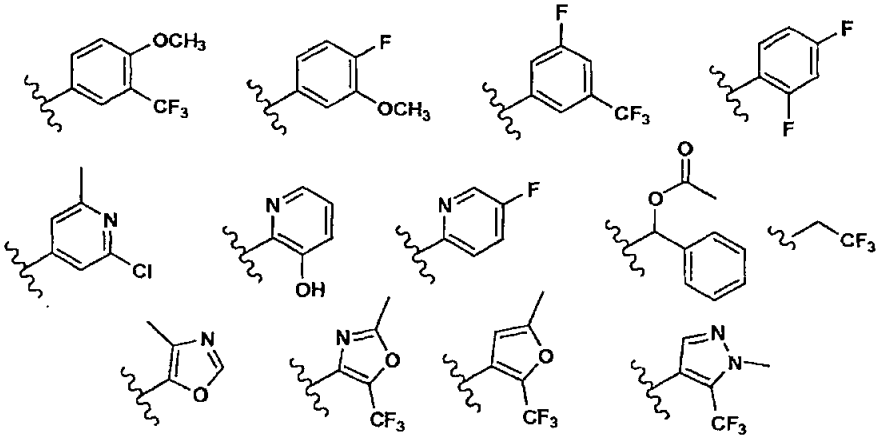


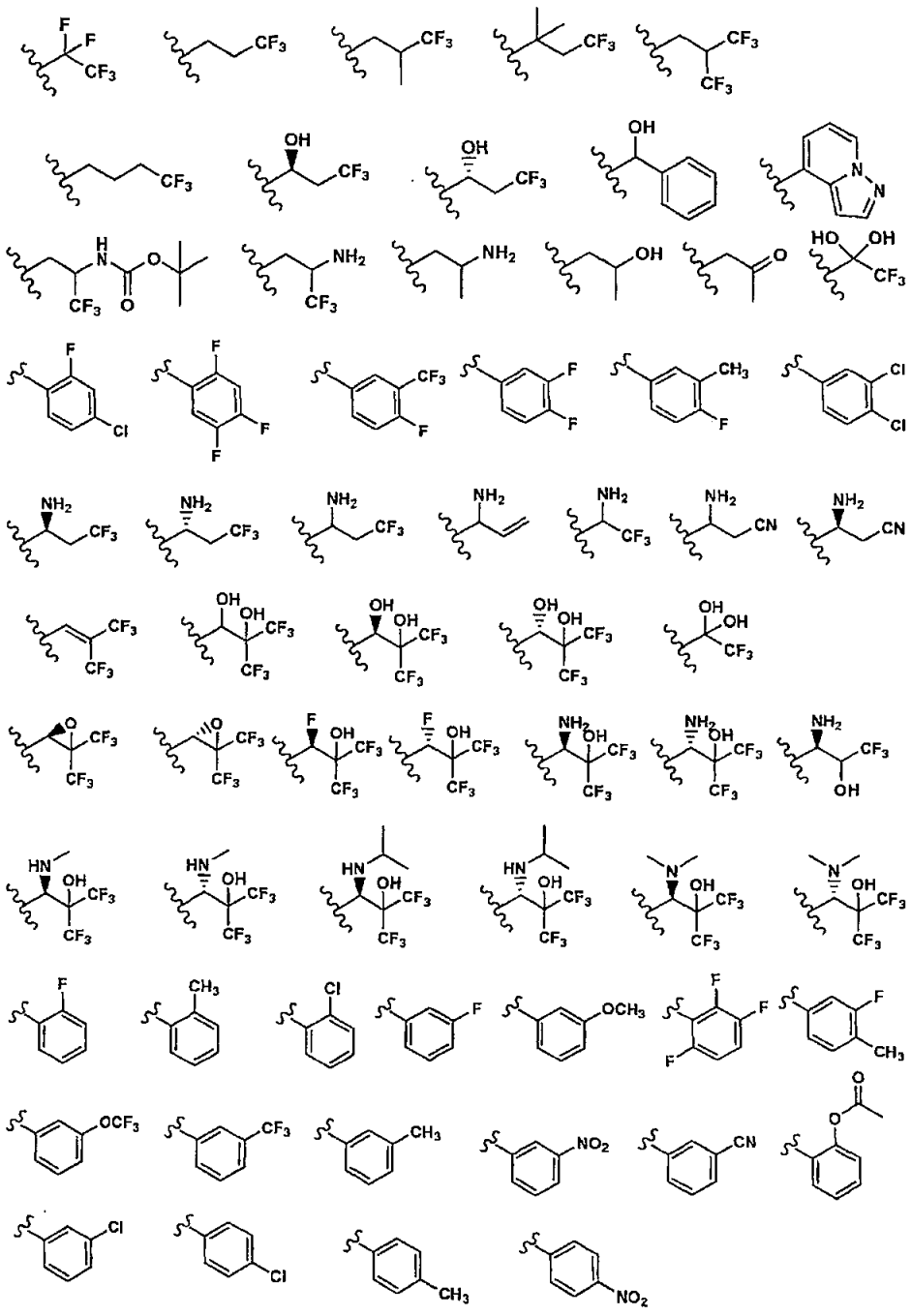


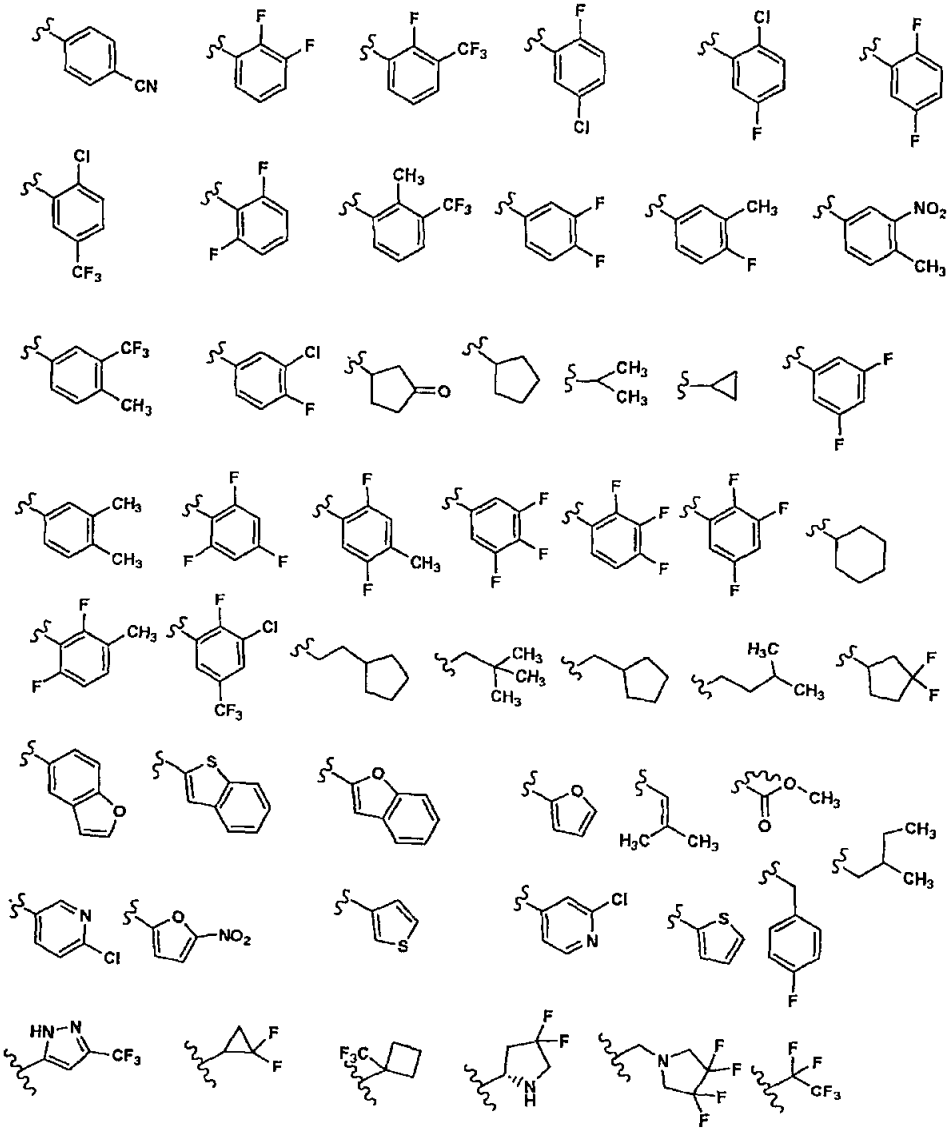


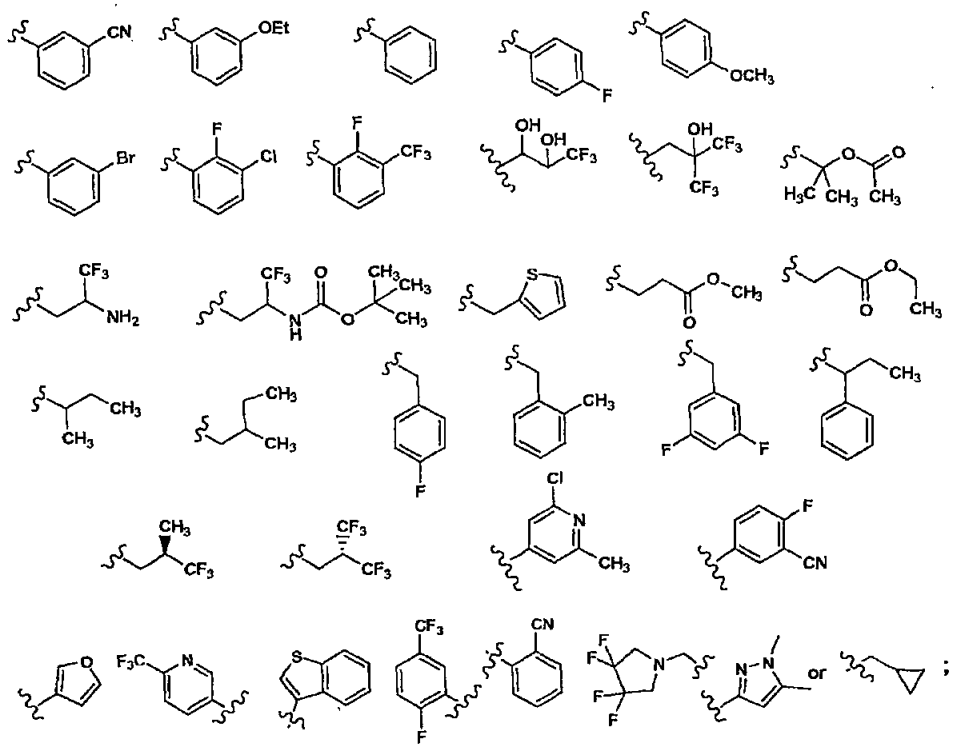
$R_1$ is H or:

(a) $-C(O)R_3$, wherein $R_3$:

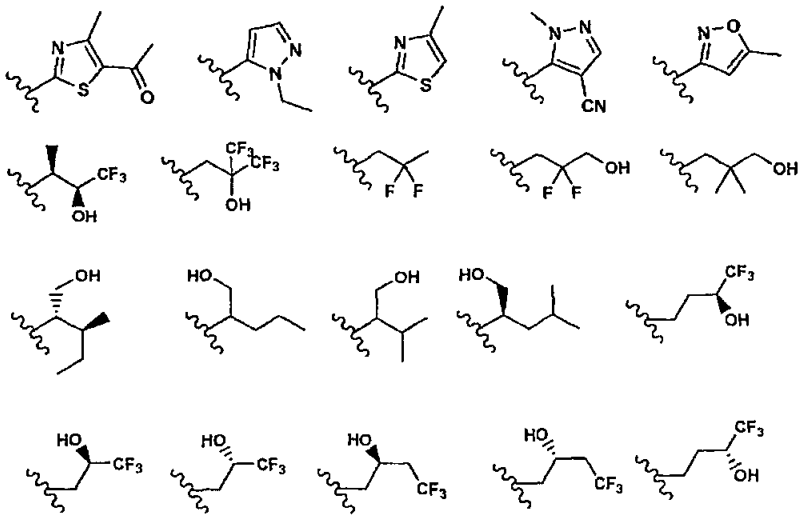


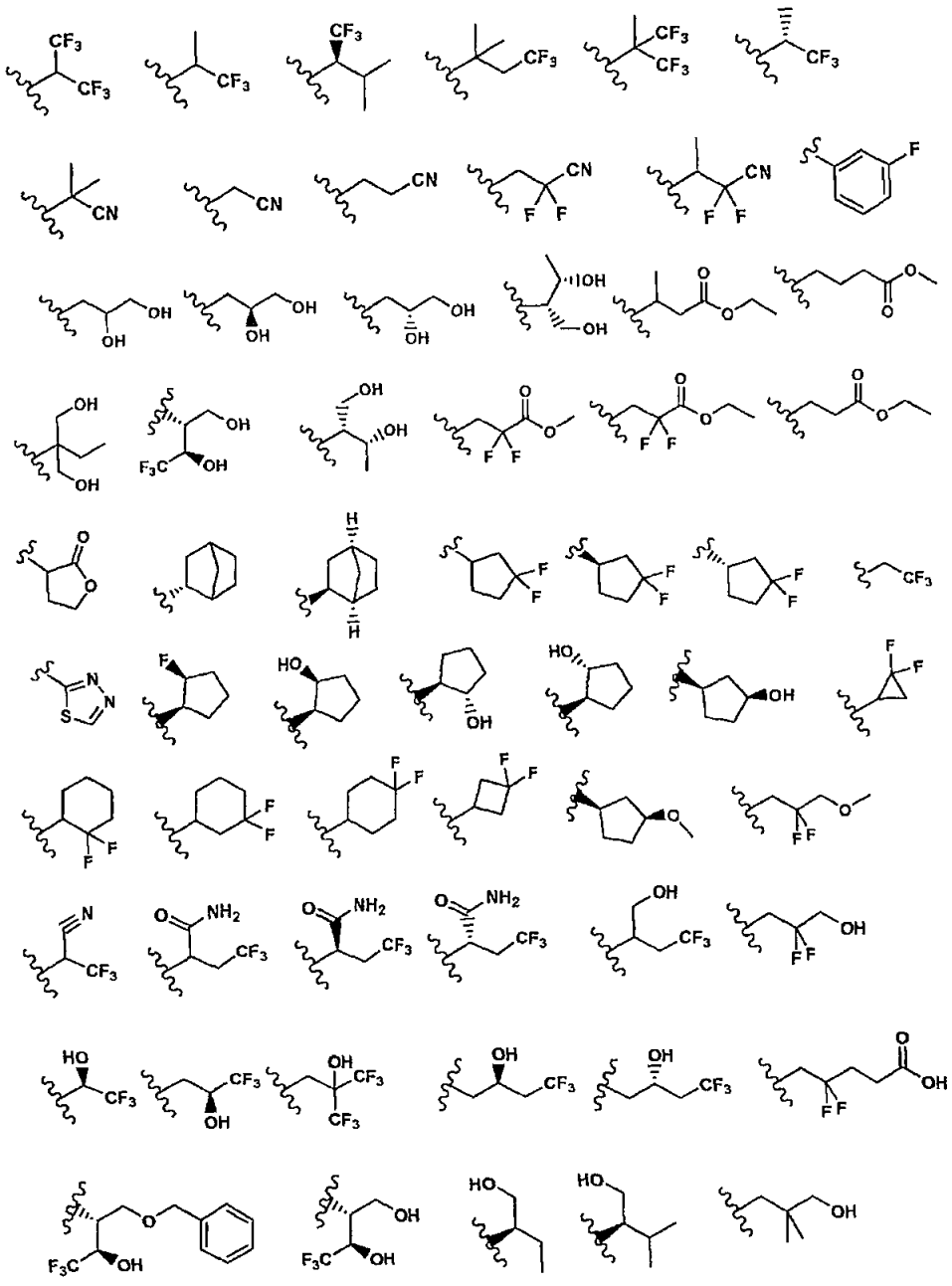


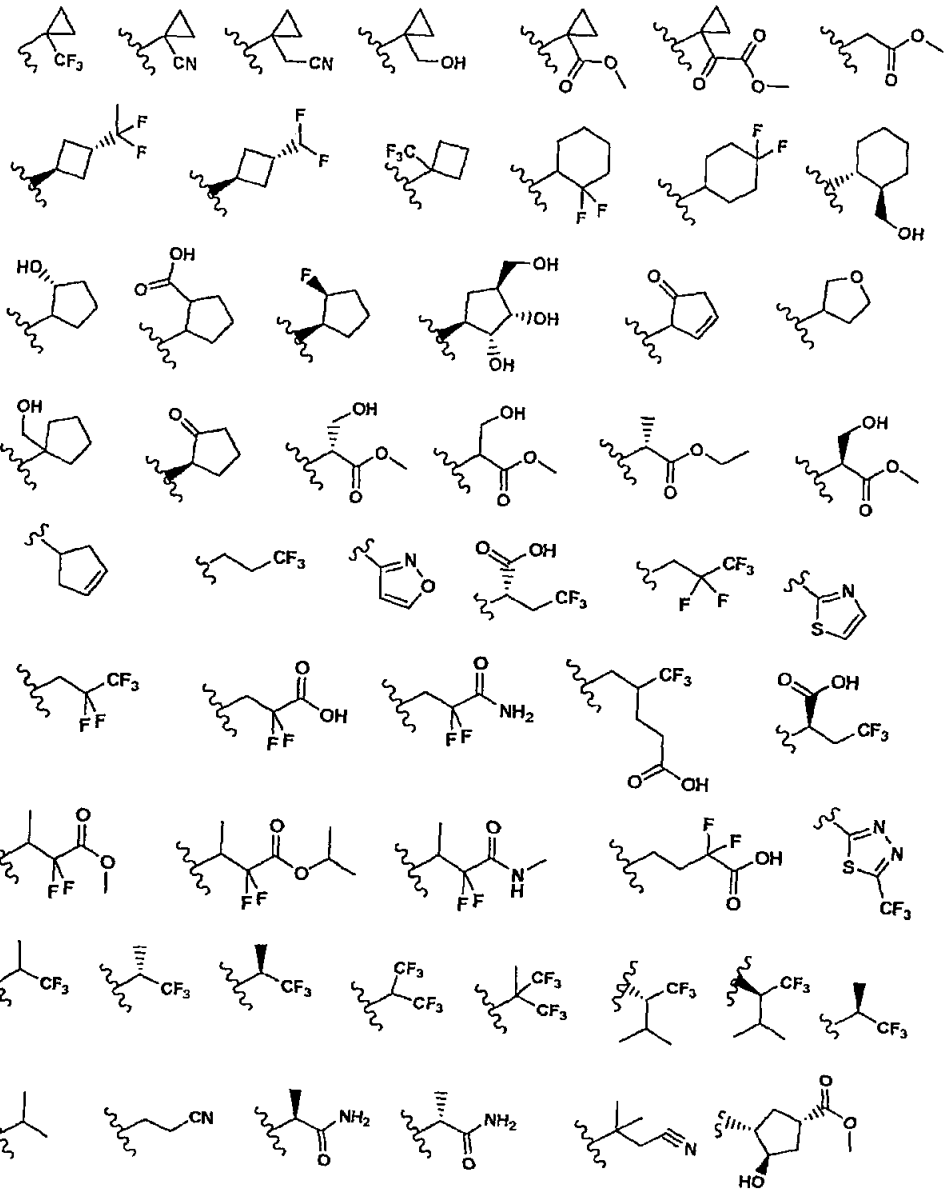




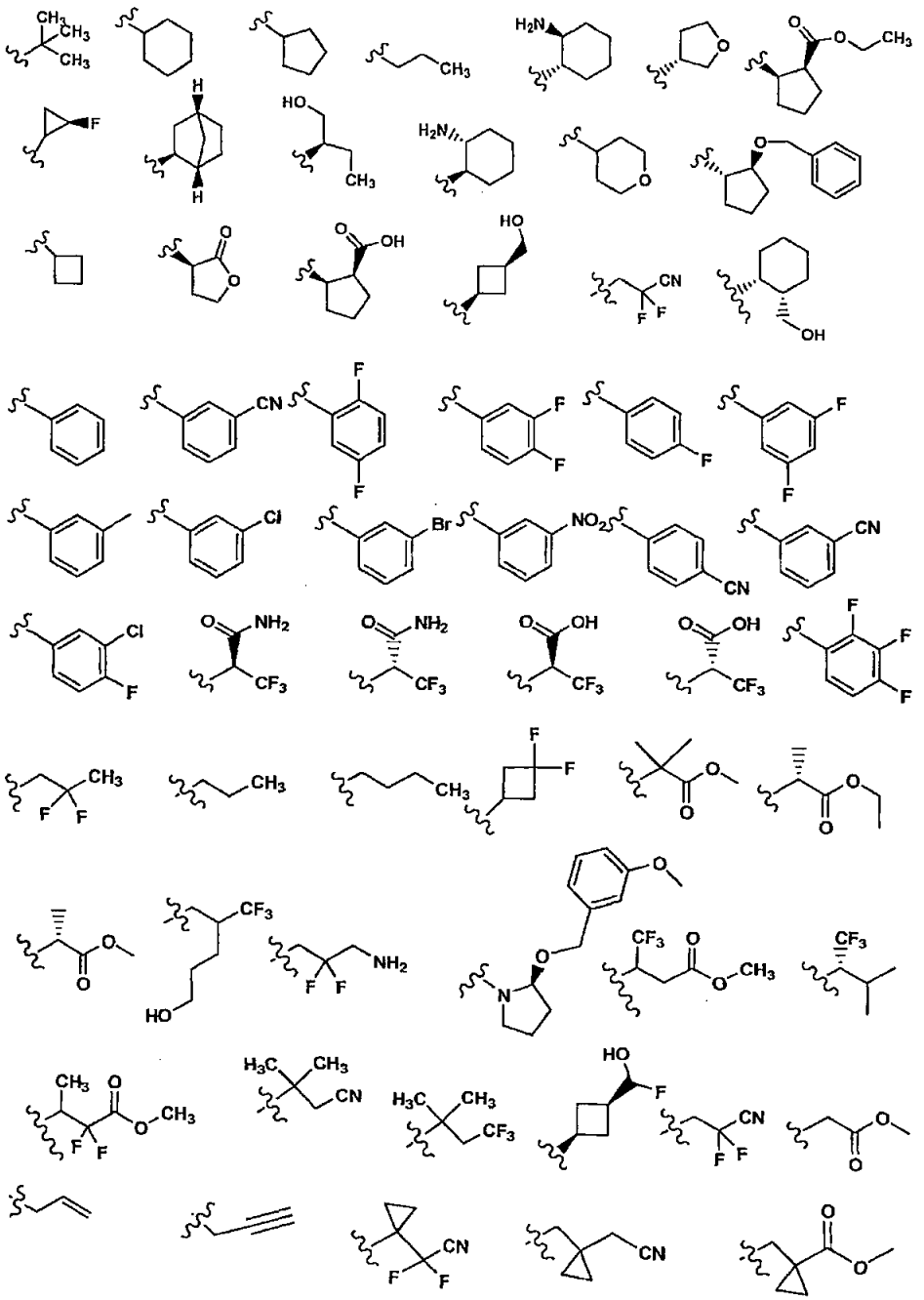
(b) -C(O)NHR$_3$, wherein the R$_3$ is:

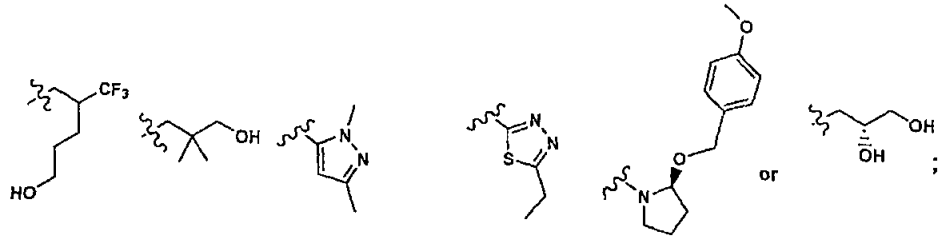




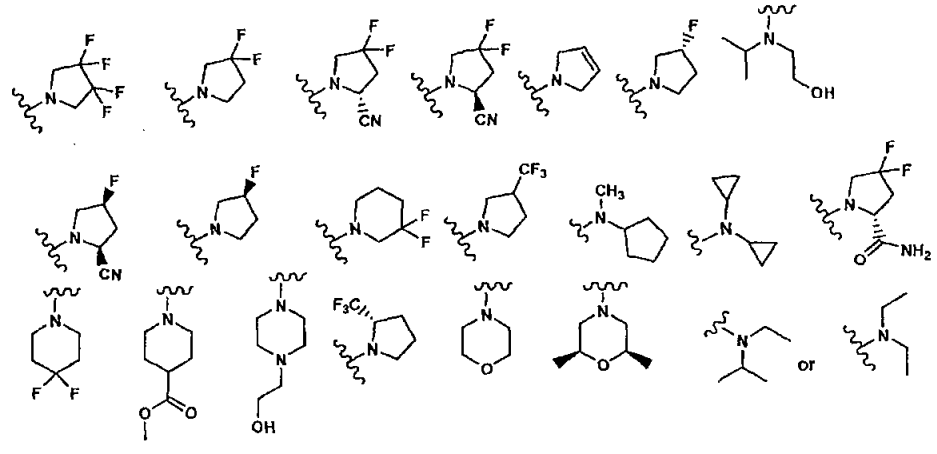


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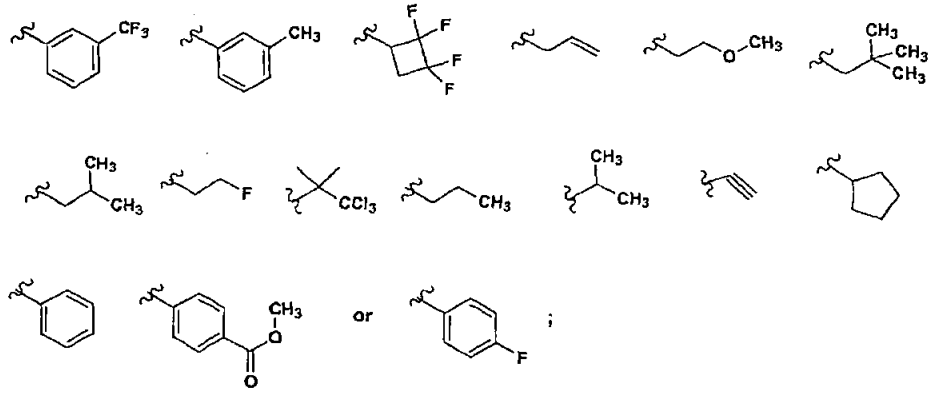




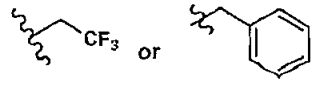
(c) -C(O)$NR_2R_3$, wherein the $NR_2R_3$ is:



(d) -C(O)$OR_4$ wherein the $R_4$ is:

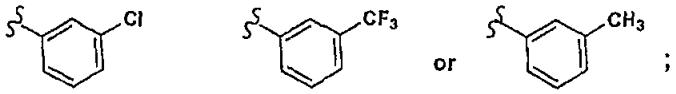


(e) $-SO_2R_5$ wherein the $R_5$ is:



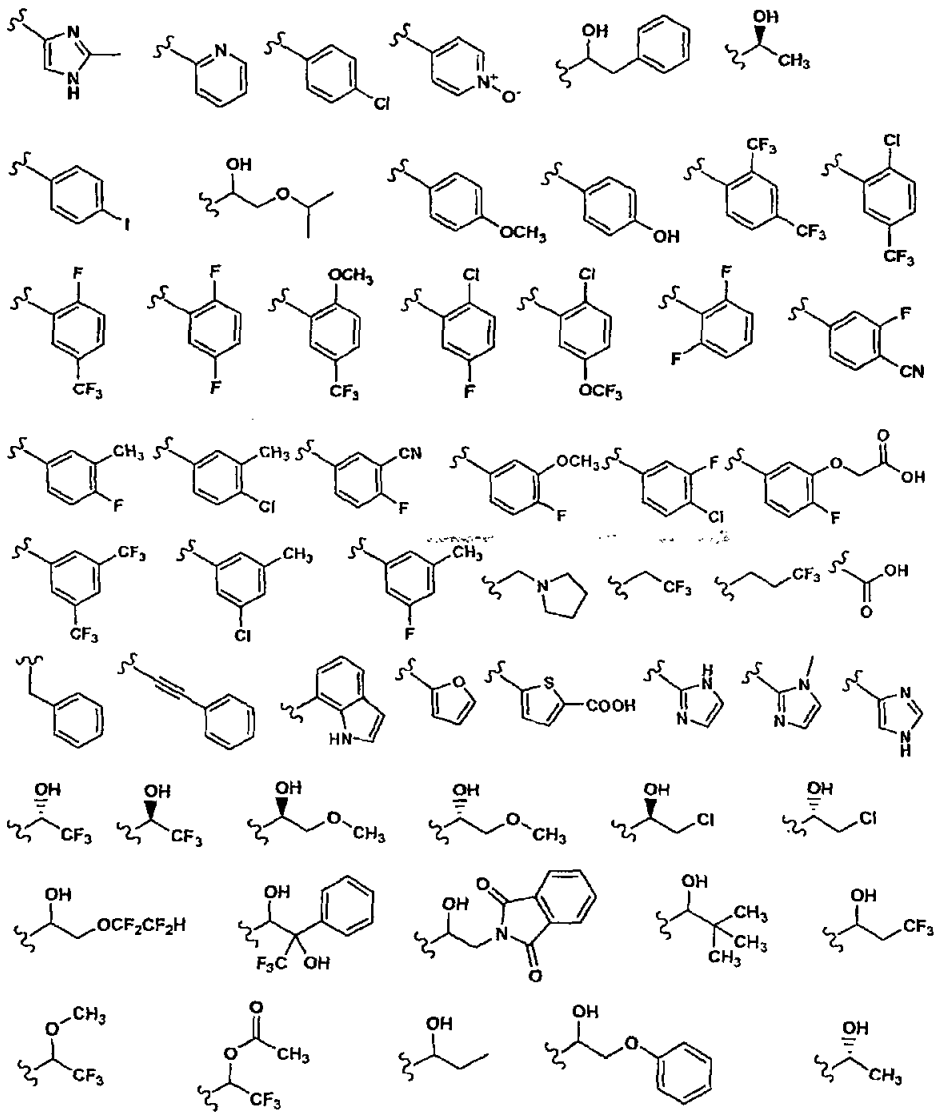
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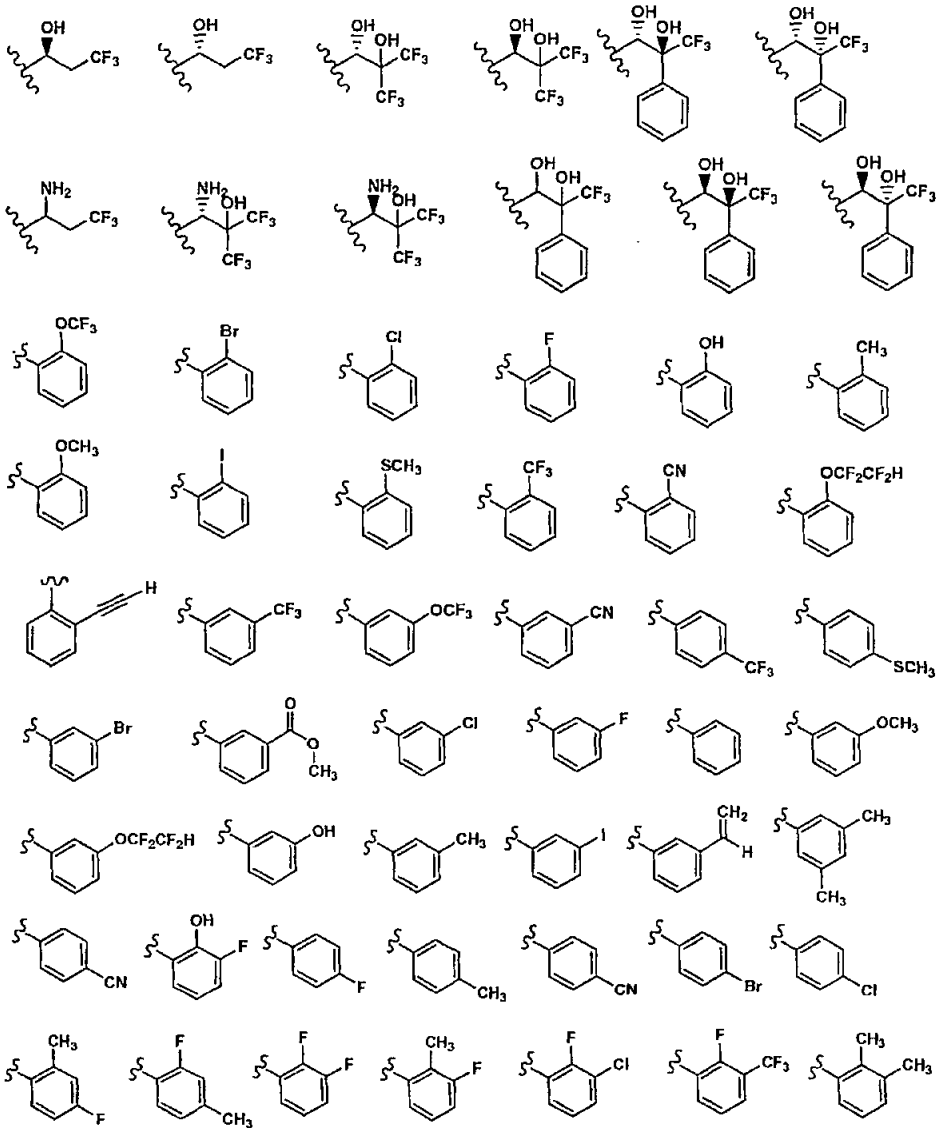
(f) -CSNHR$_7$ wherein the R$_7$ is:



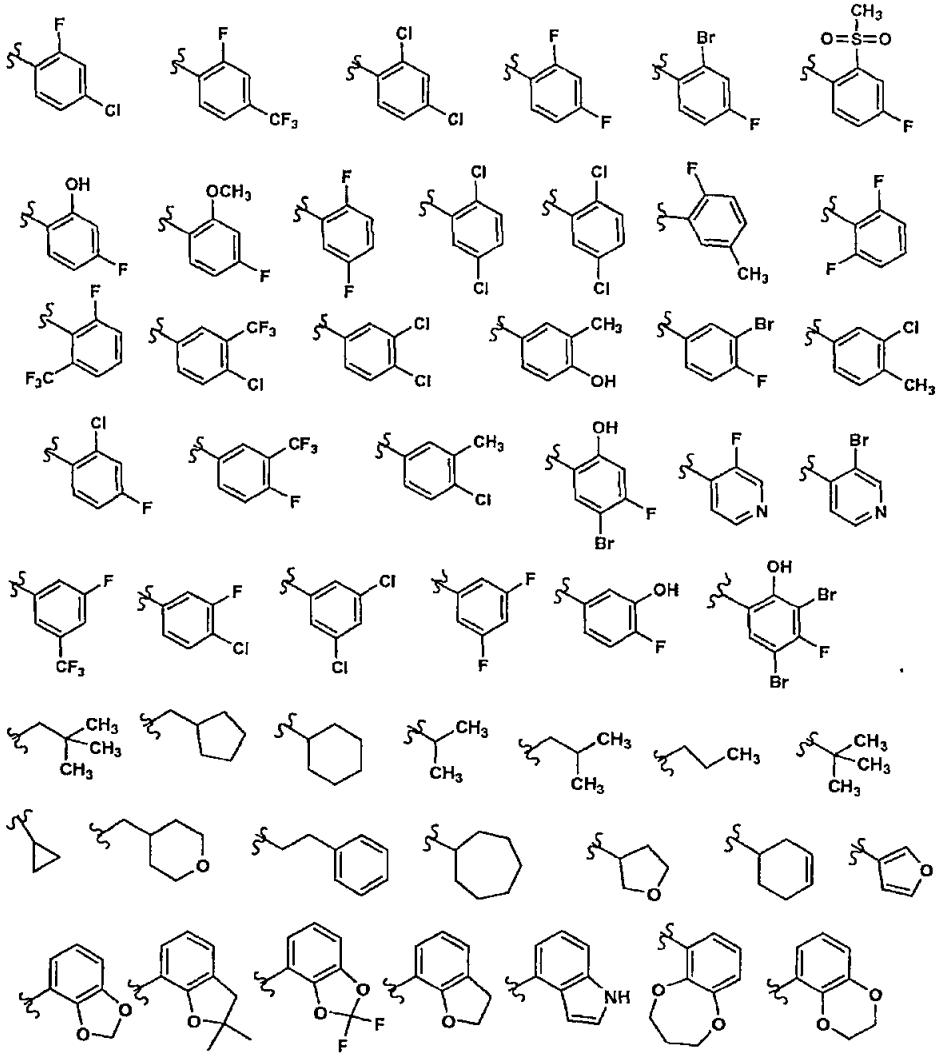
or ;

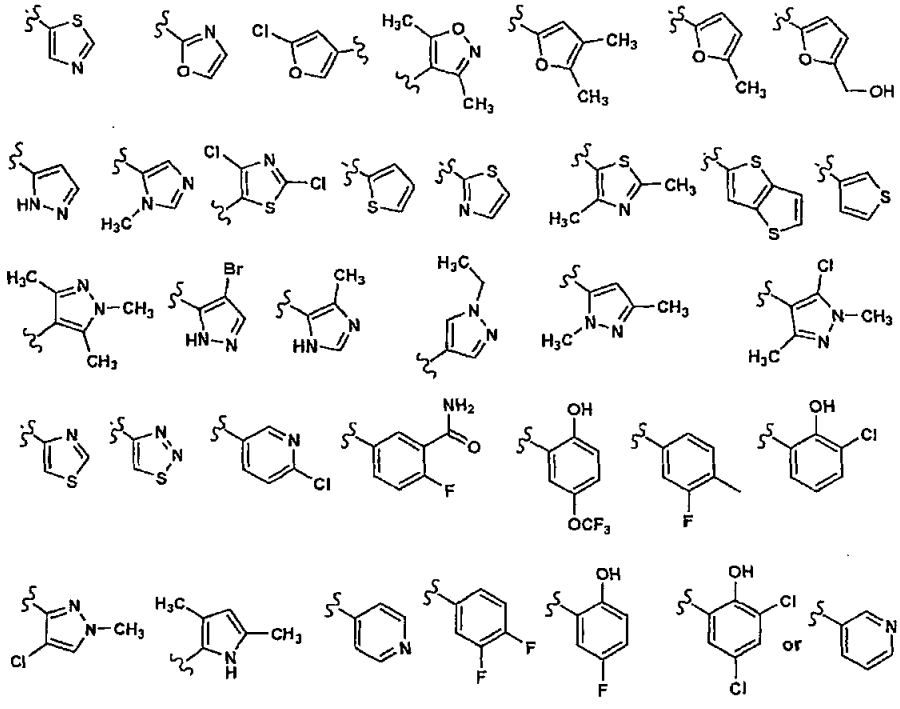
(g) –CH$_2$R$_8$ wherein the R$_8$ is:



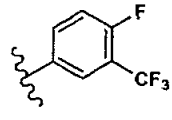


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(h) –C(S)$R_3$, wherein $R_3$:



12. A pharmaceutical composition comprising a compound of claim 1.

13. The pharmaceutical composition of claim 12 further comprising a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 12 further comprising at least one additional therapeutic agent.

15. A method of inhibiting the cholesteryl ester transfer protein which comprises administering to a mammal in need of treatment a therapeutically effective amount of a compound of claim 1.

16. A method for treating, preventing or slowing the progression of Alzheimer's, atherosclerosis, venous thrombosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia in a mammal by administering to a mammal in need of such treatment an atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia treating, preventing or slowing amount of a compound of claim 1.

17. A method for treating, preventing or slowing the progression of a disease requiring cholesteryl ester transfer protein inhibitor therapy which comprises administering, concurrently or sequentially, to a mammal in need of treatment, prevention or slowing a therapeutically effective amount of a compound of claim 1 and at least one additional therapeutic agent.

18. A method for inhibiting remnant lipoprotein production which comprises administering to a mammal a compound of claim 1.

19. A method of raising HDL cholesterol in a mammal which comprises administering to a mammal in need of treatment at least one compound of claim 1.

20. A compound of claim 1, wherein the compound is exemplified in the examples.

21. A process for the preparation of mainly a compound of formula **WW**, B-$OCF_2CF_2H$, comprising reducing a mixture comprised of a compound of formula **WW** and a compound of formula **YY**, B-$OCF_2CF_2Br$, with zinc dust under acidic conditions, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$, 19) –$NHC(CN)NHR_6$, and 20) –$CONR_6R_6$ and $R_6$, $R_9$ and $R_{10}$ are as defined in claim 1.

22. A process for the preparation of a mixture comprised of a compound of formula **WW** and a compound of formula **YY**, B-$OCF_2CF_2Br$, comprising reacting a compound of formula **ZZ**, B-OH, with 1,2-dibromotetrafluoroethane under basic conditions, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) ($C_1$-$C_6$)-alkyl, which may be optionally substituted with one or more $R_{20}$'s, 3) -$OR_6$, 4) ($C_1$-$C_6$)-alkylthio, 5) cyano, 6) nitro, 7) -$NR_9R_{10}$, 8) aryl, which may be optionally substituted with one or more $R_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more $R_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more $R_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more $R_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more $R_{20}$'s, and 14) halo($C_1$-$C_6$)alkyl, 15) –$COR_6$, 16) –$S(O)_pR_6$, 17) –$SO_2NHR_6$, 18) –$COOR_6$,

19) –NHC(CN)NHR$_6$, and 20) –CONR$_6$R$_6$ and R$_6$, R$_9$ and R$_{10}$ are as defined in claim 1.

23. A process for the preparation of a compound of formula **ZZ** comprising reacting a compound of formula **AAA**, B-F, with potassium trimethylsilanoate in a solvent other than THF, wherein B is phenyl, which may be optionally substituted with one or more substituents selected from the group consisting of: 1) halo, 2) (C$_1$-C$_6$)-alkyl, which may be optionally substituted with one or more R$_{20}$'s, 3) -OR$_6$, 4) (C$_1$-C$_6$)-alkylthio, 5) cyano, 6) nitro, 7) -NR$_9$R$_{10}$, 8) aryl, which may be optionally substituted with one or more R$_{20}$'s, 9) arylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 10) heteroaryl, which may be optionally substituted with one or more R$_{20}$'s, 11) heteroarylalkyl, which may be optionally substituted with one or more R$_{20}$'s, 12) heterocyclyl, which may be optionally substituted with one or more R$_{20}$'s, 13) heterocyclylalkyl, which may be optionally substituted with one or more R$_{20}$'s, and 14) halo(C$_1$-C$_6$)alkyl, 15) –COR$_6$, 16) –S(O)$_p$R$_6$, 17) –SO$_2$NHR$_6$, 18) –COOR$_6$, 19) –NHC(CN)NHR$_6$, and 20) –CONR$_6$R$_6$ and R$_6$, R$_9$ and R$_{10}$ are as defined in claim 1.

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835

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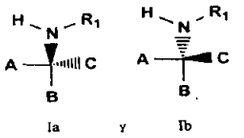
(74) Agente: **BOGIE, Terence J.** y otros; Bristo-Myers Squibb Company, Apartado Postal 4000, New Jersey 08543-4000 (US).

81) Estados Designados (*a menos que se indique otra cosa, para cada clase de protección nacional ):*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, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados Designados *(a menos que se indique otra cosa para cada tipo de protección regional disponible):* ARIPO, (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW) Eurasia (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europa (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),

*[continúa en siguiente página]*

(54) Titulo: INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTEROL




Ia y Ib

(57) Resumen: Compuestos de la fórmula (Ia) y (Ib) en donde A, B, C y $R_1$ se describen en la presente.

OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declaraciones bajo la Regla 4.17:**

___*según el derecho del solicitante para solicitar y otorgársele una patente (Regla 4.17 (ii))*

___*según el derecho del solicitante para reclamar la prioridad de la solicitud anterior (Regla 4.17 (iii)).*

**Publicada:**

___*sin reporte de búsqueda internacional y para publicarse en el caso de la recepción de ese reporte.*

*Para códigos de dos letras y otras abreviaturas, referirse a las "Notas Guía sobre Códigos y Abreviaturas" que aparecen al inicio de cada punto regular del Boletín Oficial PCT*

# COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO

## CAMPO DE LA INVENCION

Esta presente invención proporciona inhibidores de la proteína de transferencia de éster de colesterilo (CETP, por sus siglas en inglés), composiciones farmacéuticas que contienen tales inhibidores y el uso de tales inhibidores para elevar ciertos niveles de lípidos en el plasma, incluyendo lipoproteína de alta densidad (HDL, por sus siglas en inglés)-Colesterol y para reducir otros ciertos niveles de lípido en el plasma, tales como lipoproteína de baja densidad (LDL, por sus siglas en inglés)-Colesterol y triglicéridos y en consecuencia tratar enfermedades que se ven afectadas por niveles bajos de colesterol HDL y/o niveles altos de LDL-Colesterol y triglicéridos, tales como ateroesclerosis y enfermedades cardiovasculares en ciertos mamíferos (esto es, aquellos que tienen CETP en su plasma), incluyendo humanos.

## ANTECEDENTES DE LA INVENCION

La ateroesclerosis y su enfermedad arterial coronaria asociada (CAD, por sus siglas en inglés) es la causa principal de mortalidad en el mundo industrializado. A pesar de los intentos por modificar los factores de riesgo secundarios (fumar, obesidad, carencia de ejercicio) y tratamiento de dislipidemia con modificación de dieta y terapia de fármaco, la enfermedad cardiaca coronaria (CHD,

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por sus siglas en inglés) se mantiene como la causa más común de muerte en los Estados Unidos de América, donde la muerte cardiovascular representa el 44% de todas las muertes, con el 53% de estas asociadas con enfermedad cardiaca coronaria ateroesclerótica.

El riesgo de desarrollar ateroesclerosis se ha mostrado que está fuertemente correlacionado con ciertos niveles de lípidos en el plasma. Aunque el LDL-C elevado puede ser la forma más reconocida de dislipidemia, puede no ser el único contribuidor asociado con lípidos importante para la CHD. El HDL-C bajo también es un factor de riesgo conocido para CHD (Gordon, D. J., y col., "High-density Lipoprotein Colesterol and Cardiovascular Disease", Circulation, (1989), 79: 8-15).

Los altos niveles de colesterol LDL y triglicéridos se correlacionan positivamente, mientras que los altos niveles de colesterol HDL se correlacionan negativamente con el riesgo para desarrollar enfermedades cardiovasculares. De esta manera, la dislipidemia no es un perfil de riesgo unitario para CHD, pero puede estar comprendida de una o más aberraciones lípidas.

Entre los muchos factores que controlan los niveles de plasma de estos principios que dependen de la enfermedad, la actividad de la proteína de transferencia del éster de colesterilo (CETP) afecta los tres. El papel de esta

glicoproteína de plasma de 70,000 daltones que se encuentra en un número de especies animales, incluyendo humanos, es el transferir el éster de colesterilo y triglicérido entre las partículas de lipoproteína, incluyendo lipoproteínas de alta densidad (HDL), lipoproteínas de baja densidad (LDL), lipoproteínas de muy baja densidad (VLDL, por sus siglas en inglés), y quilomicrones. El resultado puro de la actividad de CETP es una reducción del colesterol HDL y un incremento en el colesterol LDL. Este efecto en el perfil de la lipoproteína se considera que es pro-aterogénico, especialmente en sujetos cuyo perfil de lípidos constituye un riesgo incrementado para CHD.

No existen terapias que eleven el HDL completamente satisfactorias. La niacina puede incrementar el HDL significativamente, pero tiene serios resultados de tolerancia que reducen su aceptación. Los fibratos y los inhibidores de reductasa HMG CoA enfrentan el HDL-C sólo modestamente (alrededor de 10-12%). Como resultado, hay una necesidad médica no cubierta importante para un agente bien tolerado que pueda elevar significativamente los niveles de HDL en plasma, por ello invirtiendo o retardando el progreso de la ateroesclerosis.

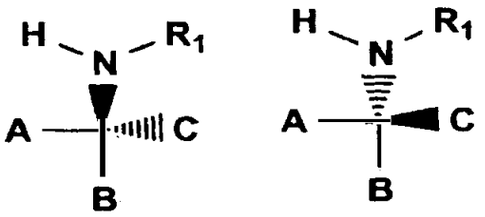
De esta manera, no obstante que hay una variedad de terapias anti-ateroesclerosis, hay una necesidad continua y una búsqueda continua en este campo de la técnica para

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terapias alternativas.

BREVE DESCRIPCION DE LA INVENCION

De conformidad con la presente invención, se proporcionan los compuestos heterocíclicos y compuestos relacionados que tienen las estructuras generales:




Ia y Ib

en donde A, B, C y $R_1$ son como se definen a continuación.

Por el uso de una cantidad efectiva respectiva de al menos un compuesto descrito en la presente, se proporcionan métodos para tratar, prevenir o retardar la progresión de una enfermedad que requiere la inhibición de proteína de transferencia de éster de colesterilo, o inhibir la proteína de transferencia de éster de colesterilo.

También se proporcionan composiciones farmacéuticas que comprende una cantidad terapéuticamente efectiva de al menos un compuesto descrito en la presente y un vehículo o portador farmacéuticamente aceptable del mismo. Tales composiciones pueden además comprender uno o más agentes terapéuticamente adicionales.

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**Definiciones**

Los términos "alq" o "alquilo" se refieren a grupos de hidrocarburo de cadena recta o ramificada, que tienen de 1 hasta 12 átomos de carbono, o 1 hasta 8 átomos de carbono, tales como metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, t-butilo, pentilo, hexilo, heptilo, octilo, o cualquier subgrupo de los anteriores. El término "alquilo substituido" se refiere a grupos alquilo substituidos con uno o más grupos (tales como por los grupos descritos arriba en la definición de $R^{10}$), tales como seleccionados de arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano y sulfonilo, o cualquier subgrupo de los anteriores.

El término "alquenilo" se refiere a grupos hidrocarburo de cadena recta o ramificada que tienen 2 hasta 12 átomos de carbono, ó 2 hasta 4 átomos de carbono, y al menos un enlace doble carbono a carbono (ya sea cis o trans), tal como etenilo. El término "alquenilo substituido" se refiere a grupos alquenilo substituidos con uno o más grupos

(tales como por grupos descritos arriba en la definición de $R^{10}$), tales como arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), alcanoilo (opcionalmente substituido, ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano y sulfonilo o cualquier subgrupo de los anteriores.

El término "alquinilo" se refiere a grupos hidrocarburo de cadena recta o ramificada que tienen 2 hasta 12 átomos de carbono, ó 2 hasta 4 átomos de carbono, y al menos un enlace triple carbono a carbono, tal como etinilo. El término "alquinilo substituido" se refiere a grupos alquinilo substituidos con uno o más grupos (tales como por grupos descritos arriba en la definición de $R^{10}$), tales como arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), alcanoilo (opcionalmente substituido, ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano y sulfonilo o cualquier subgrupo de

los anteriores.

El término "arilo" se refiere a grupos que contienen anillos aromáticos homocíclicos (esto es, hidrocarburo) mono, bi o tricíclico que tienen 6 hasta 12 miembros tales como fenilo, naftilo y bifenilo. Fenilo es un ejemplo de un grupo arilo. El término "arilo substituido" se refiere a grupos arilo substituidos con uno o más grupos (tales como por grupos descritos arriba en la definición de $R^{10}$), tales como seleccionados de alquilo, alquilo substituido, alquenilo (opcionalmente substituido), arilo (opcionalmente substituido), heterociclo (opcionalmente substituido), halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano y sulfonilo o cualquier subgrupo de los anteriores, en donde opcionalmente uno o más pares de substituyentes junto con los átomos a los cuales se enlazan forman un anillo de 3 hasta 7 miembros.

El término "cicloalquilo" se refiere a grupos de anillo mono, bi o tri homocíclicos de 3 hasta 15 átomos de carbono los cuales son, respectivamente, completamente saturados y parcialmente insaturados. Los anillos de grupos

cicloalquilo de anillos múltiples pueden ya sea fusionarse, conectarse y/o unirse a través de una o más uniones espiro. El término "cicloalquilo substituido" se refiere a un grupo cicloalquilo substituido con uno o más grupos (tales como por grupos descritos arriba en la definición de $R^{10}$), tales como seleccionados de arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano y sulfonilo, o cualquier subgrupo de los anteriores.

Los términos "halógeno" y "halo" se refieren a flúor, cloro, bromo y yodo.

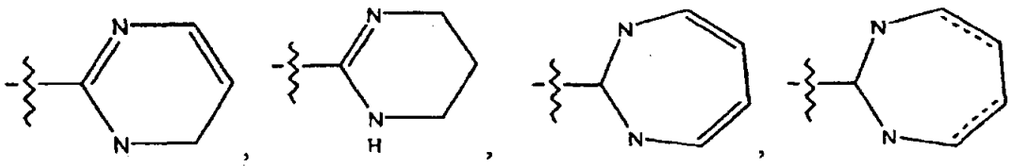
Los términos "heterociclo", "heterocíclico", "grupo heterocíclico" o "heterociclilo" se refieren a grupos completamente saturados o parcialmente o completamente insaturados, incluyendo aromáticos ("heteroarilo") o no aromáticos cíclicos (por ejemplo, sistemas de anillo monocíclico de 3 hasta 13 miembros, anillo bicíclico de 7 hasta 17 miembros, o anillos tricíclicos de 10 hasta 20 miembros, tales como, en ciertas modalidades, un anillo monocíclico o bicíclico que contiene un total de 3 hasta 10

átomos en el anillo) los cuales tiene al menos un heteroátomo en al menos un anillo que contiene átomos de carbono. Cada uno de los anillos del grupo heterocíclico que contiene un heteroátomo puede tener 1, 2, 3 ó 4 heteroátomos seleccionados del grupo de átomos de nitrógeno, átomos de oxígeno y/o átomos de azufre, en donde los heteroátomos de nitrógeno y azufre pueden opcionalmente oxidarse y los heteroátomos de nitrógeno pueden opcionalmente cuaternizarse. El grupo heterocíclico puede enlazarse a cualquier heteroátomo o átomo de carbono del anillo o sistema de anillo. Los anillos de heterociclos de anillos múltiples pueden ya sea fusionarse, conectarse y/o unirse a través de una o más uniones espiro.

Los grupos monocíclicos heterocíclicos ejemplares incluyen azetidinilo, pirrolidinilo, pirrolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahidrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolodinilo, 2-oxoazepinilo, azepinilo, 4-piperidonilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, tetrahidropiranilo, tetrazoilo, triazolilo, morfolinilo, tiamorfolinilo, tiamorfolinilo, sulfóxido, tiamorfolinilo

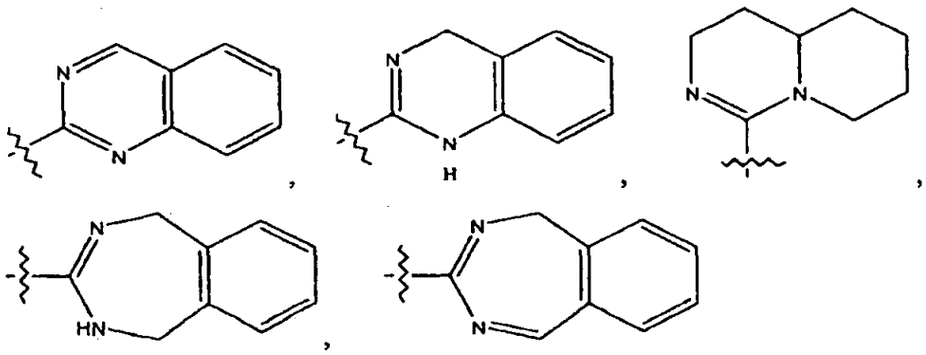
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sulfona, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo,



y similares.

Los grupos bicíclicos heterocíclicos ejemplares incluyen indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinuclidinilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofurilo, benzofuranilo, dihidrobenzofuranilo, cromonilo, coumarinilo, benzodioxolilo, dihidrobenzodioxolilo, benzodioxinilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo (tales como furo[2,3-C]piridinilo, furo[3,2-b]piridinilo] o furo[2,3-piridinilo), dihidroisoindolilo, dihidroquinazolinilo (tales como 3,4-dihidro-4-oxo-quinazolinilo), tetrahidroquinolinilo, azabicicloalquilos (tales como 6-azabiciclo[3.2.1]octano), azaspiroalquilos (tales como 1,4 dioxa-8-azaspiro[4.5]decano) imidazopiridinilo (tales como imidazo[1,5-a]piridin-3-ilo), triazolopiridinilo (tales como 1,2,4-triazolo[4,3-a]piridin-3-ilo) y hexahidroimidazopiridinilo (tal como 1,5,6,7,8,8a-hexahidroimidazo[1,5-a]piridin-3-ilo),



y similares.

Los grupos tricíclicos heterocíclicos ejemplares incluyen carbazolilo, bencidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

Los términos "heterociclo substituido", "heterocíclico substituido", "grupo heterocíclico substituido" y "heterociclilo substituido" se refiere a grupos heterociclo, heterocíclico y heterociclo substituidos con uno o más grupos (tales como por grupos descritos arriba en la definición de $R^{10}$), tales como seleccionados de alquilo, alquilo substituido, alquenilo, oxo, arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo (opcionalmente substituido), halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido, alcanoilo (opcionalmente substituido), aroilo (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), ciano, nitro, amido, amino, amino substituido, lactama, urea, uretano, sulfonilo, o cualquier subgrupo de los anteriores,

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en donde opcionalmente uno o más pares de substituyentes junto con los átomos a los cuales se enlaza forma un anillo de 3 hasta 7 miembros.

A través de la especificación, los grupos y substituyentes de los mismos pueden ser elegidos para proporcionar las porciones estables y compuestos.

Los compuestos de las fórmulas Ia y Ib forman sales y solvatos los cuales están también dentro del alcance de esta invención. La referencia a un compuesto de la fórmula Ia o Ib en la presente se entenderá que incluye referencias para la sales del mismo, a menos de que se indique de otra manera. El término "sales", como se emplea en la presente, significa sales ácidas y/o básicas formadas con ácidos inorgánicos y/u orgánicos y bases. Además, cuando un compuesto de la fórmula Ia o Ib contiene ambas porciones básicas y porciones ácidas, pueden formarse zwiteriones ("sales internas") y se incluyen dentro del término "sales" como se usa en la presente. Se prefieren las sales farmacéuticamente aceptables (esto es, no tóxicas, fisiológicamente aceptables), sin embargo otras sales también son útiles, por ejemplo, en las etapas de aislamiento y purificación las cuales pueden emplearse durante la preparación. La sales de los compuestos de la fórmula Ia y Ib pueden formarse, por ejemplo, por hacer reaccionar un compuesto de la fórmula Ia o Ib con un compuesto del ácido o base, tales como una cantidad

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equivalente, en un medio tales como uno en la cual se precipita la sal o en un medio acuoso seguido por liofilización.

Los compuestos de la fórmula Ia y Ib los cuales contienen una porción básica pueden formar sales con una variedad de ácidos orgánicos e inorgánicos. La sales de adición ácida ejemplares incluyen acetatos (tales como aquellos formados con ácido acético o ácido tihaloacético, por ejemplo, ácido trifluoroacético), adipatos, alginatos, ascorbatos, aspartatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, ciclopentanpropionatos, digluconatos dodecilsulfatos, etansulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos, hemisulfatos, heptanoatos, hexanoatos, clorhidratos (formados con ácido clorhídrico), bromhidratos (formados con bromuro de hidrógeno), yodohidratos, 2-hidroxietansulfonatos, lactatos, maleatos (formados con ácido maleico), metansulfonatos (formados con ácido metansulfónico), 2-naftalensulfonatos, nicotinatos, nitratos, oxalatos, pectinatos, persulfatos, 3-fenilpropionatos, fosfatos, picratos, pivalatos, propionatos, salicilatos, succinatos, sulfatos (tales como aquellos formados con ácido sulfúrico), tales como aquellos mencionados en la presente), tartratos, tiocianatos, toluensulfonatos tales como tosilatos, undecanoatos, y los similares.

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Los compuestos de la fórmula Ia y Ib los cuales contienen una porción ácida pueden formas sales con una variedad de bases orgánicas e inorgánicas. Las sales básicas ejemplares incluyen sales de amonio, sales de metal alcalino tales como sales de sodio, litio y potasio, sales de metal alcalino térreo tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como benzatinas, diciclohexilaminas, hidrabaminas (formadas con N,N-bis(dehidroabietil)etilenodiamina), N-metil-D-glucaminas, N-metil-D-glucamidas, t-butil aminas y sales con aminoácidos tales como arginina, lisina y similares.

Los grupos que contienen nitrógeno básico pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ejemplo, metilo, etilo, propilo y cloruro de butilo, bromuros y yoduros), dialquil sulfatos (por ejemplo, sulfatos de dimetilo, dietilo, dibutilo y diamilo), haluros de cadena larga (por ejemplo, decilo, laurilo, miristilo y cloruro de estearilo, bromuros y yoduros), haluros de aralquilo (por ejemplo, bromuro de bencilo y fenetilo) y otros.

Cualquier compuesto que puede convertirse *in vivo* para proporcionar el agente bioactivo (esto es, un compuesto de la fórmula Ia o Ib) es un profármaco dentro del alcance y espíritu de la invención.

El término "profármacos" como se emplea en la

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presente incluye ésteres y carbonatos formados por hacer reaccionar uno o más hidroxilos de los compuestos de la fórmula Ia y Ib con agentes acilantes substituidos con alquilo, alcoxi o arilo empleando procedimientos conocidos por los expertos en la técnica para generar acetatos, pivalatos, metilcarbonatos, benzoatos, y similares.

Varias formas de profármacos son bien conocidas en la técnica y se describen en:

a) The Practice of Medicinal Chemistry, Camille G. Wermuth y col., Ch 31 (Academic Press, 1996);

b) Design of Prodrugs, editado por H. Bundgaard (Elsevire, 1985);

c) A Textbook of Drug Design and Development, P. Krogsgaard-Larson and H. Bundgaard, eds. C. 5, pgs 113-191 (Harwood Academic Publishers, 1991); y

d) Hydrolysis in Drug and Prodrug Metabolism, Bernard Testa and Joachim M. Mayer, (Wiley-VCH, 2003).

Las referencias se incorporan en la presente para referencia.

Además, los compuestos de la presente invención son, posterior a su preparación, aislados y purificados preferiblemente para obtener una composición que contiene una cantidad en peso igual o mayor a 99% del compuesto de la fórmula Ia o Ib (compuesto "substancialmente puro" Ia o Ib), el cual puede usarse o formarse como se describe en la presente. Tales compuestos

"substancialmente puros" de la fórmula Ia y Ib también se contemplan en la presente como parte de la presente invención.

Al grado de que los compuestos de la fórmula Ia y Ib, y sales de los mismos, puedan existir en su forma tautomérica, todas las formas tautoméricas se contemplan en la presente como parte de la presente invención.

Todos los estereoisómeros de los compuestos de la presente, tales como aquellos los cuales pueden existir debido a carbonos asimétricos en varios substituyentes, incluyendo formas enantioméricas (las cuales pueden existir aún en la ausencia de carbonos asimétricos) y formas estereoisoméricas de los compuestos de la invención pueden, por ejemplo, estar substancialmente libres de otros isómeros, o pueden ser mezclados, por ejemplo, como racematos o todos los otros u otros seleccionados, estereoisómeros.

Los términos "incluyendo", "tales como", "por ejemplo" y similares se entienden para referirse a modalidades ejemplares y no se limita el alcance de la presente invención.

## BREVE DESCRIPCION DE LA FIGURA

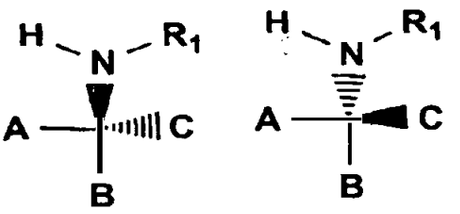
La figura 1 ilustra las moléculas cristalizadas de (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropano-2-sulfinamida la cuál se cristalizó a partir de $CDCl_3$.

## DESCRIPCION DETALLADA DE LA INVENCION

Se entenderá que cualquier modalidad ejemplar dada puede combinarse con una o más modalidad ejemplares

adicionales.

De conformidad con la presente invención, los compuestos de la fórmula Ia y Ib se proporcionan




Ia o Ib

o estereoisómeros o profármacos o formas de sal farmacéuticamente aceptables de los mismos, en donde:

A es fenilo, el cual es substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$ el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) =O, 17) -$S(O)_pR_6$, 18) -$SO_2NHR_6$, 19) -$COOR_6$, 20) -$NHC(CN)NHR_6$, 21) -$CONR_6R_6$, 22) alquinilo de $C_2$-$C_6$, el cual

puede estar opcionalmente substituido con uno o más $R_{20}$, 23) alquenilo de $C_2$-$C_6$ el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 24) $-OCOR_6$, 25) $-OCOOR_6$, o 26) $-OCONR_6R_6$; o 27) cicloalquilo, que puede opcionalmente sustituirse con uno o más $R_{20}$; o cualquiera de dos substituyentes adyacentes se pueden unir juntos para formar un anillo de 4 a 8 miembros, el cual puede contener opcionalmente 1-4 heteroátomos seleccionados de N, O y S, y se puede opcionalmente substituir con uno o más $R_{20}$;

B es:

(a) fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NRH_6$, 18) $-COOR_6$, 19) $-NHC(CN)NRH_6$, 20) $-CONR_6R_6$; y 21) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(b) heteroarilo, que puede substituirse

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opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;n 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) -$S(O)_pR_6$, 17) -$SO_2NHR_6$, 18) -$COOR_6$, 19) -$NHC(CN)NHR_6$, 20) -$CONR_6R_6$; y 21) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

C es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$,

12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, 17) $-NHC(CN)NHR_6$; y 18) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más de $R_{20}$, 3)-$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$; y 15) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más de $R_{20}$, 3) $-OR_6$, 4) -alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) heteroarilo, que puede substituirse opcionalmente

con uno o más de $R_{20}$; 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, 17) $-NHC(CN)NHR_6$; y 18) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(d) heterociclo que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3)-$OR_6$, 4 alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9NR_{10}$, 8) arilo, que puede substituirse opcionalmente por uno o más de $R_{20}$; 9) heteroarilo que puede substituirse opcionalmente por uno o más de $R_{20}$; 10) heterociclilo que puede substituirse opcionalmente por uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NRH_6$, 16) $COOR_6$, 17) $-NHC(CN)NHR_6$; y 18) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es H, $-C(O)R_3$, $-C(O)NR_2R_3$, $-C(O)OR_4$, $-SO_2R_5$, $-C(S)NHR_7$, $-CR_8R_8R_8$ o $-C(S)R_3$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar

opcionalmente substituido con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$; 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$; y 20) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3)-$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, 19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, 22) $-NHC(CN)NHR_6$;

y 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CO_2$alquilo de $C_1$-$C_6$, 18) $-CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, 20) alquinilo de $C_2$-$C_6$; y 21) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$; y 20) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; 24) cicloalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_6$, 19) -$S(O)_pR_6$, 20) -$SO_2NHR_6$, 21) -$COOR_6$, 22) -$NHC(CN)NHR_6$; y 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_4$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que

consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, 20) -$S(O)_pR_6$, 21) -$SO_2NHR_6$, 22) -$COOR_6$, 23) -$NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(d) alquenilo de $C_2$-$C_6$; o

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(e) alquinilo de $C_2$-$C_6$;

$R_5$ es arilalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10)

heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, 24) $-NHC(CN)NHR_{36}$; y 25) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) cicloalquilo, que puede substituirse

opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) -$COR_{36}$, 22) -$S(O)_pR_{36}$, 23) -$SO_2NHR_{36}$, 24) -$COOR_{36}$, 25) -NHC(CN)$NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17)

alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_7$ es arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_8$ puede ser independientemente:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, 18) $-S(O)_pR_{26}$, 19) $-SO_2NHR_{26}$, 20) $-COOR_{26}$, 21) $-NHC(CN)NHR_{26}$; y 22) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(e) heteroarilo, que puede substituirse

opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(f) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11)

heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$; (c) $-[(C=O)O_r]_s$alquenilo ($C_2$-$C_8$), en donde el alquenilo puede substituirse opcionalmente con uno o más de $R_{20}$; (d) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$; (e) heterociclilo substituido opcionalmente con uno o más $R_{20}$; (f) $-CONR_{26}R_{26}$; (g) alquinilo de $C_2$-$C_6$; (h) $-COR_{26}$; (i) $-S(O)_pR_{26}$; (j) $-SO_2NHR_{26}$; (k) $-COOR_{26}$; o (l) $-NHC(CN)NHR_{26}$; o m) $-[(C=O)O_r]_s$cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros,

que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) =O; (q) alquinilo de $C_2$-$C_6$; (r) $-COR_{26}$; (s) $-S(O)_pR_{26}$; (t) $-SO_2NHR_{26}$; (u) $-COOR_{26}$; (v) $-NHC(CN)NHR_{26}$; (w) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (x) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (y) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$;

(p) alquenilo de $C_2$-$C_6$; (q) =O; (r) alquinilo de $C_2$-$C_6$; (s) cicloalquilo; (t) cicloalquilalquilo; (u) $-COR_{26}$; (v) $-S(O)_pR_{26}$; (w) $-SO_2NHR_{26}$; (x) $-COOR_{26}$; o (y) $-NHC(CN)NHR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$; y 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, 24) $-NHC(CN)NHR_{36}$; y 25) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede

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substituirse opcionalmente con uno o más de $R_{20}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede

substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$S(O)_pR_{36}$, 20) -$SO_2NHR_{36}$, 21) -$COOR_{36}$, 22) -$NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, -$[(C=O)O_r]_s$arilo, -$[(C=O)O_r]_s$alquenilo, -$[(C=O)O_r]_s$alquilo, heterociclilo, -$CONR_{46}R_{46}$, alquinilo, -$COR_{36}$, -$S(O)_pR_{36}$, -$SO_2NHR_{36}$, -$COOR_{36}$,-$C(CN)NHR_{36}$, o cicloalquilo, en donde el arilo, alquilo, alquenilo, cicloalquilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros,

que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, o $-NHC(CN)NHR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo;

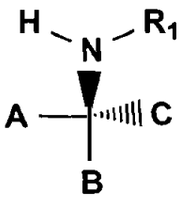
r es 0 hasta 5;

s es 0 hasta 4; y

p es 1 ó 2.

En una modalidad, los compuestos de la presente invención se proporcionan en donde los compuestos son compuestos de la fórmula Ia

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Ia

En otra modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) $-S(O)_pR_6$, 18) $-SO_2NHR_6$, 19) $-COOR_6$, 20) $-NHC(CN)NHR_6$, 21) $-CONR_6R_6$, 22) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 23) alquenilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 24) $-OCOR_6$, 25) $-OCOOR_6$, o 26) $-OCONR_6R_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos

para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$; o

(b) heteroarilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, y 20) $-CONR_6R_6$;

C es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, y 17) $-NHC(CN)NHR_6$;

(b) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$; o

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, y 17) $-NHC(CN)NHR_6$;

$R_1$ es H, $-C(O)R_3$, $-C(O)NR_2R_3$, $-C(O)OR_4$, $-SO_2R_5$, $-C(S)NHR_7$, $-CR_8R_8R_8$, o $-C(S)R_3$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$COR_6$, 13) -$CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$S(O)_pR_6$, 17) -$SO_2NHR_6$, 18) -$COOR_6$, y 19) -$NHC(CN)NHR_6$;

(c) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_6$, 19) -$S(O)_pR_6$, 20) -$SO_2NHR_6$, 21) -$COOR_6$, y 22) -$NHC(CN)NHR_6$; o

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$, 16) -COOH, 17) -$CO_2$alquilo de $C_1$-$C_6$, 18) -$CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, y 20) alquinilo de $C_2$-$C_6$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, y 19) $-NHC(CN)NHR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del

grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, 20) -$S(O)_pR_6$, 21) -$SO_2NHR_6$, 22) -$COOR_6$, y 23) -$NHC(CN)NHR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4)

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alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, 19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, y 22) $-NHC(CN)NHR_6$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_4$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(c) cicloalquilo, que puede substituirse

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opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(d) alquenilo de $C_2$-$C_6$; o

(e) alquinilo de $C_2$-$C_6$;

$R_5$ es arilalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede

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substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7)

nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede

substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_7$ es arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

$R_8$ puede ser independientemente:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, 18) $-S(O)_pR_{26}$, 19) $-SO_2NHR_{26}$, 20) $-COOR_{26}$, y 21) $-NHC(CN)NHR_{26}$;

(c) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste

de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, 20) -$S(O)_pR_{26}$, 21) -$SO_2NHR_{26}$, 22) -$COOR_{26}$, y 23) -$NHC(CN)NHR_{26}$;

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

(e) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$; o

(f) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más

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de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$; (c) $-[(C=O)O_r]_s(C_2-C_8)$-alquenilo, en donde el alquenilo puede substituirse opcionalmente con uno o más de $R_{20}$; (d) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$; (e) heterociclilo substituido opcionalmente con uno o más $R_{20}$; (f) $-CONR_{26}R_{26}$; (g) alquinilo de $C_2$-$C_6$; (h) $-COR_{26}$; (i) $-S(O)_pR_{26}$; (j) $-SO_2NHR_{26}$; (k) $-COOR_{26}$; o (l) -

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$NHC(CN)NHR_{26}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) =O; (q) alquinilo de $C_2$-$C_6$; (r) $-COR_{26}$; (s) $-S(O)_pR_{26}$; (t) $-SO_2NHR_{26}$; (u) $-COOR_{26}$; (v) $-NHC(CN)NHR_{26}$; (w) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (x) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (y) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h)

arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) =O; (r) alquinilo de $C_2$-$C_6$; (s) cicloalquilo; (t) cicloalquilalquilo; (u) $-COR_{26}$; (v) $-S(O)_pR_{26}$; (w) $-SO_2NHR_{26}$; (x) $-COOR_{26}$; o (y) $-NHC(CN)NHR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$,

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24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11)

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heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que

consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, $-[(C=O)O_r]_s$arilo, $-[(C=O)O_r]_s$alquenilo, $-[(C=O)O_r]_s$alquilo, heterociclilo, $-CONR_{46}R_{46}$, alquinilo, $-COR_{36}$, $-S(O)_pR_{36}$, $-SO_2NHR_{36}$, $-COOR_{36}$, o $-C(CN)NHR_{36}$, en donde el arilo, alquilo, alquenilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente

con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, o $-NHC(CN)NHR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo;

r es 0 hasta 5;

s es 0 hasta 4; y

p es 1 ó 2.

Todavía en otra modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de

$C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) $-COOR_6$, 18) $-CONR_6R_6$, 19) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 20) alquenilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 21) $-OCOR_6$, 22) $-OCOOR_6$, o 23) $-OCONR_6R_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

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arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-COOR_6$, y 17) $-CONR_6R_6$; o

(b) un heteroarilo que contiene nitrógeno, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-COOR_6$, y 17) $-CONR_6R_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) $-OR_6$, 3) $-NR_9R_{10}$, 4) arilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 5) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 6) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 7) $-CONR_6R_6$, y 8) $-COOR_6$;

$R_1$ es $-C(O)R_3$, $-C(O)NR_2R_3$, $-C(O)OR_4$ o $-CH_2R_8$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, y 16) $-COOR_6$;

(c) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o

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más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_6$, y 19) -$COOR_6$; o

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$-, 16) -COOH, 17) -$CO_2$alquilo de $C_1$-$C_6$, 18) -$CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, y 20) alquinilo de $C_2$-$C_6$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente

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con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_6$, y 16) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_6$, y 19) -$COOR_6$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_4$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7)

nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) -$CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) -$COR_{26}$, y 18) -$COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$; (c) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$; o (d) heterociclilo substituido opcionalmente con uno o más $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano, (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m)

heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse

opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) -$COR_{36}$, 22) -$S(O)_pR_{36}$, 23) -$SO_2NHR_{36}$, 24) -$COOR_{36}$, y 25) -$NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, $-[(C=O)O_r]_s$arilo, $-[(C=O)O_r]_s$alquilo, o heterociclilo, en donde el arilo, alquilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse

opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$ o $-COOR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presentan, son independientemente hidrógeno, alquilo, arilo, heteroarilo o heterociclilo, diferente a heteroarilo;

r es 0 hasta 3;

s es 0 hasta 2; y

p es 1 ó 2.

Todavía en otra modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) $-COOR_6$, 18) $-CONR_6R_6$, 19) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 20) $-OCOR_6$, 21) $-OCOOR_6$, o 22) $-OCONR_6R_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COOR_6$, y 16) $-CONR_6R_6$; o

(b) un heteroarilo que contiene nitrógeno de 6 hasta 10 miembros, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COOR_6$, y 16) $-CONR_6R_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) $-OR_6$, 3) $-NR_9R_{10}$, 4) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 5) un heteroarilo que contiene nitrógeno, que puede substituirse opcionalmente con uno o más de $R_{20}$, 6) $-CONR_6R_6$, y 7) $-COOR_6$;

$R_1$ es $-C(O)R_3$, $-C(O)NR_2R_3$ o $-CH_2R_8$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente

con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$COR_6$, 13) -$CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, y 16) -$COOR_6$; o

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$, 16) -COOH, 17) -$CO_2$alquilo de $C_1$-$C_6$, 18) -$CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, y 20) alquinilo de $C_2$-$C_6$;

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$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_6$, y 16) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$,

15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)$-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, y 19) $-COOR_6$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$,

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9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20)

alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, y 18) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$,

15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse

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opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno, (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$, o (c) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo,

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que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste

de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno

o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, $-[(C=O)O_r]_s$arilo, o $-[(C=O)O_r]_s$alquilo, en donde el arilo o alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más

de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$ o $-COOR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo o heteroarilo;

r es 0 hasta 2;

s es 0 hasta 1; y

p es 1 ó 2.

En una modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) $-COOR_6$, 18) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 19) $-OCOR_6$, y 20) $-OCOOR_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, y 15) $-COOR_6$; o

(b) un heteroarilo que contiene nitrógeno de 6 miembros, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, y 15) $-COOR_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) fenilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, o 3) un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NR_2R_3$ o $-CH_2R_8$;

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$R_2$ es:

(a) H; o

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$COR_6$, 13) -$CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, y 16) -$COOR_6$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_6$, y 16) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7)

$-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste

de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o

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más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno

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o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) -

$CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, y 18) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo

de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno, o (b) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente

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con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20)

$-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente

con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25)

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$-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno o $-[(C=O)O_r]_s$alquilo, en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$, o $-COOR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo, o heteroarilo;

r es 0 hasta 2;

s es 0 hasta 1; y

p es 1 ó 2.

En otra modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 18) $-OCOR_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1)

halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) fenilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, o 2) un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es -C(O)$R_3$, -C(O)NH$R_3$ o -$CH_2R_8$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, y 16) $-COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4)

alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de

$C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$,

9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20)

alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4)

alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) -$CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) -$COR_{26}$, y 18) -$COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del

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grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; o (b) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de

$R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5)

alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse

opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno o -

$[(C=O)O_r]_s$alquilo, en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo o cicloalquilalquilo;

r es 0 hasta 2;

s es 0 hasta 1; y

p es 1 ó 2.

Todavía en otra modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, y 17) $-OCOR_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$;

C es metilo, que está substituido con uno o más

substituyentes seleccionados del grupo que consiste de: 1) fenilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, o 2) un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NHR_3$ o $-CH_2R_8$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, y 16) $-COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de

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$R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente

con unc o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$SO_2NHR_{36}$, 20) -$COOR_{36}$, y 21) -NHC(CN)$NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) -$COR_{36}$, 21) -$SO_2NHR_{36}$, 22) -$COOR_{36}$, y 23) -NHC(CN)$NHR_{36}$;

(c) heteroarilo, que puede substituirse

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opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) -$COR_{36}$, 22) -$SO_2NHR_{36}$, 23) -$COOR_{36}$, y 24) -NHC(CN)$NHR_{36}$; o

(d) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) -

$CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, y 18) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; o (b) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o

(u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-SO_2NHR_{36}$, 20) $-COOR_{36}$, y 21) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo,

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que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-SO_2NHR_{36}$, 22) $-COOR_{36}$, y 23) $-NHC(CN)NHR_{36}$;

(c) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$; o

(d) hidrógeno;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno o $-[(C=O)O_r]_s$alquilo, en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo o heteroarilo, en donde el alquilo, arilo o heteroarilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, o cicloalquilalquilo;

r es 0 hasta 2; y

s es 0 hasta 1.

Todavía en otra modalidad, los compuestos de la presente invención se proporcionan en donde:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, y 15) $-COR_6$;

B es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$;

C es metilo, que es substituido con un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NHR_3$ o $-CH_2R_8$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) haloalquilo de $C_1$-$C_6$, 11) alquenilo de $C_2$-$C_6$, 12) alquinilo de $C_2$-$C_6$, 13) -$COR_6$, y 14) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_6$, y 17) -$COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del

grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_6$, y 17) -$COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_6$, y

17) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_6$, y 17) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) -COOH, 14) alquinilo de $C_2$-$C_6$, 15)

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$-COR_{36}$, y 16) $-COOR_{36}$; o

(b) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) haloalquilo de $C_1$-$C_6$, 11) alquenilo de $C_2$-$C_6$, 12) alquinilo de $C_2$-$C_6$, 13) $-COR_{26}$, y 14) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de

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$C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_{26}$, y 17) $-COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_{26}$, y 17) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_{26}$, y 17) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_{26}$, y 17) $-COOR_{26}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (h) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) haloalquilo de $C_1$-$C_6$; (n) alquenilo de $C_2$-$C_6$; (o) alquinilo de $C_2$-$C_6$; (p) $-COR_{26}$; (q) $-COOR_{26}$; (r) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (s) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) arilo; (h) arilalquilo; (i) heteroarilo; (j) heteroarilalquilo; (k) heterociclilo; (l) heterociclilalquilo; (m) haloalquilo de $C_1$-$C_6$; (n) alquenilo de $C_2$-$C_6$; (o) alquinilo de $C_2$-$C_6$; (p) cicloalquilo; (q) cicloalquilalquilo; (r) $-COR_{26}$; o (s) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) -COOH, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_{36}$, o 16) $-COOR_{36}$; o

1005

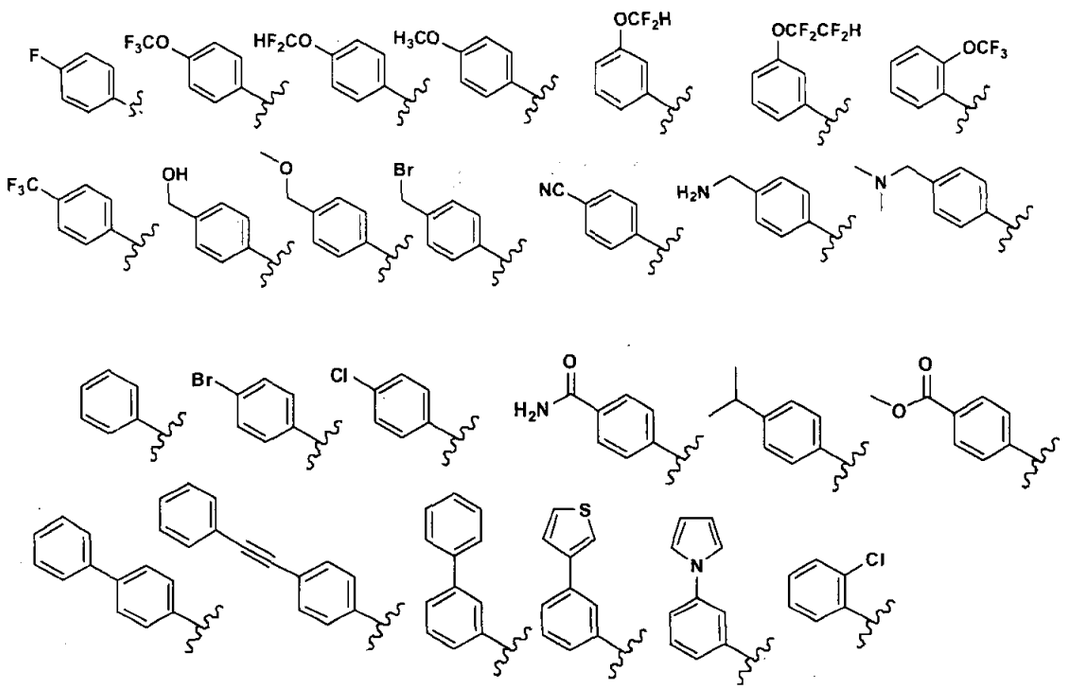
(b) hidrógeno;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo o heteroarilo, en donde el alquilo, arilo o heteroarilo puede substituirse opcionalmente con uno o más de $R_{40}$; y

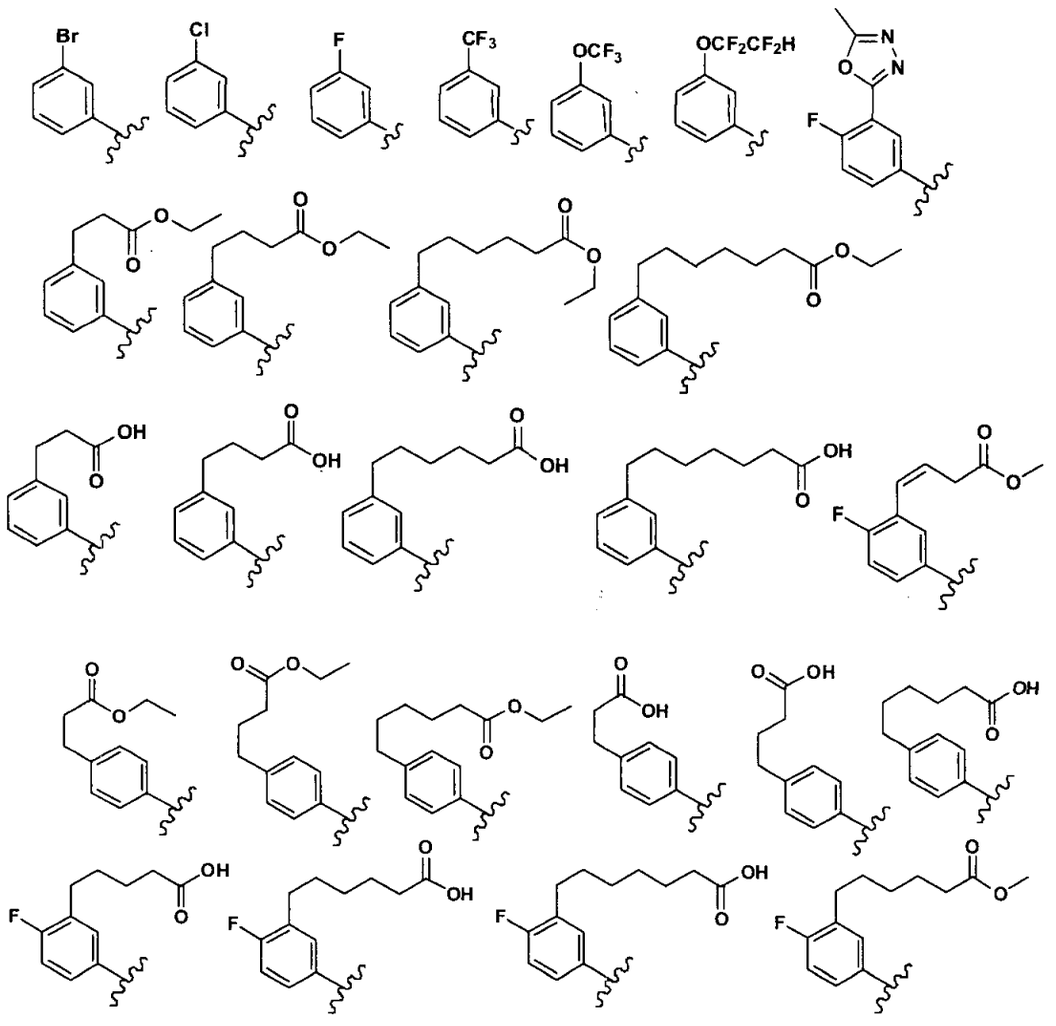
$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, alquenilo, arilalquiloxi, alquinilo, cicloalquilo o cicloalquilalquilo.

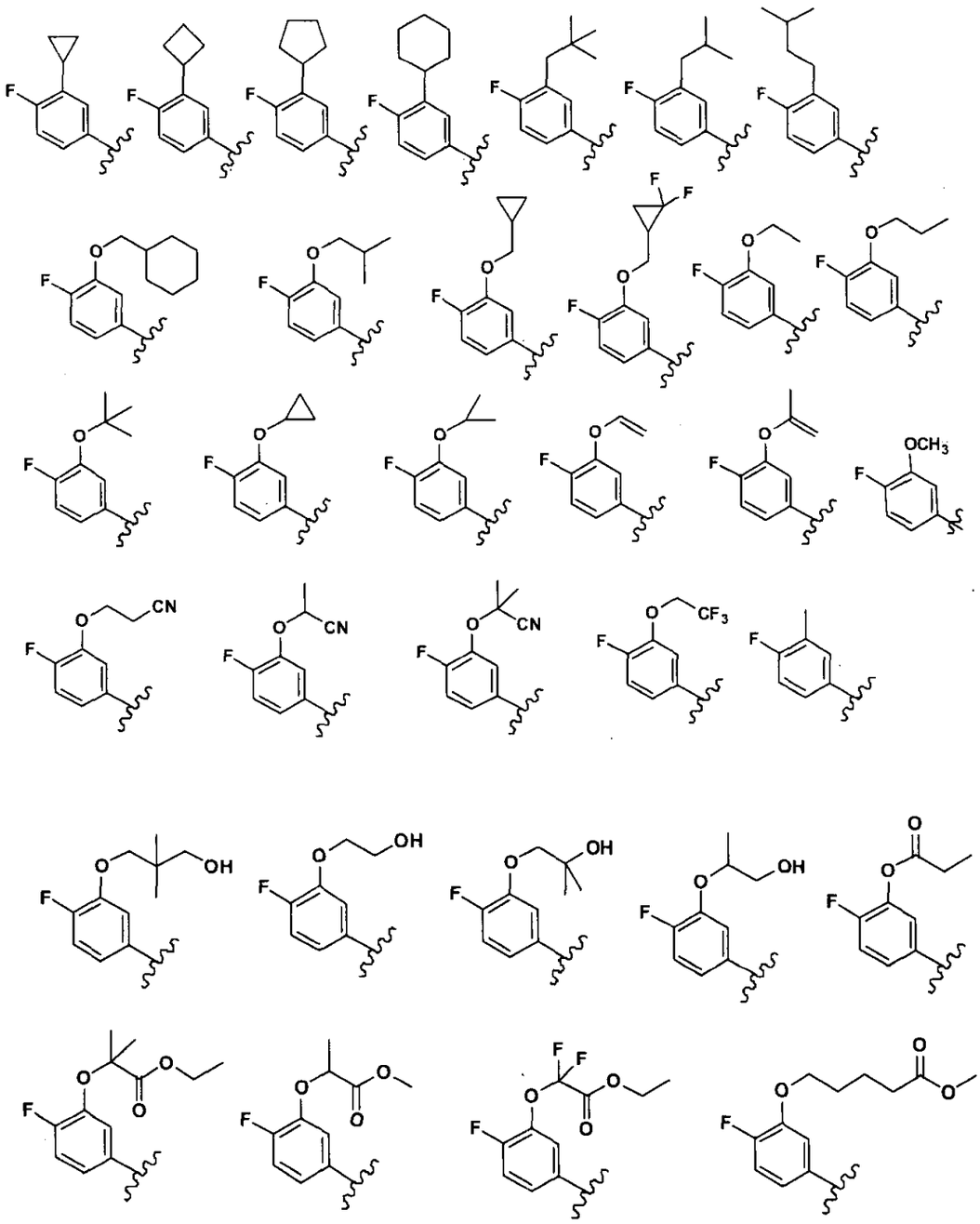
También de acuerdo con la presente invención, los compuestos de la presente invención son aquellos en donde:

A es:

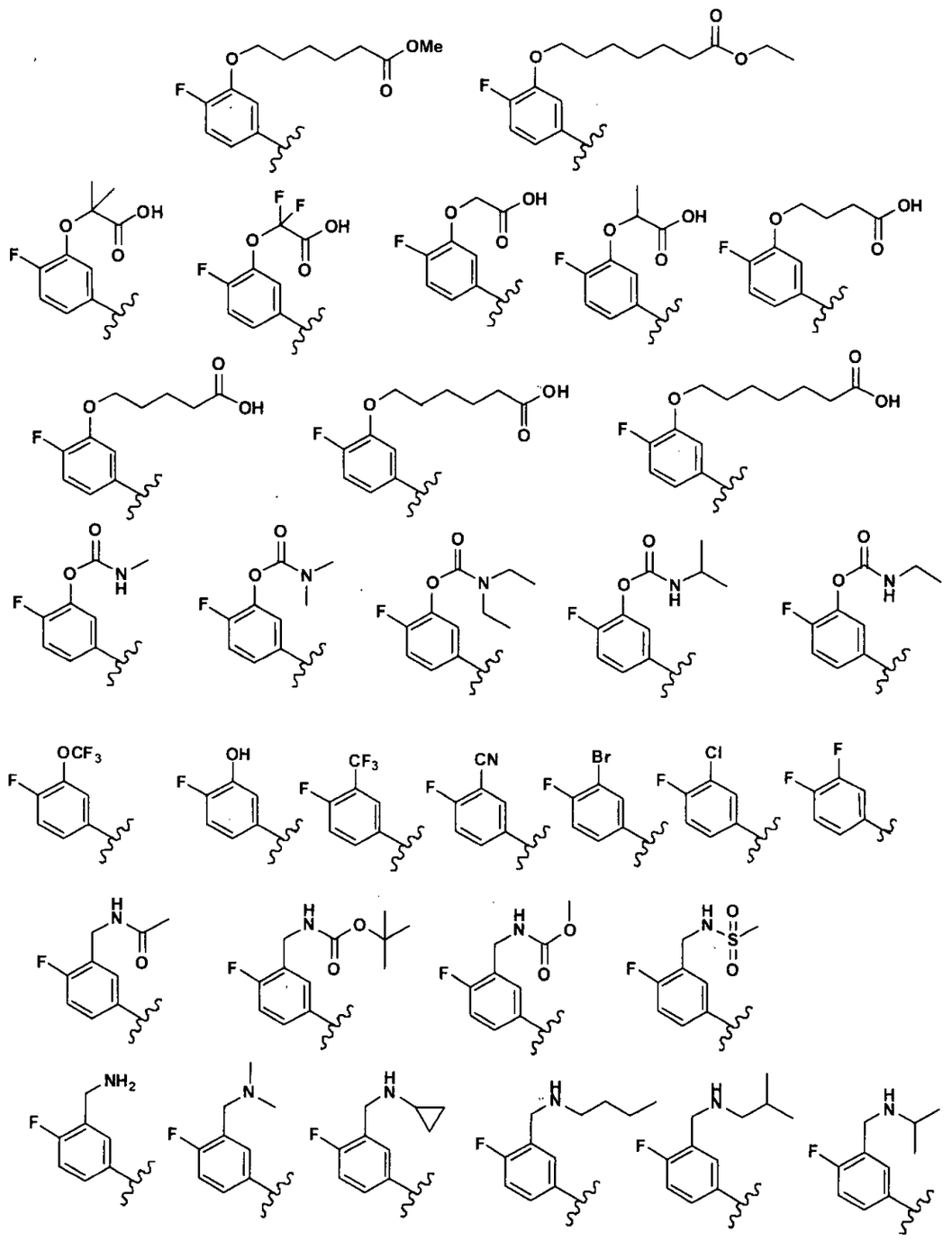


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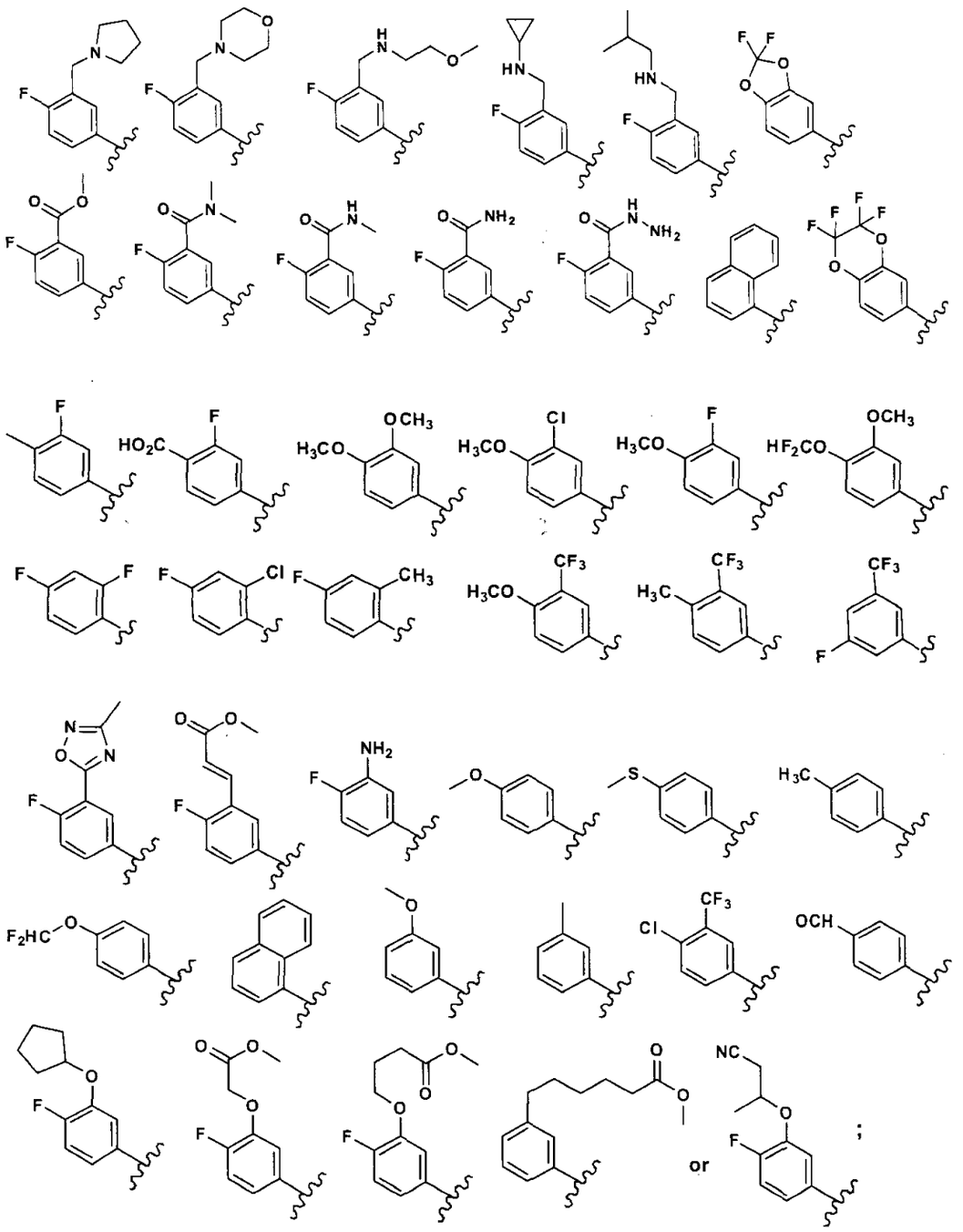

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1008



1009

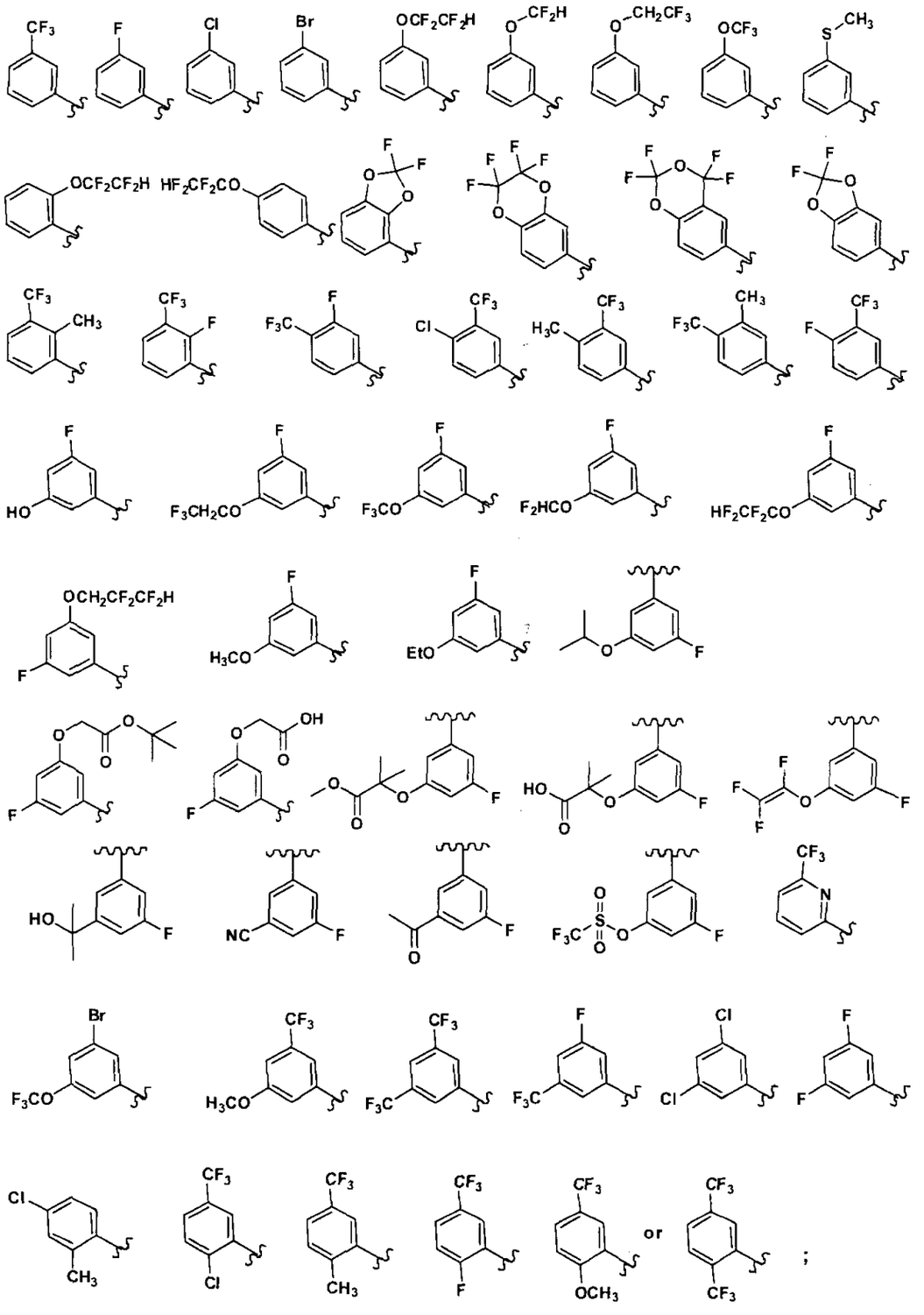


or

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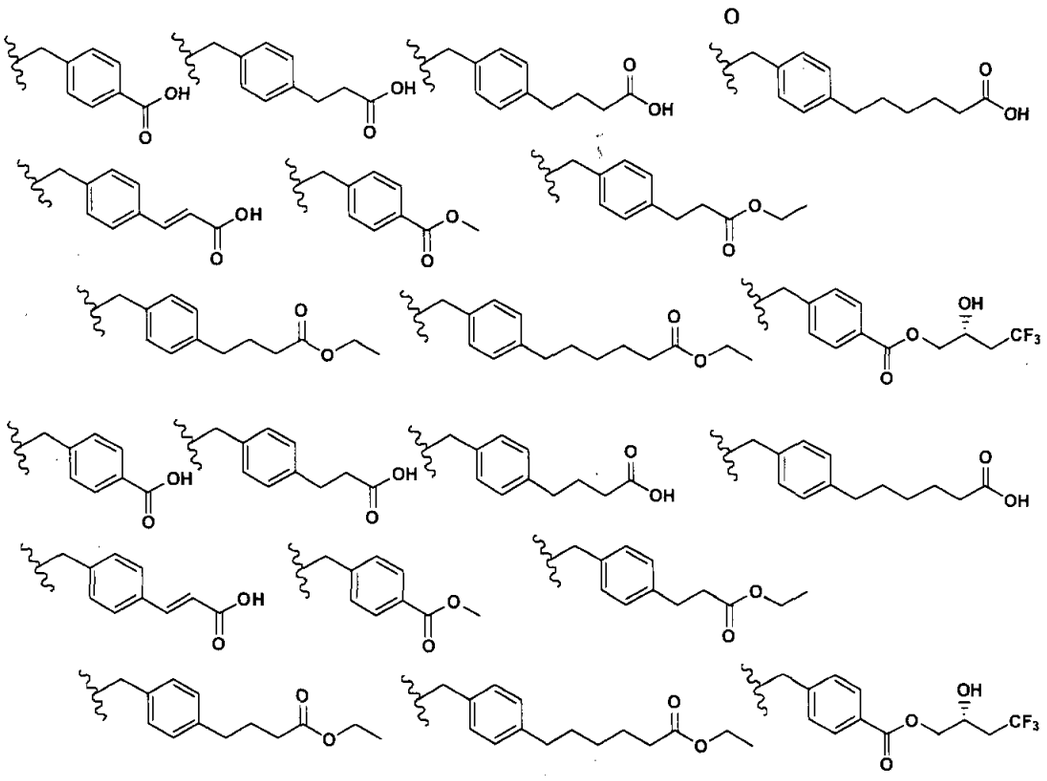
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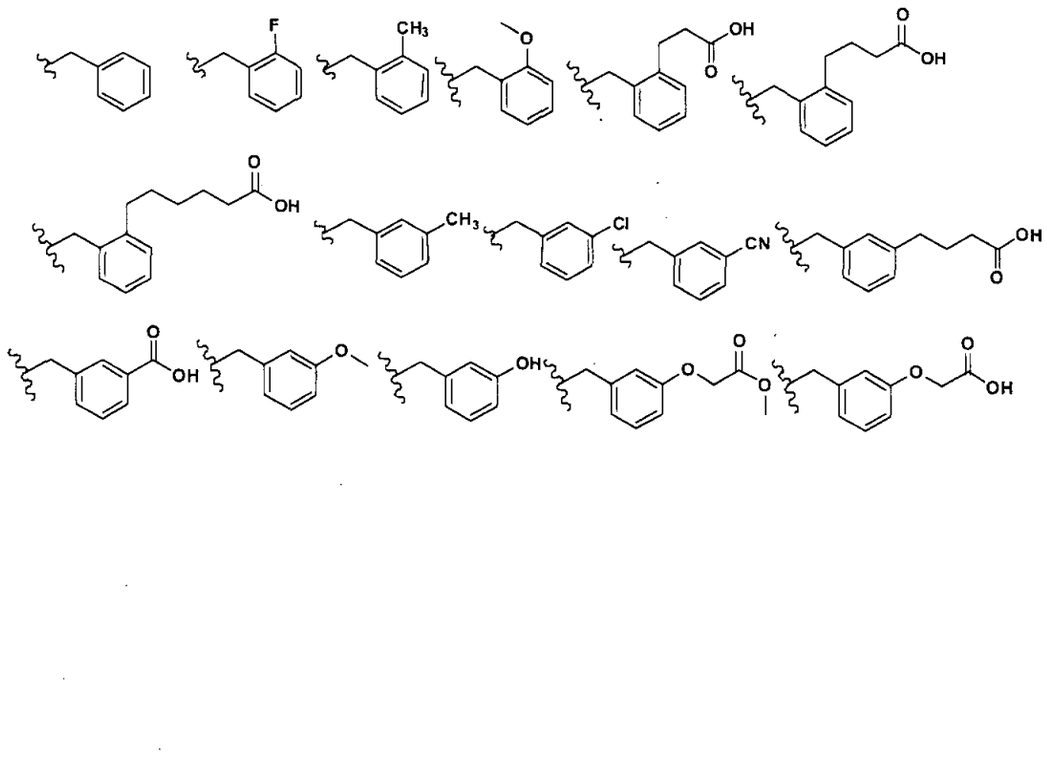
B es:



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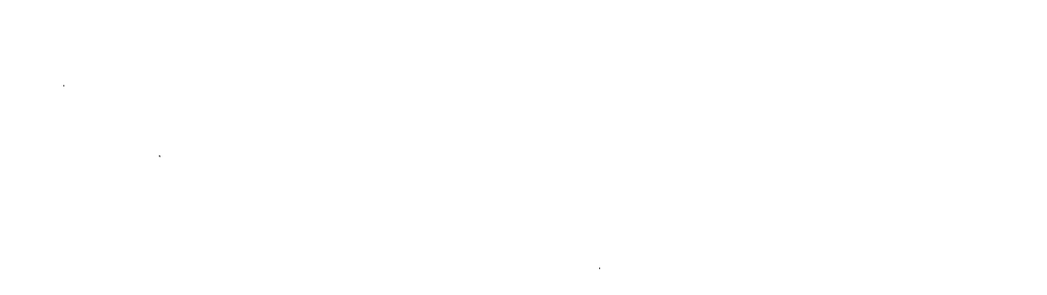
C es:

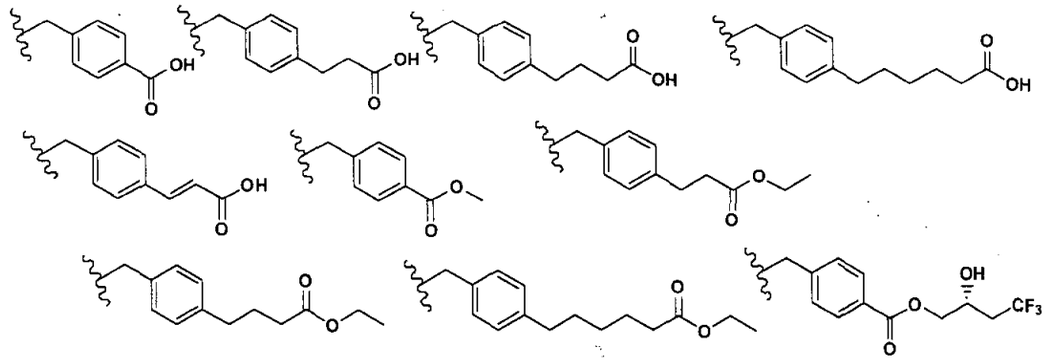


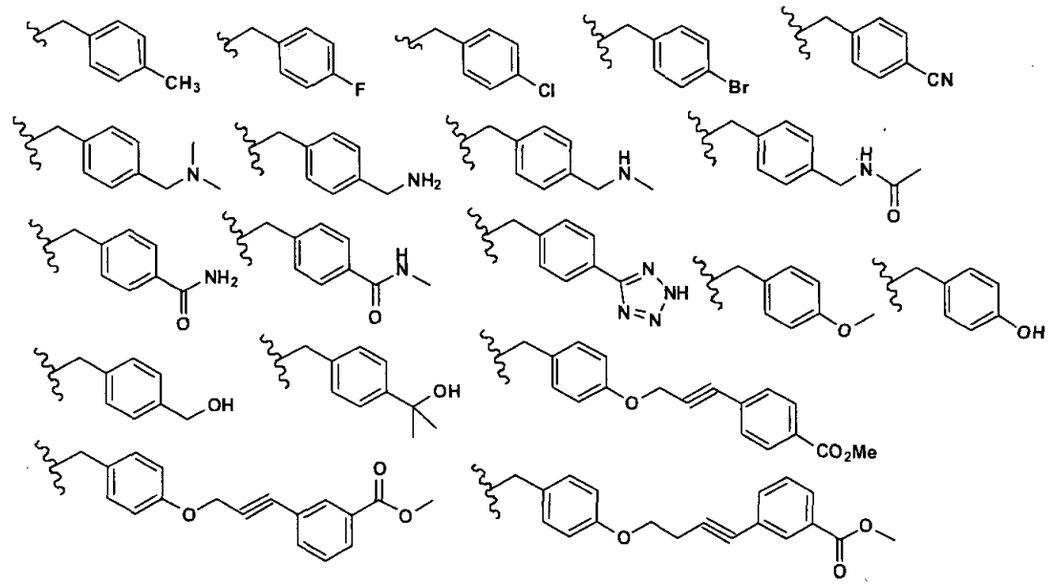


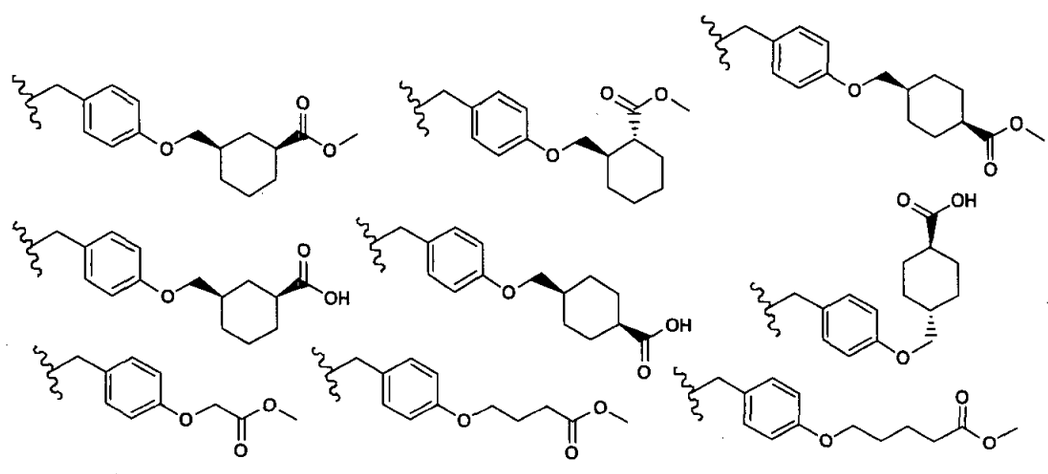


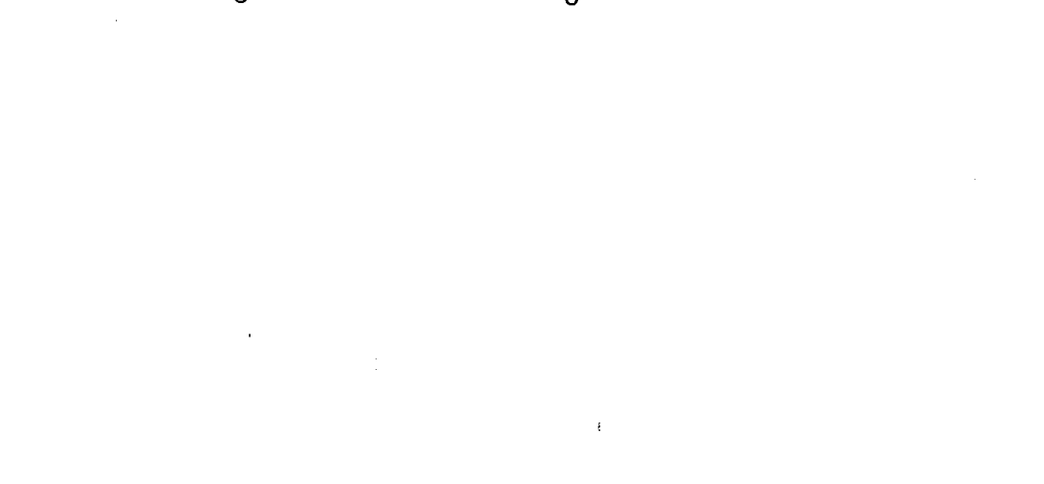


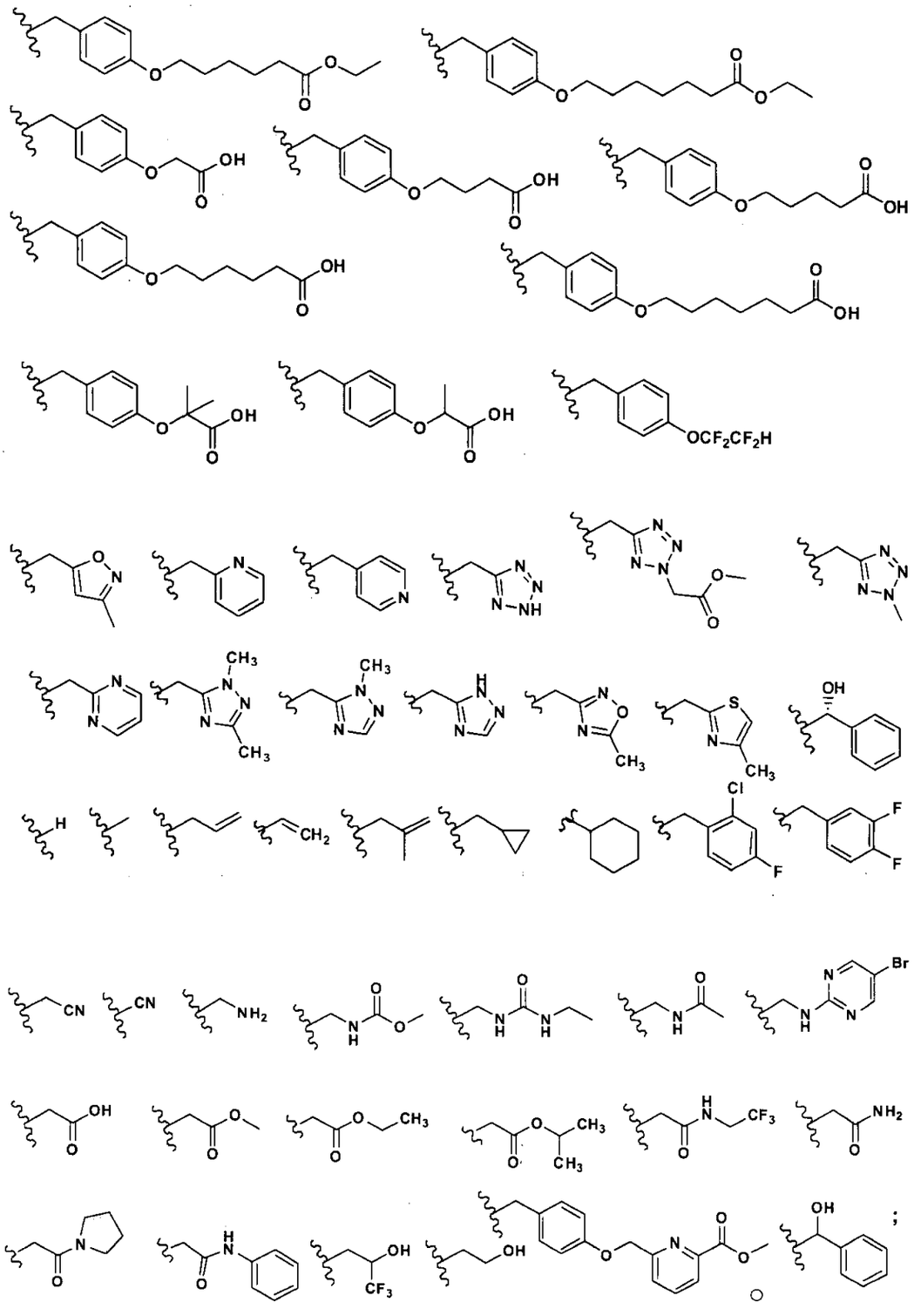








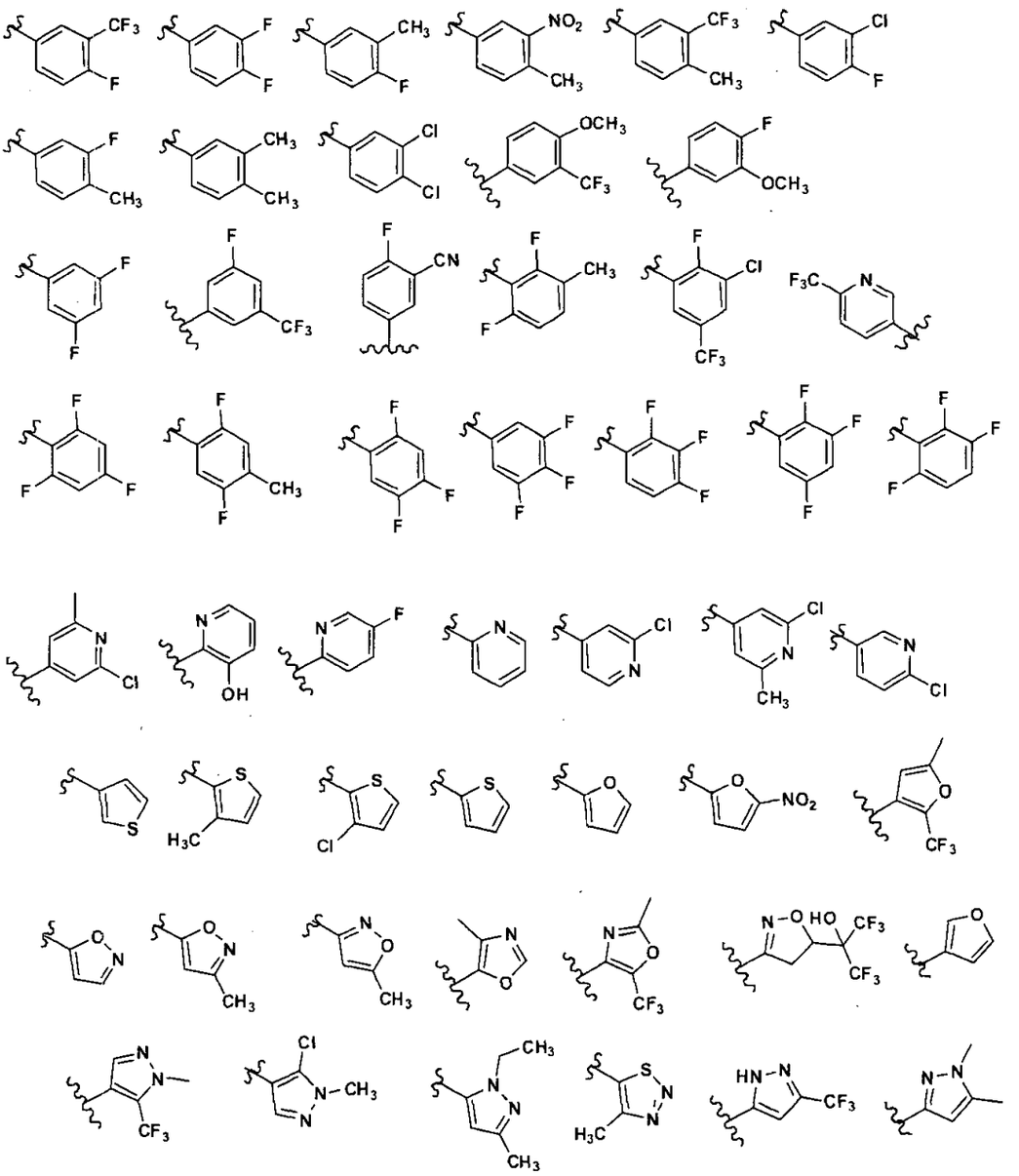


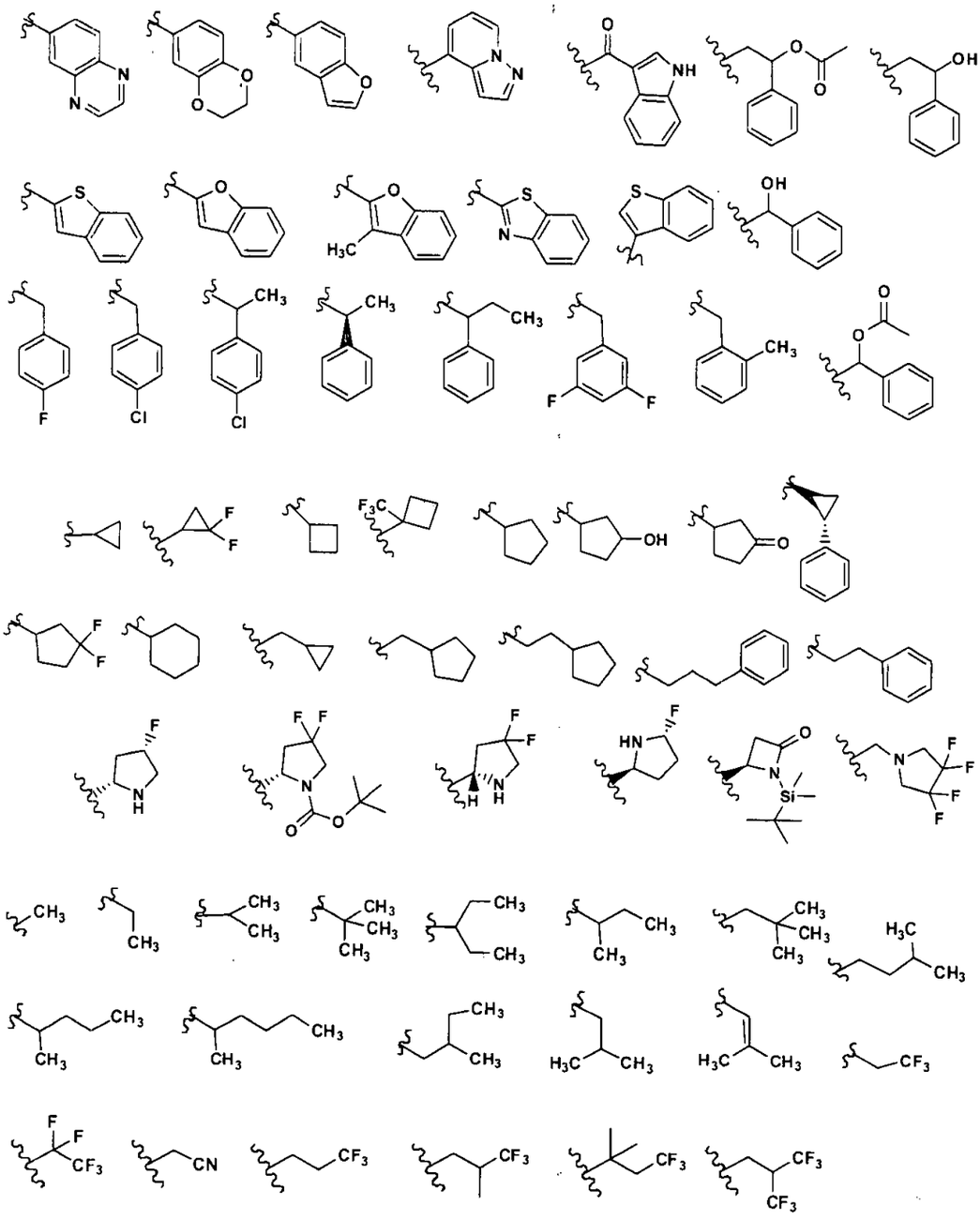


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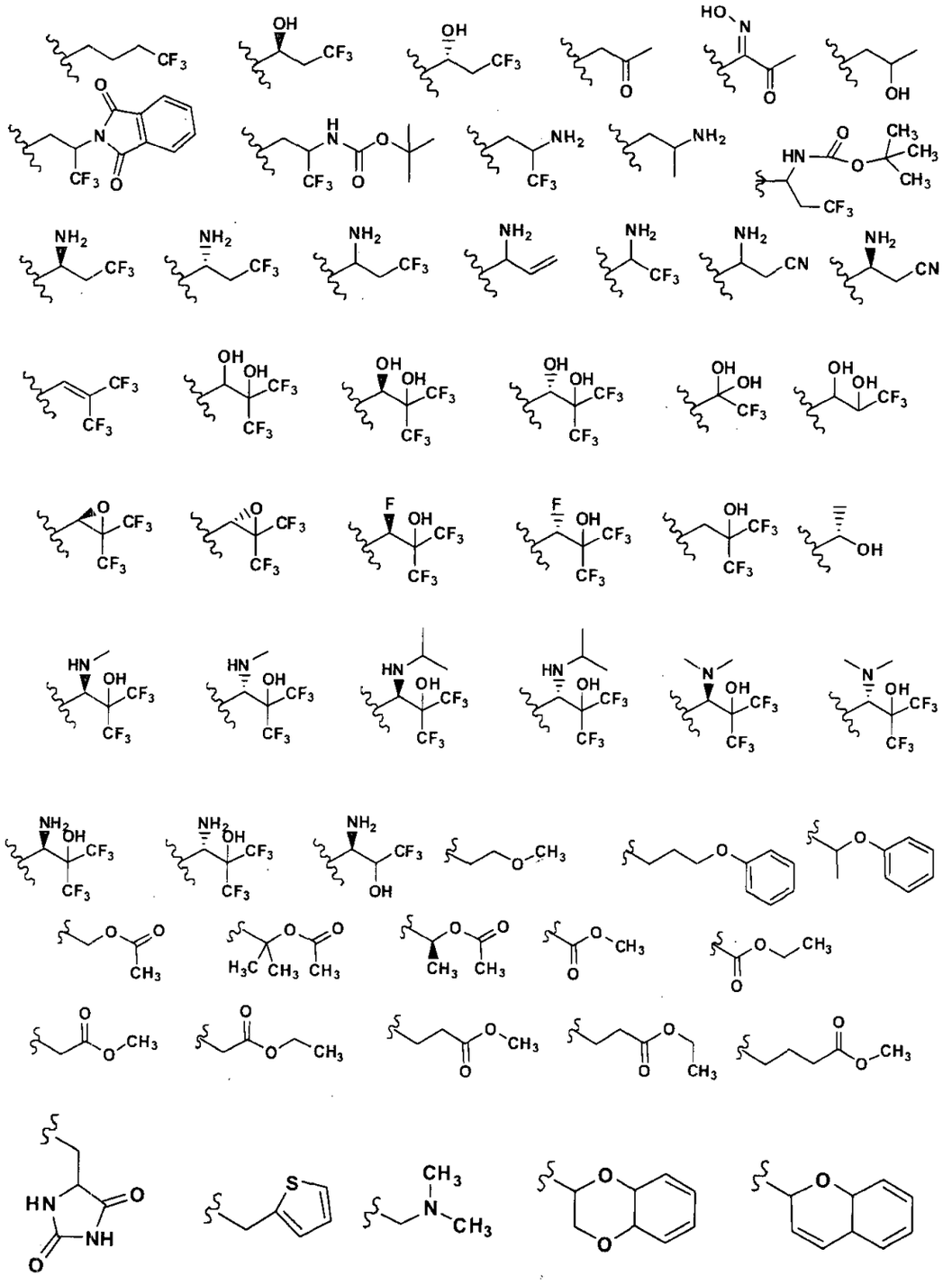
$R_1$ es:

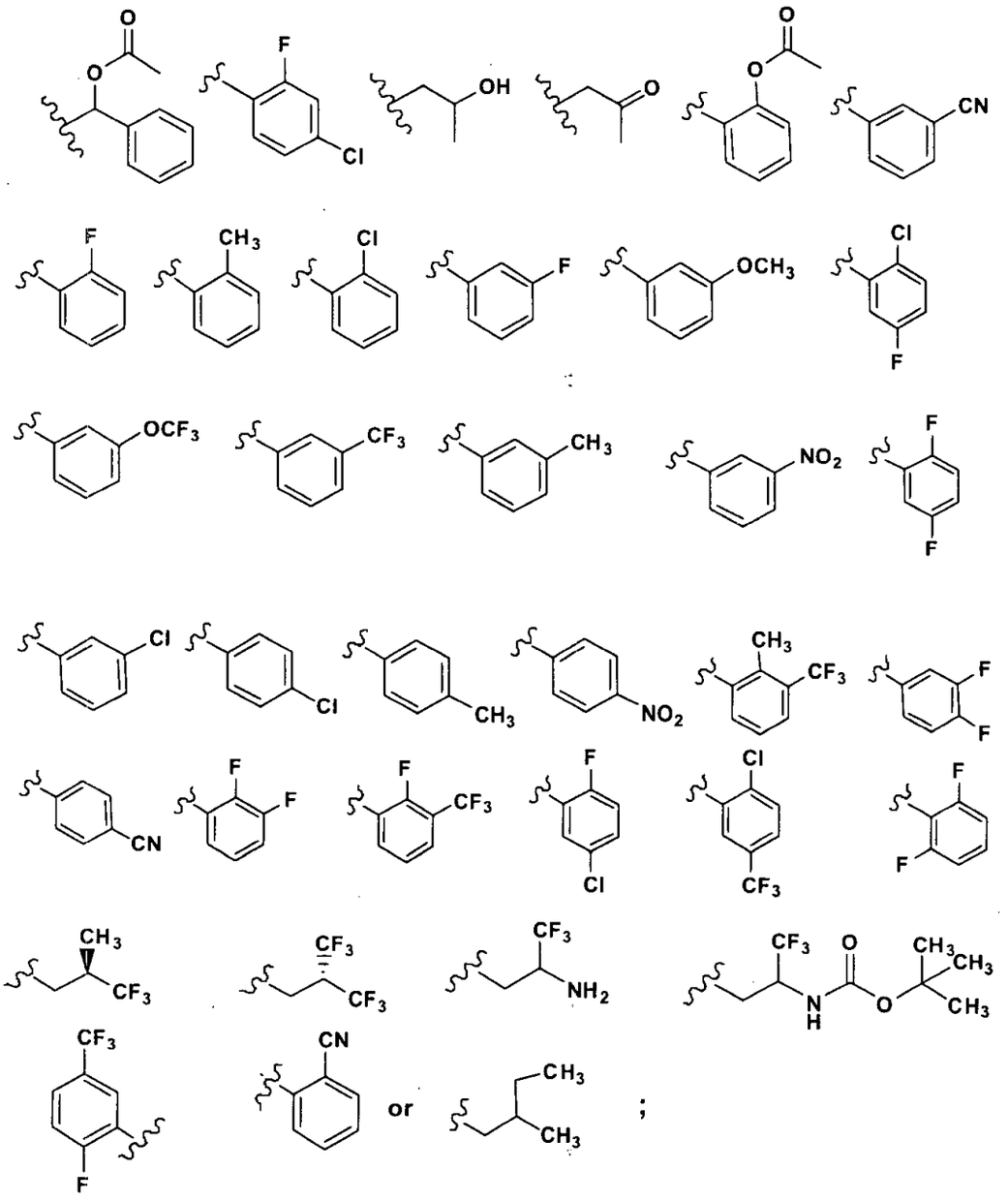
(a) $-C(O)R_3$, en donde $R_3$:





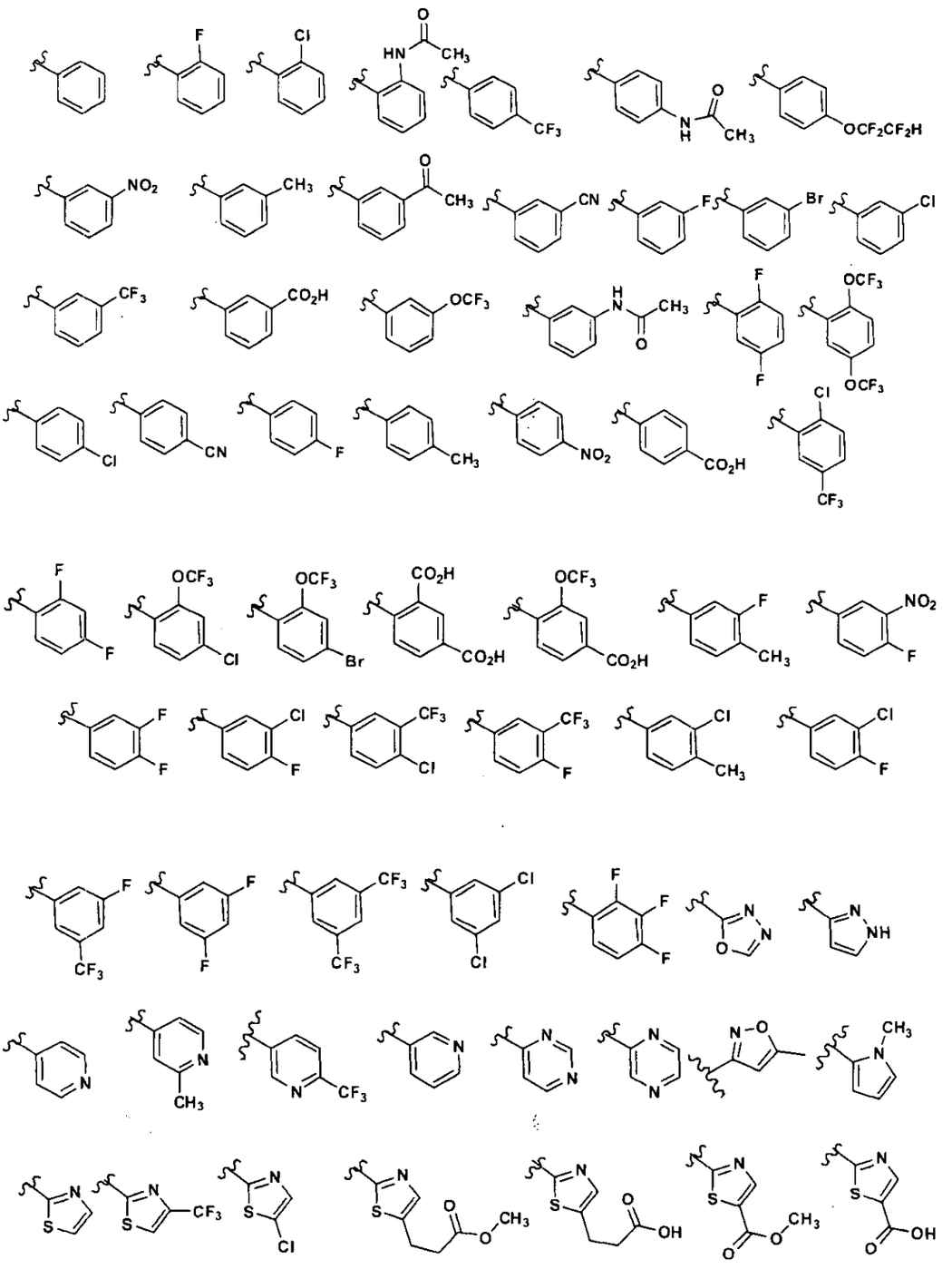
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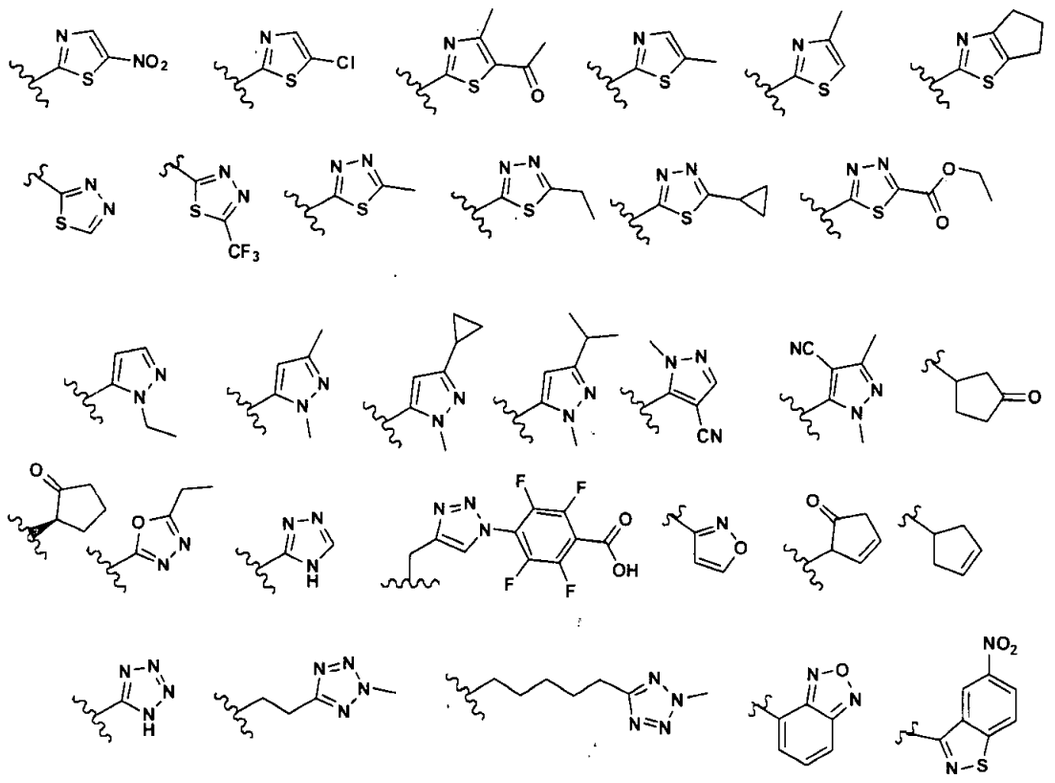

O
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Cl
OH
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CN
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CH3
Cl
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OCH3
Cl
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OCF3
CF3
CH3
NO2
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F
Cl
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CH3
CH3
NO2
CH3
CF3
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CN
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CN
or
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CH3

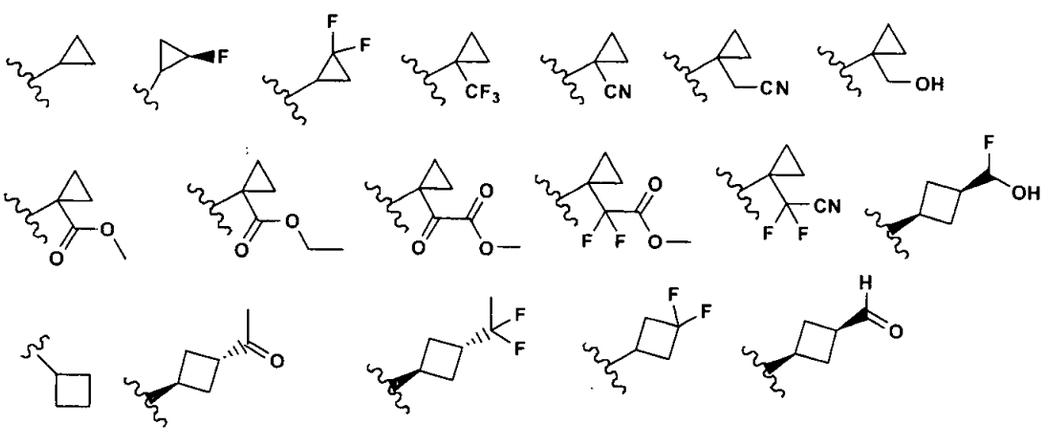
;

(b) $-C(O)NHR_3$, en donde el $R_3$ es:



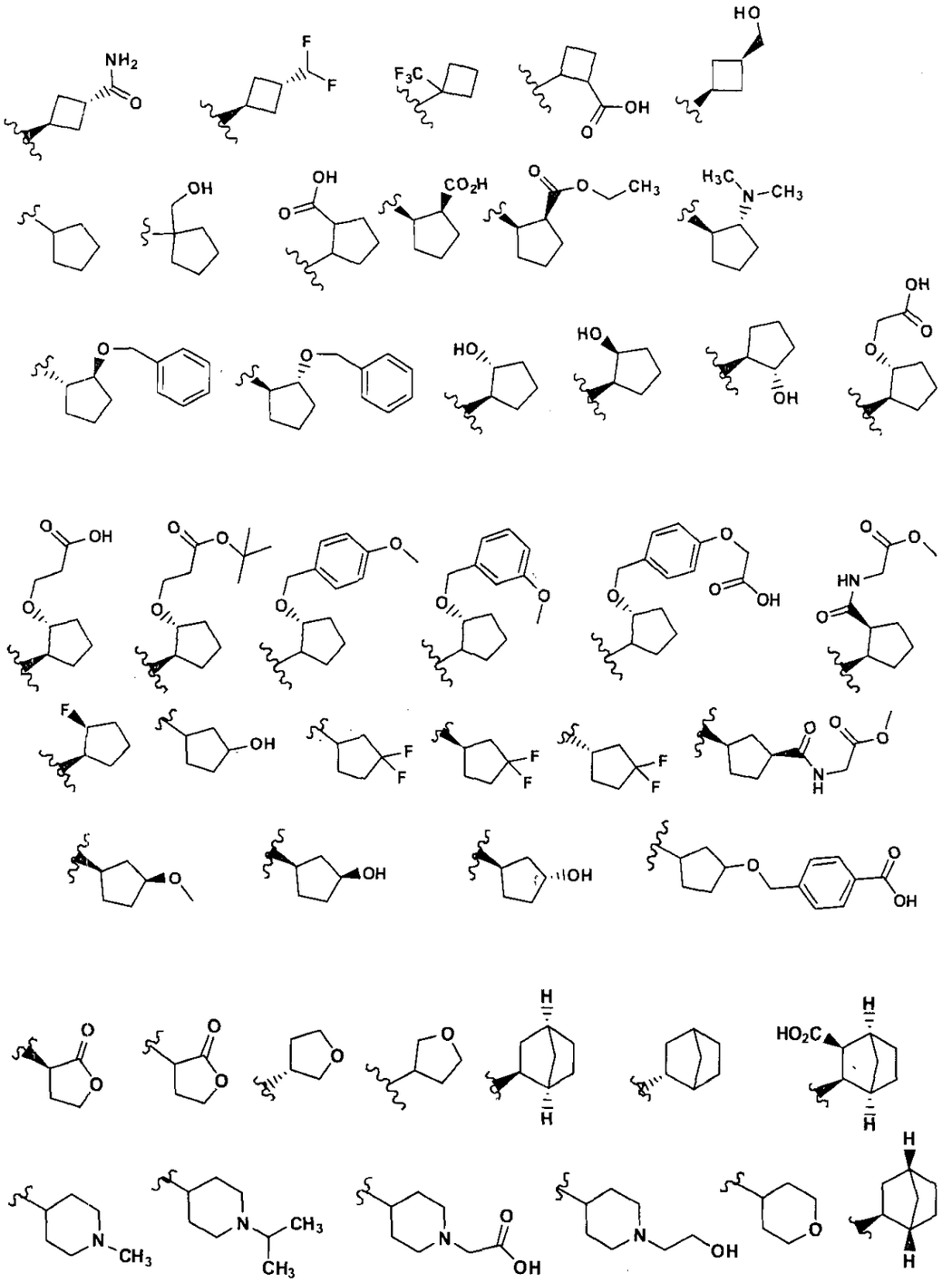
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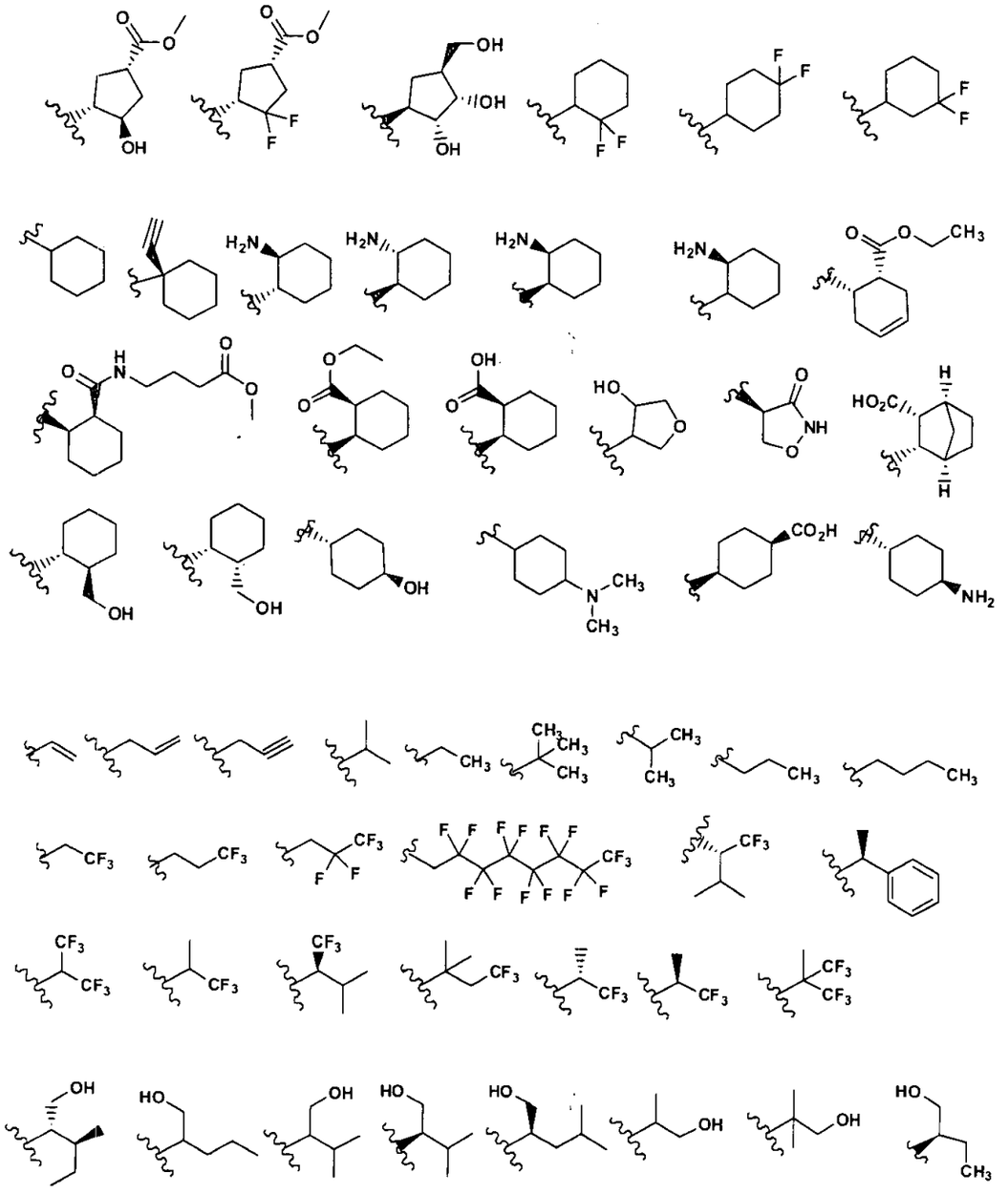




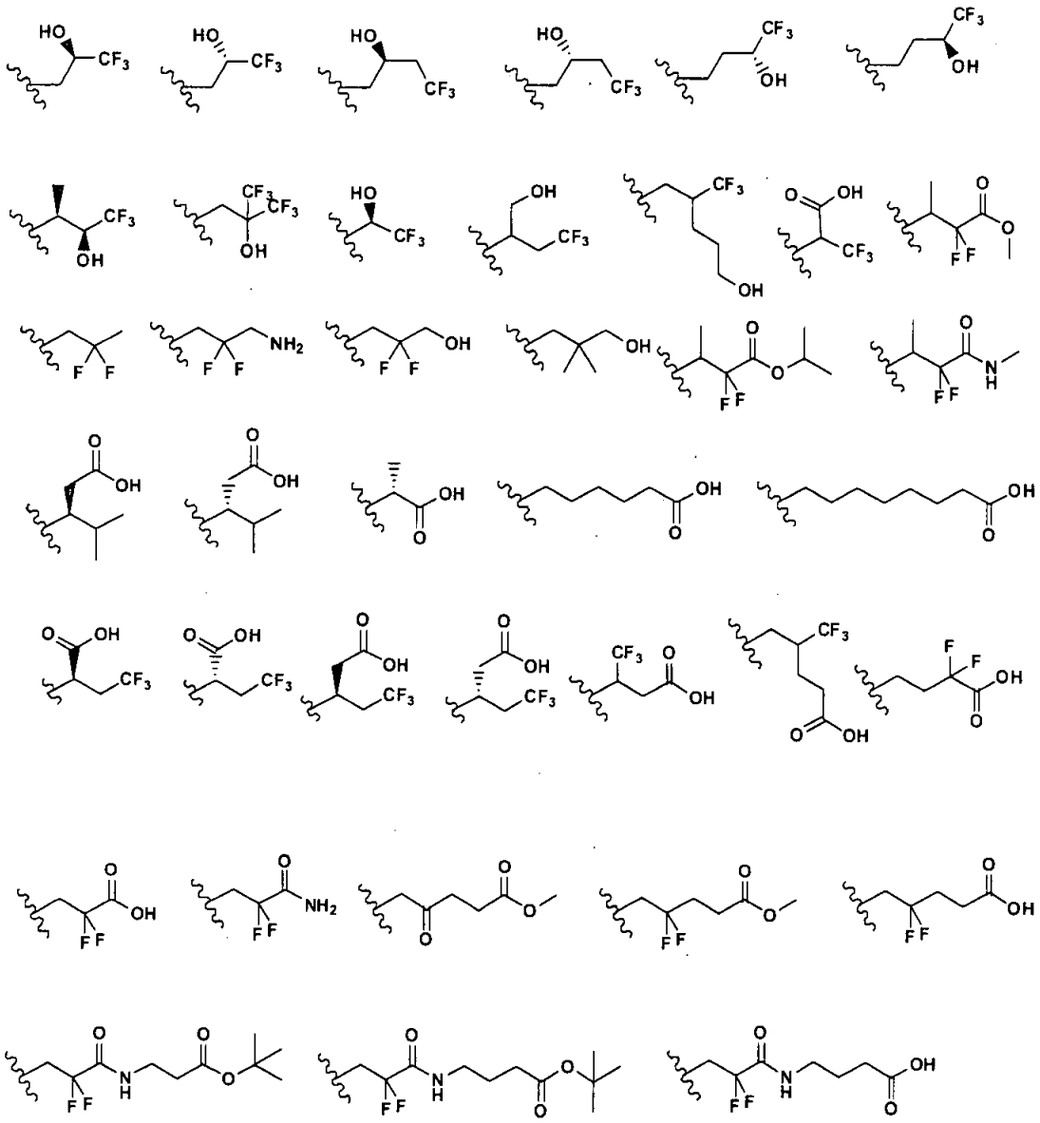


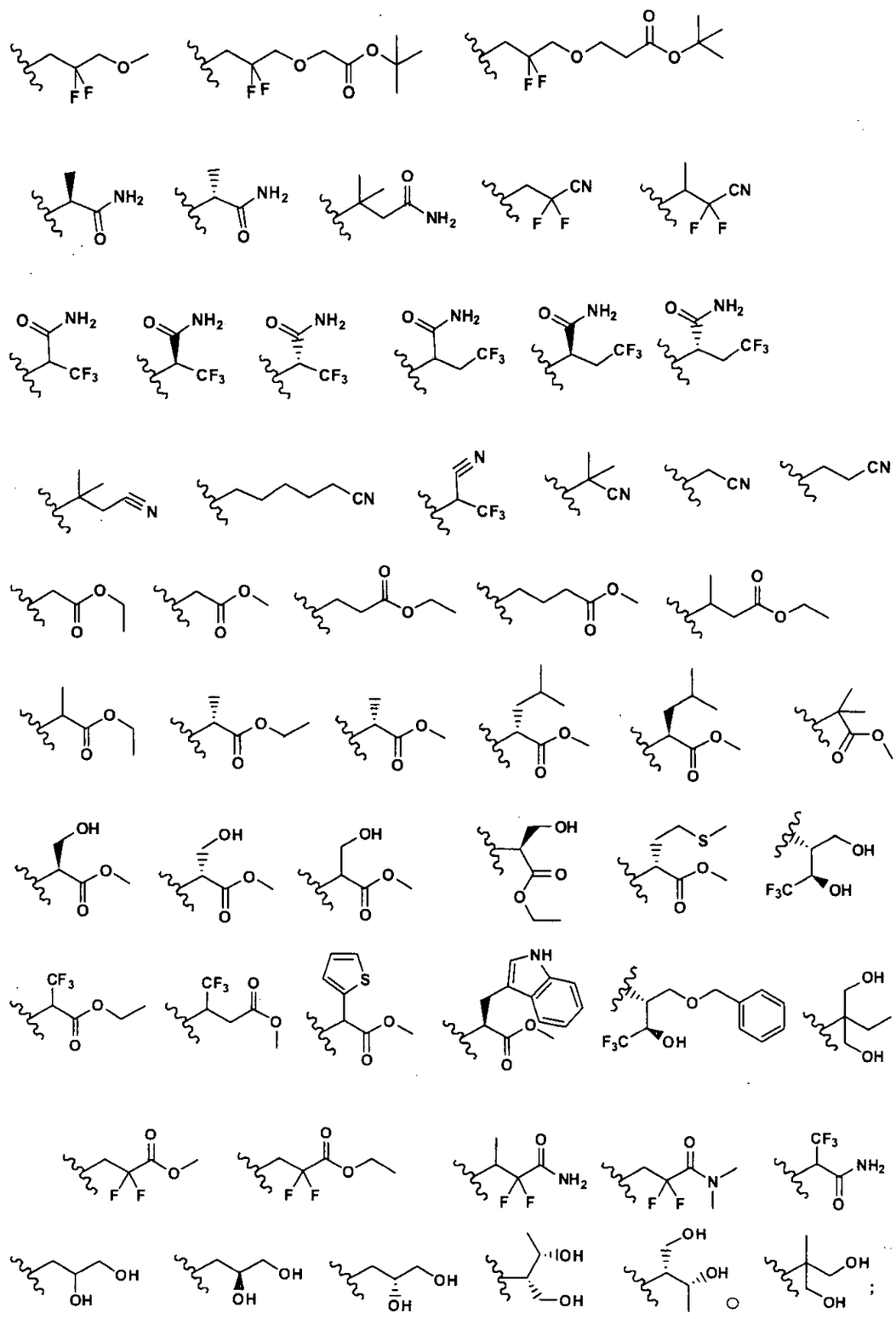
1020


NH2
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F3C
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HO
OH
OH
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CO2H
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CH3
H3C
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OH
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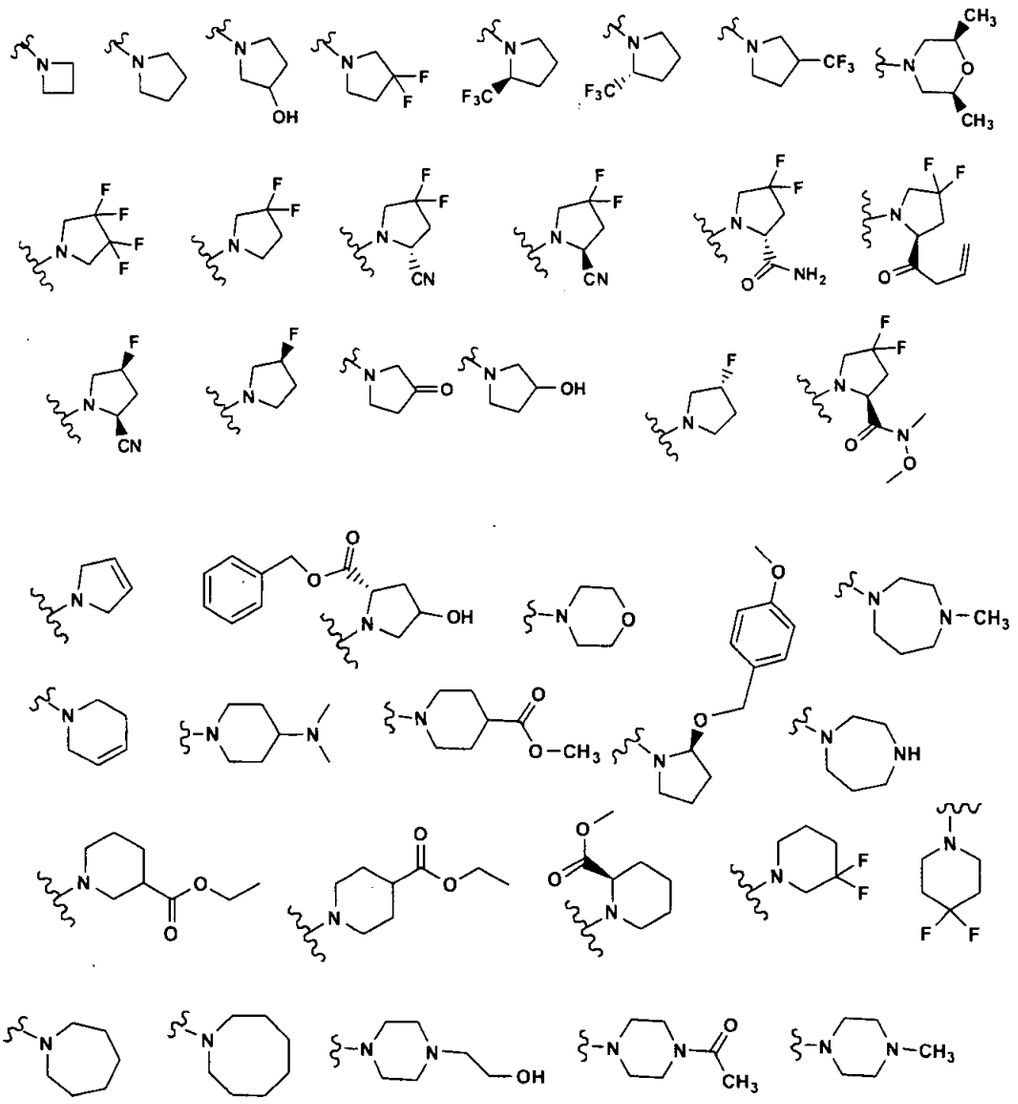
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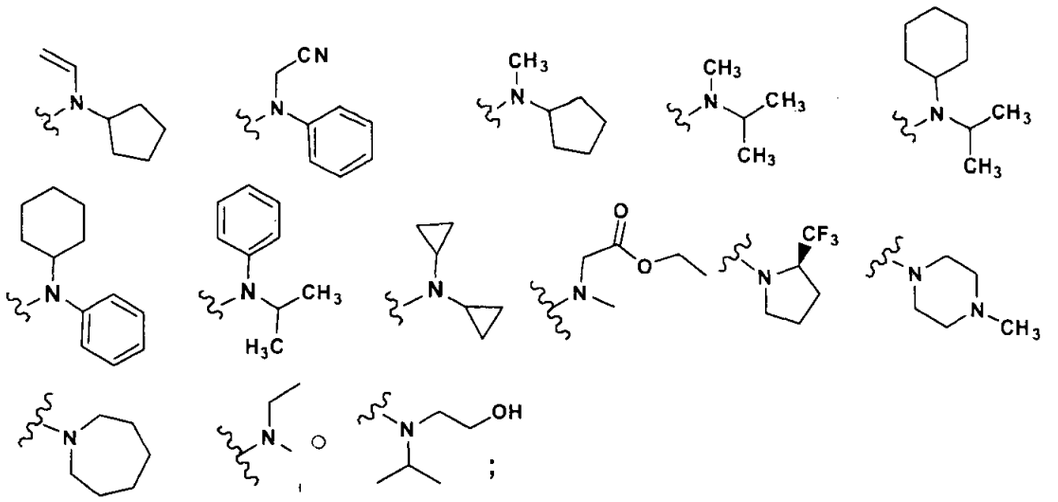




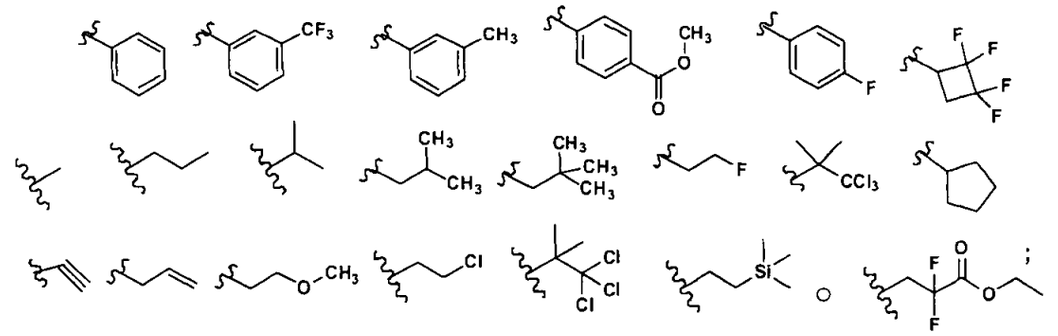
1024

(c) $-C(O)NR_2R_3$, en donde el $NR_2R_3$ es:

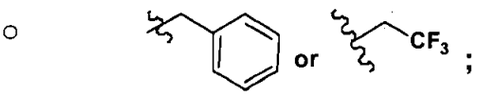




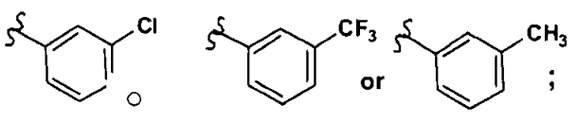
(d) $-C(O)OR_4$ en donde el $R_4$ es:



(e) $-SO_2R_5$ en donde el $R_5$ es:

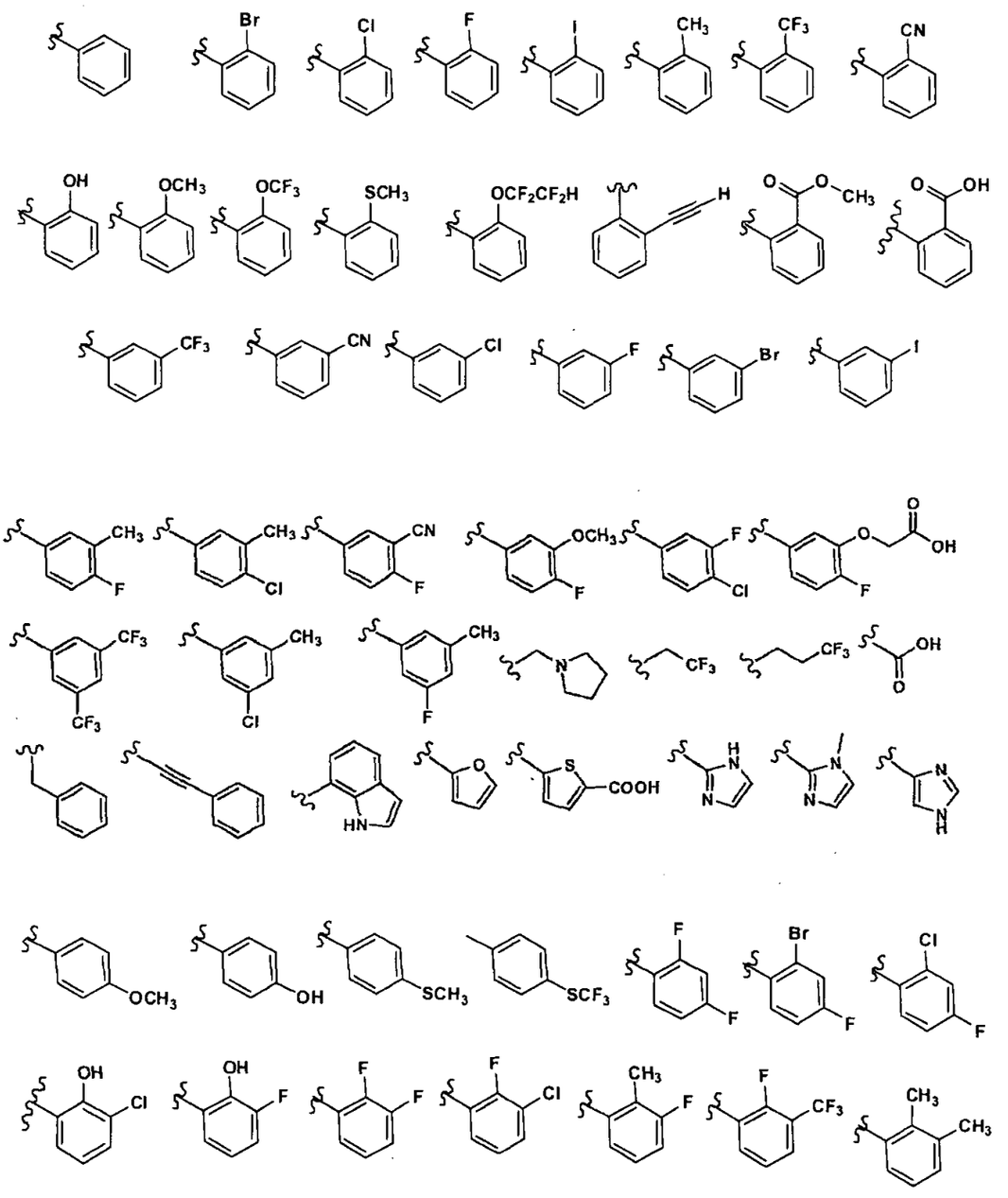


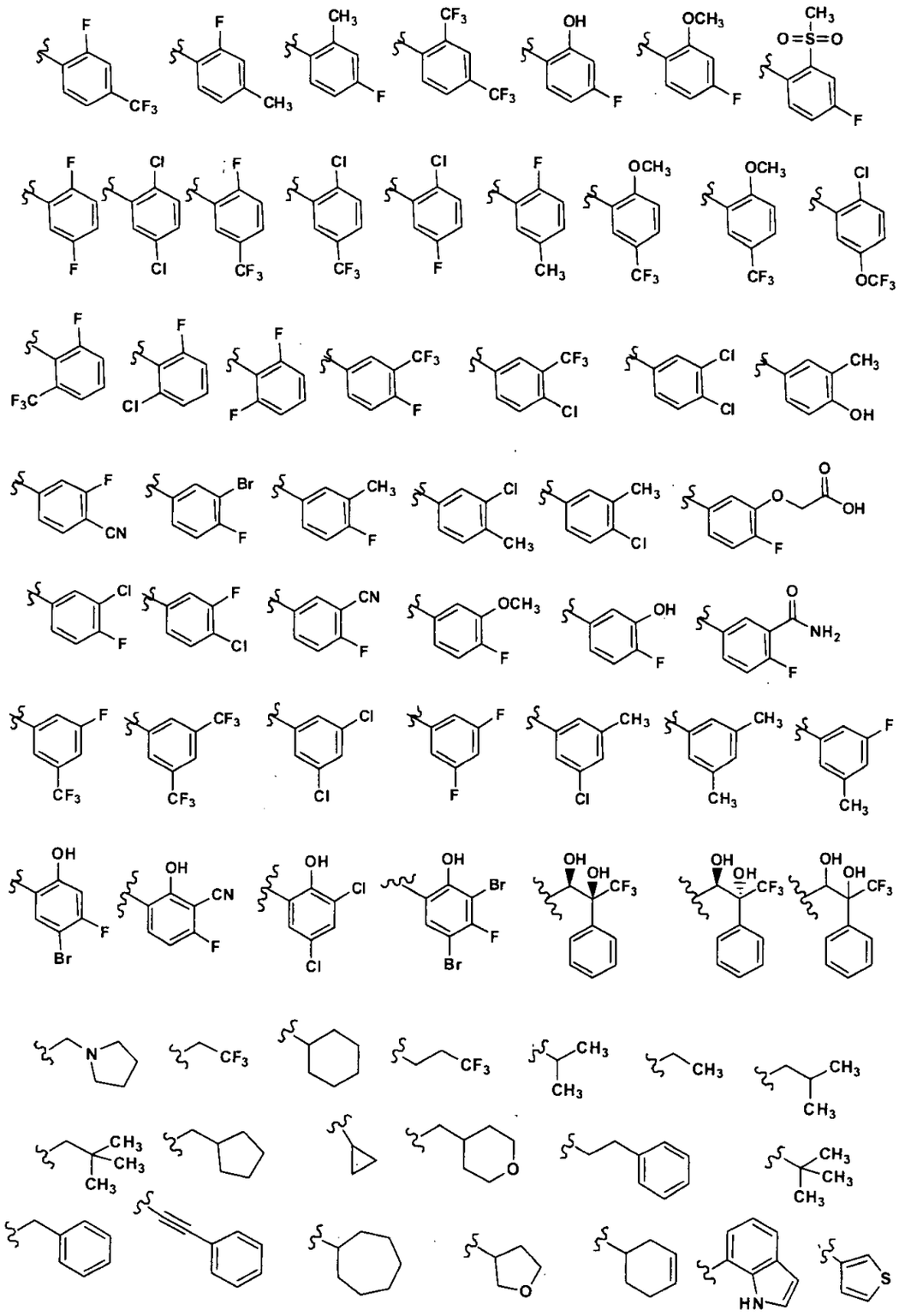
(f) $-CSNHR_7$ en donde el $R_7$ es:

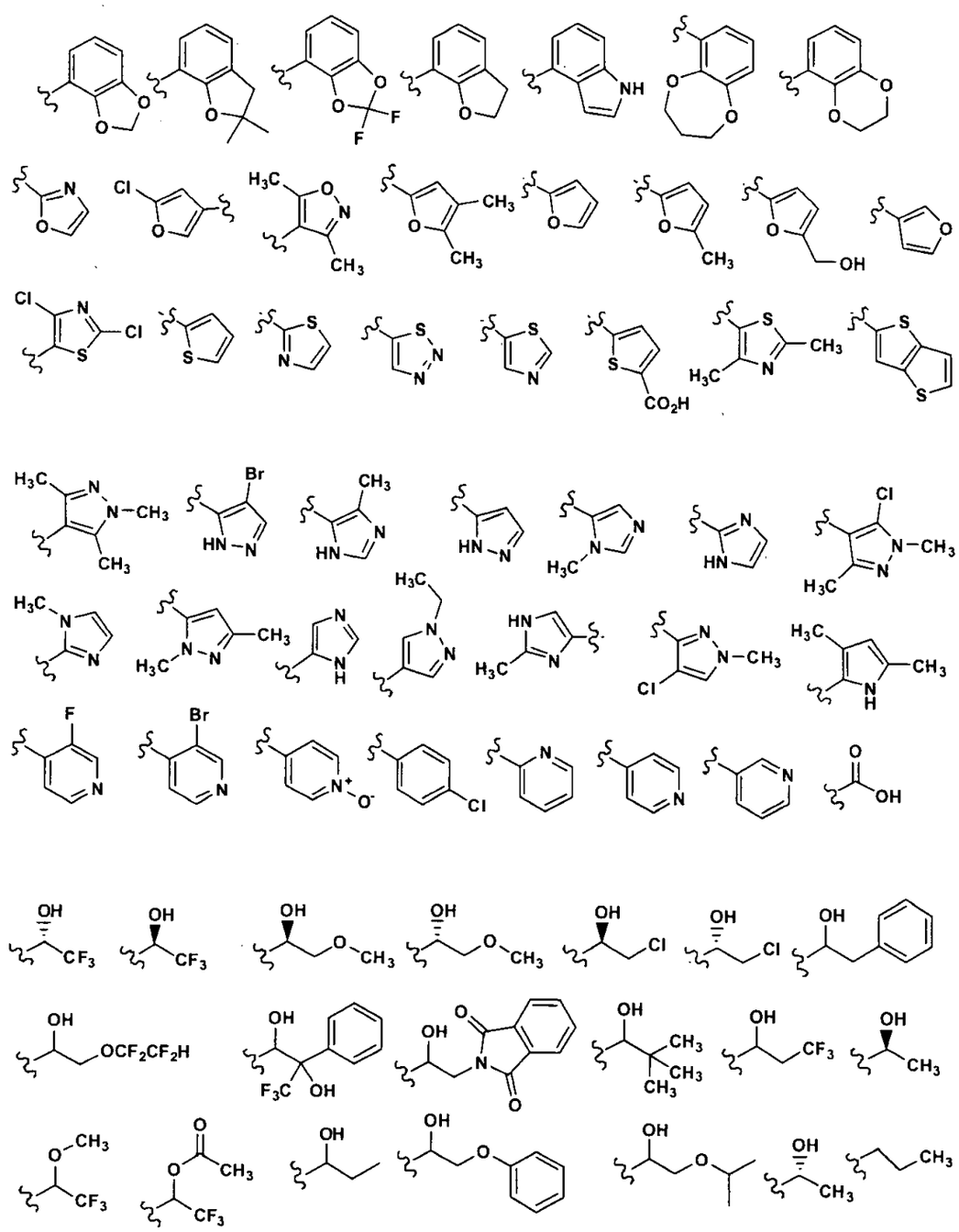


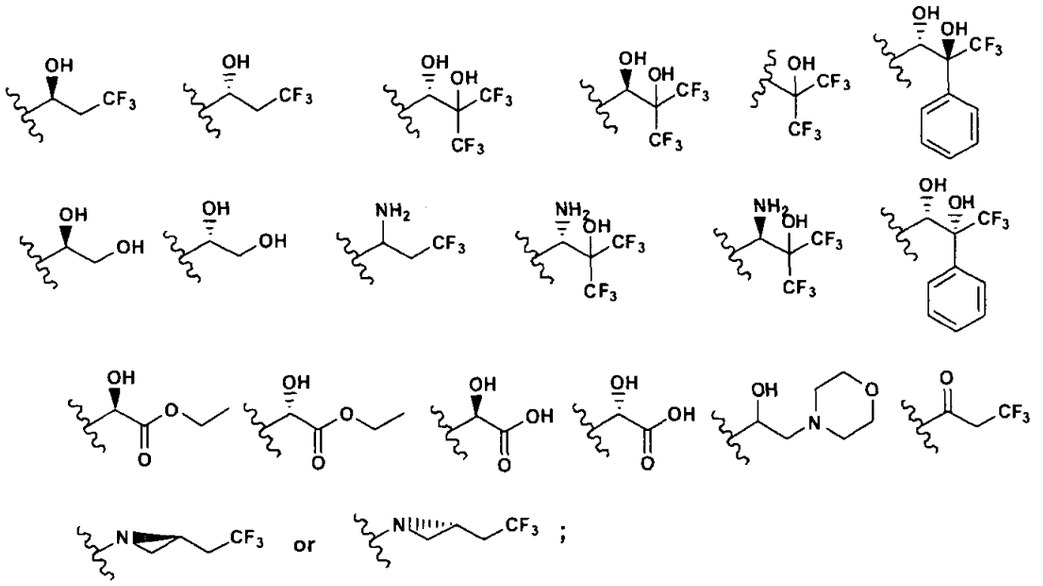
1026

(g) $-CH_2R_8$ en donde el $R_8$ es:



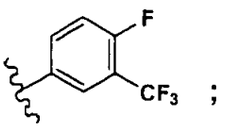




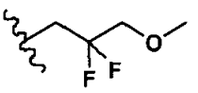




(h) $-C(S)R_3$ en donde el $R_3$ es:



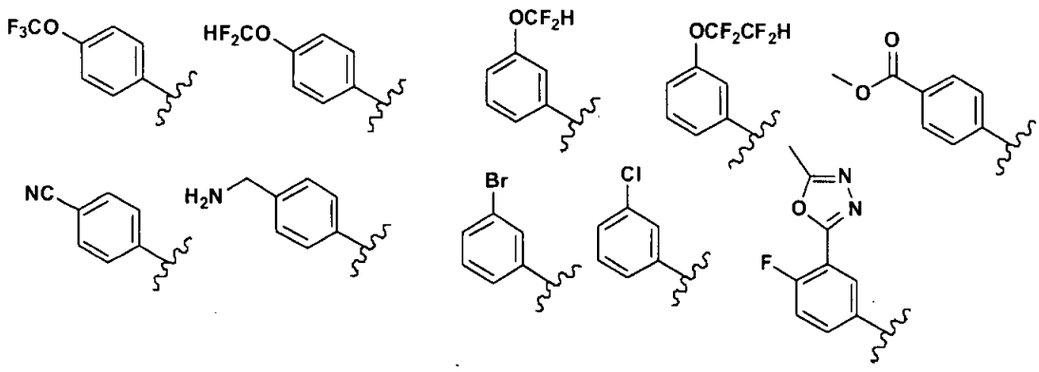
(i) $-C(=NR_3)Oalquilo$ en donde el $R_3$ es:

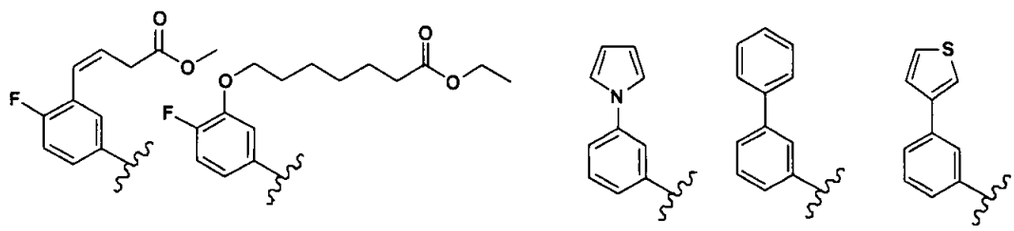


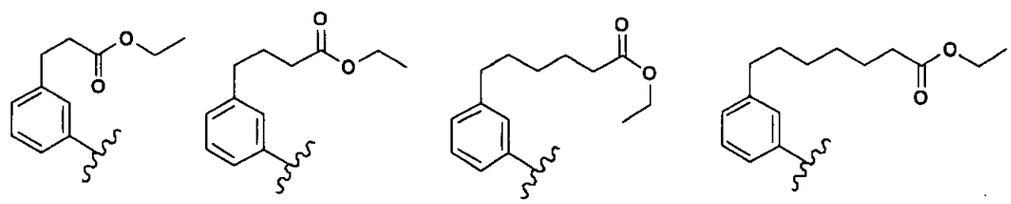
También de acuerdo con la presente invención, los compuestos de la presente invención son aquellos en donde:

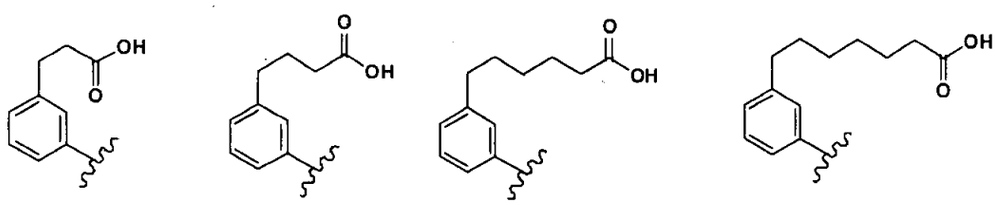
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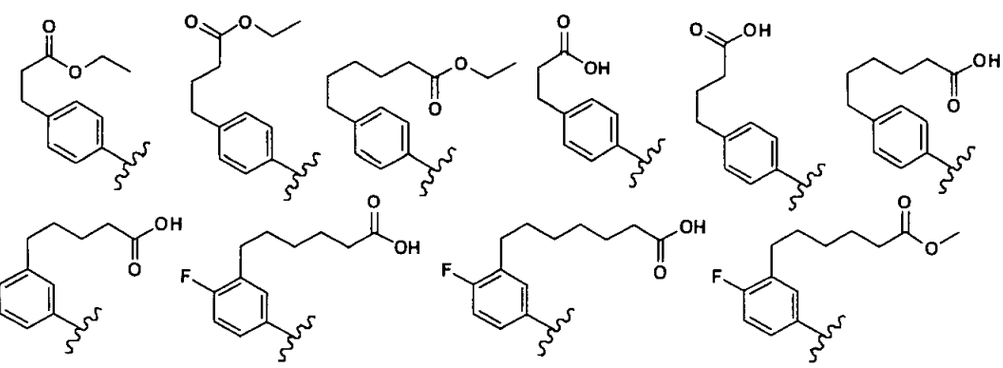
A es:

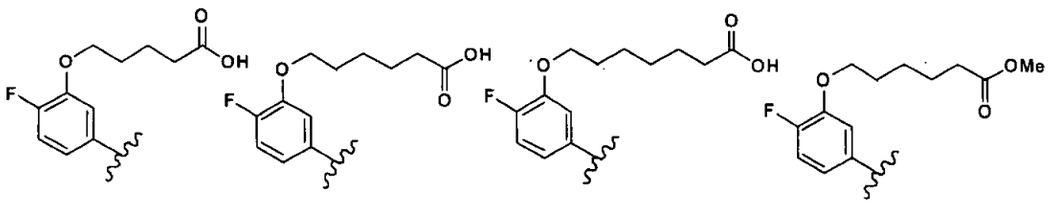

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OCF2H
OCF2CF2H
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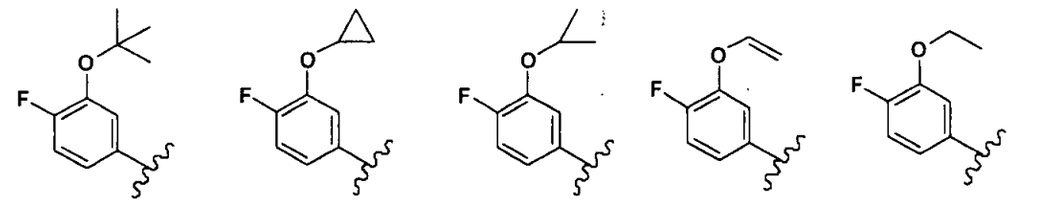

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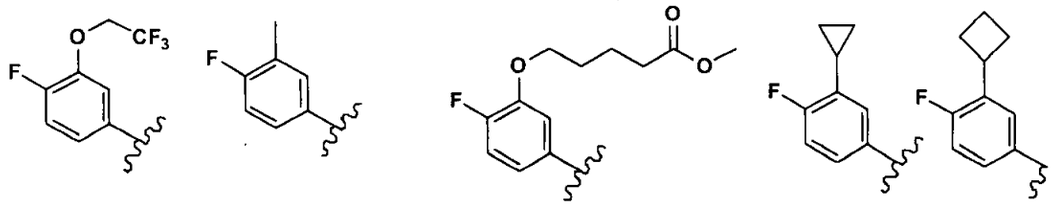

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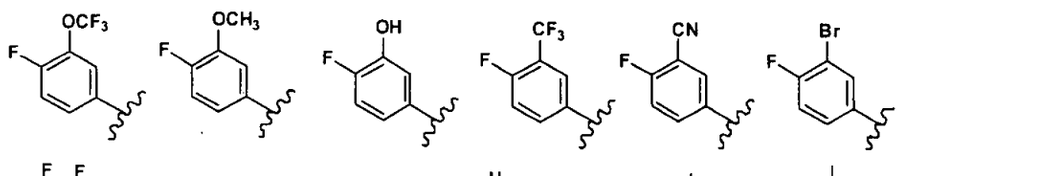

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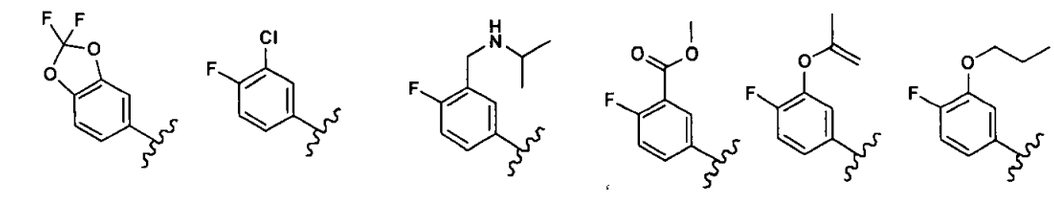

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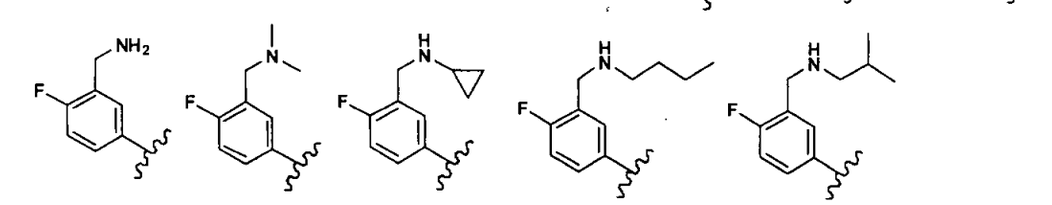


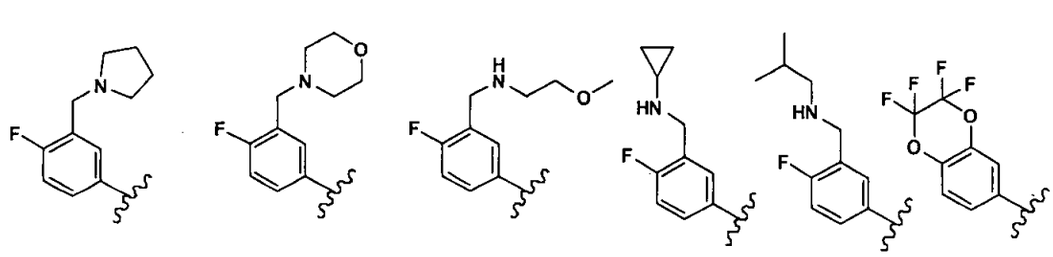


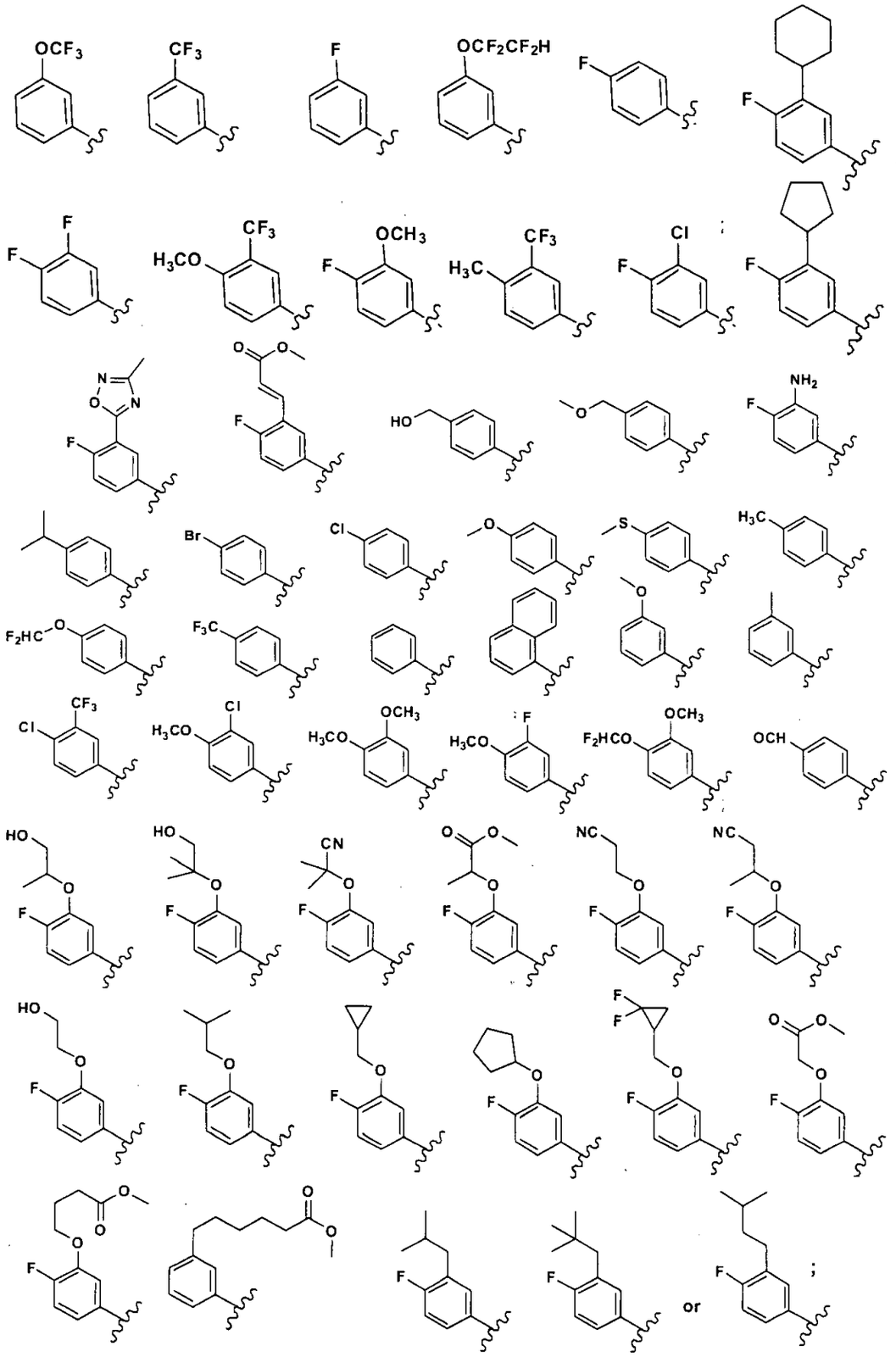






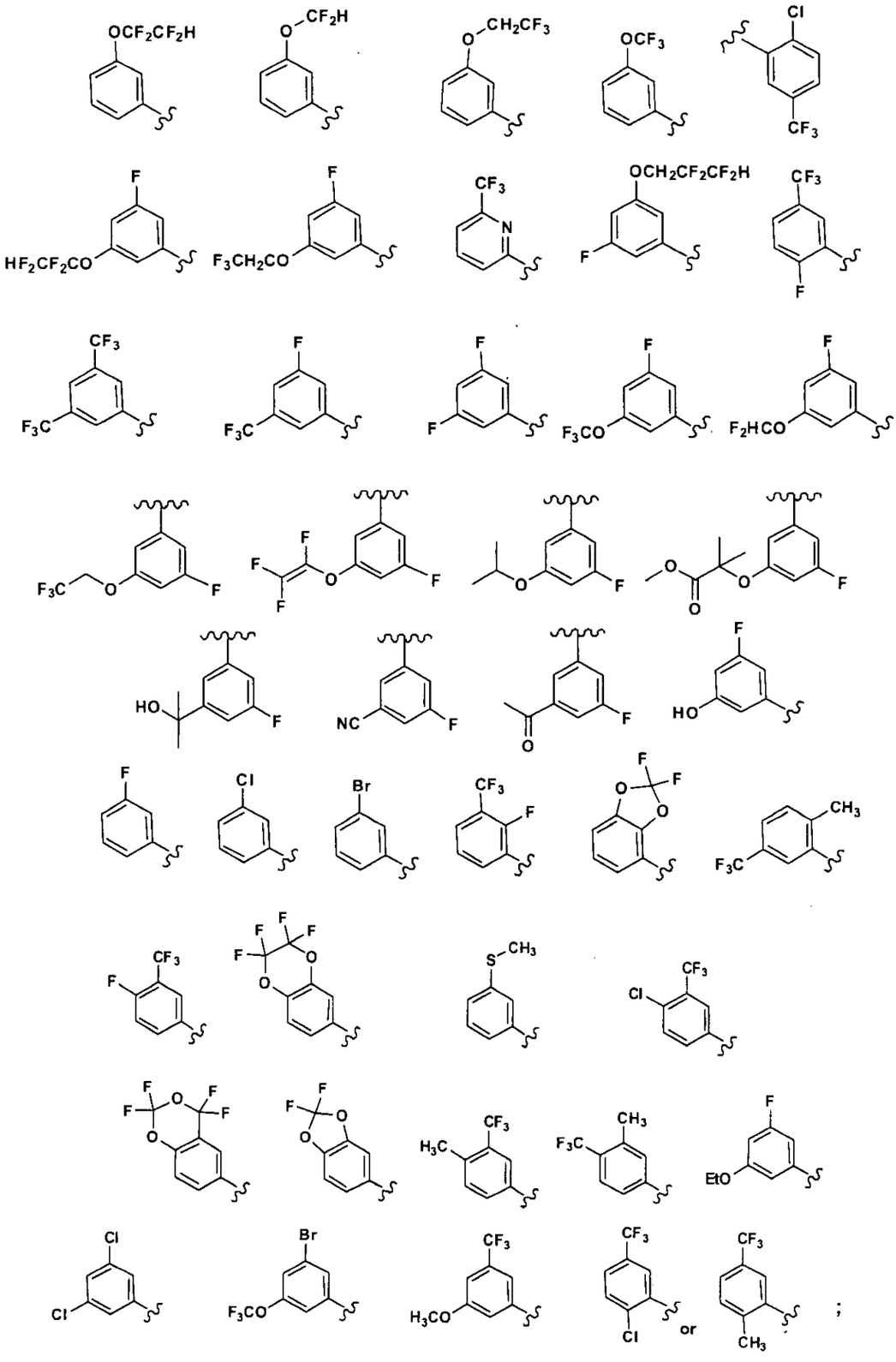





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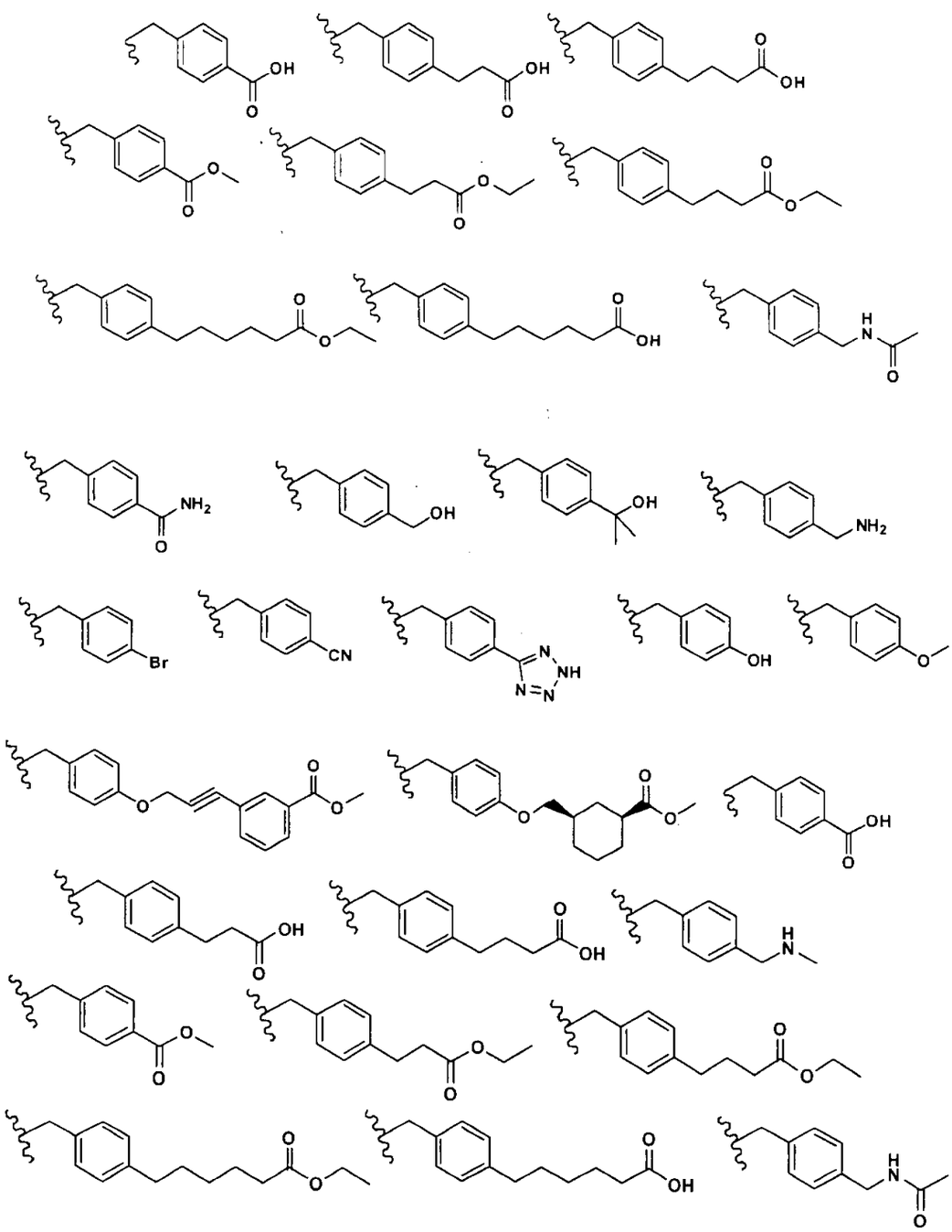
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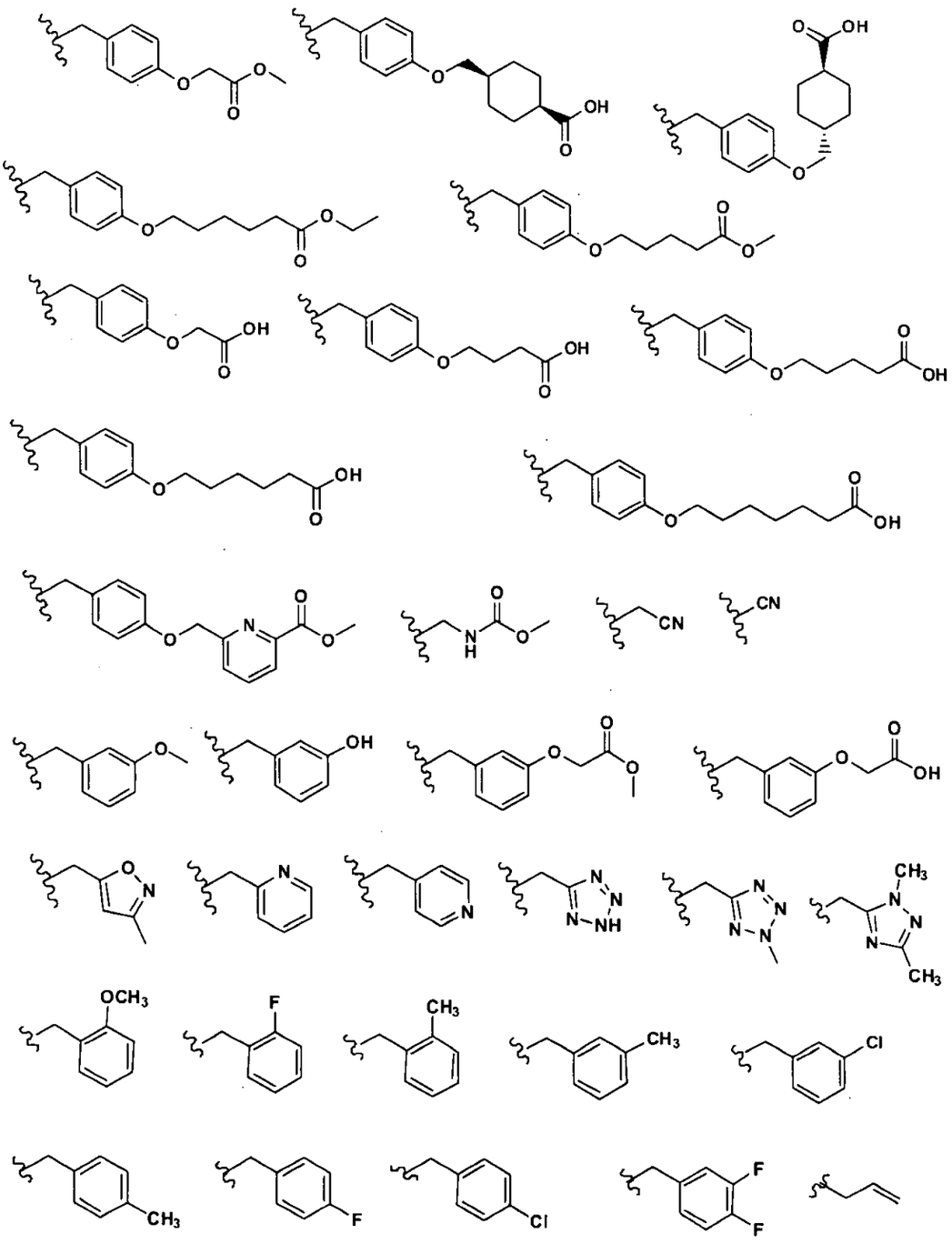


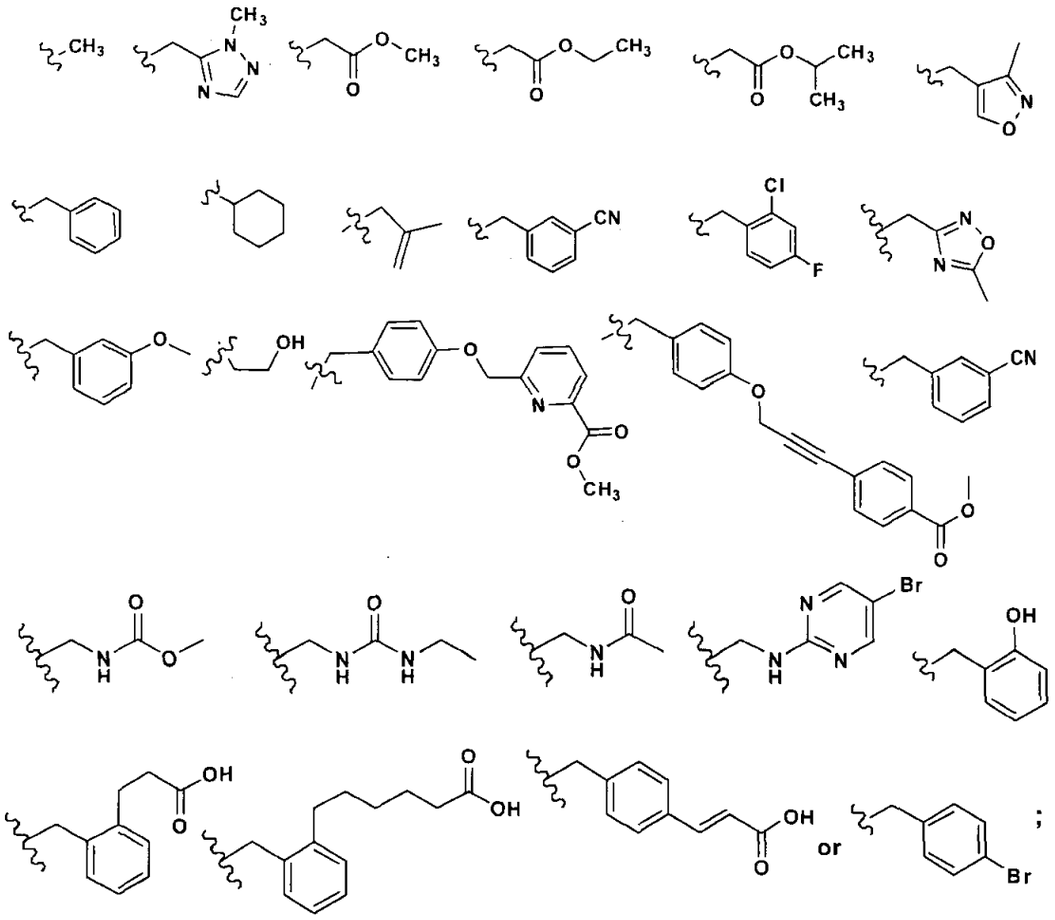
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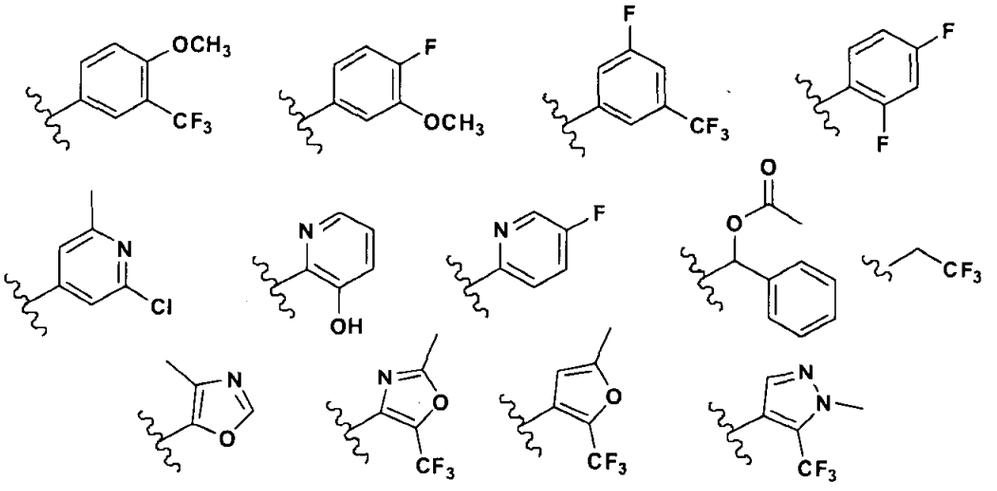


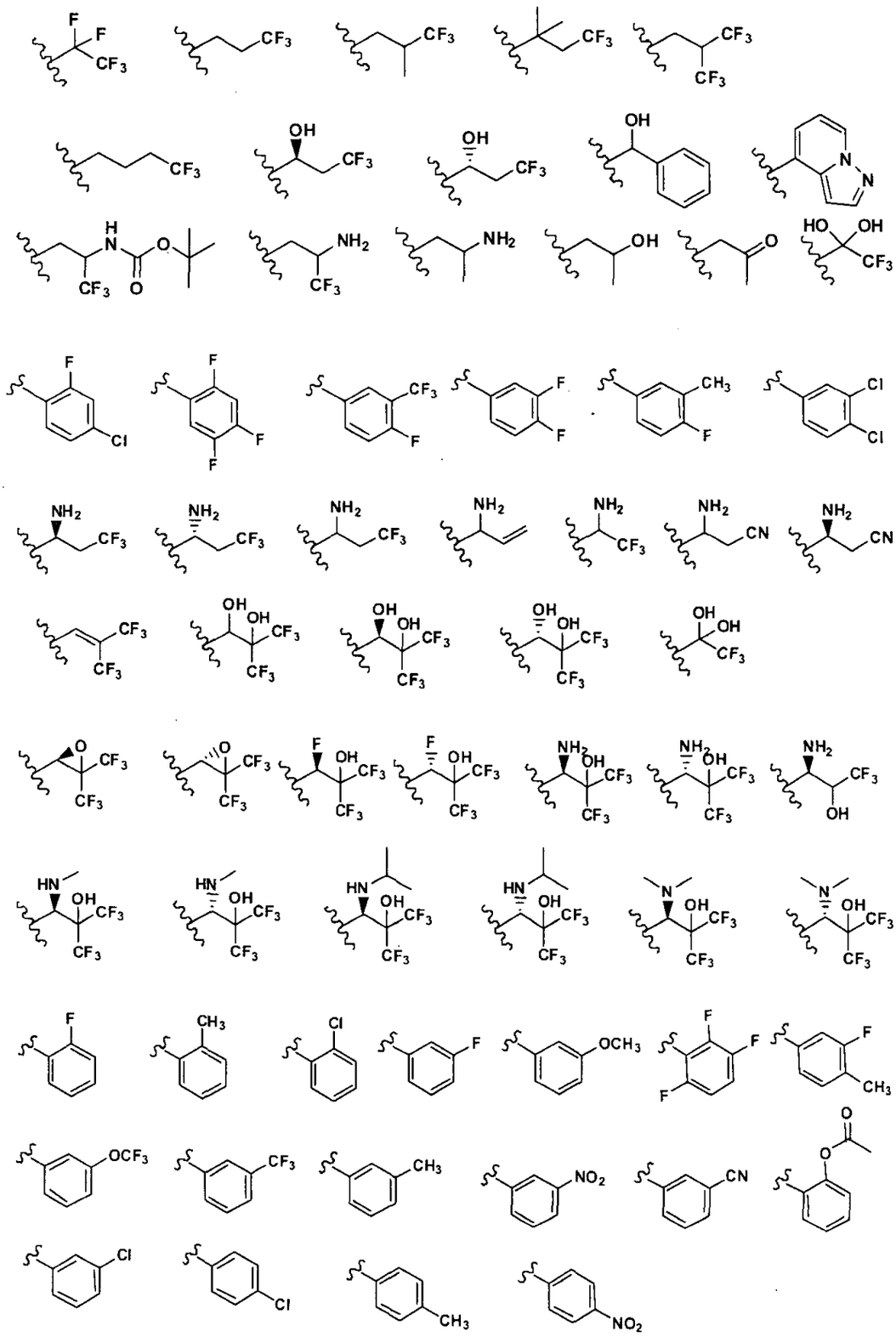


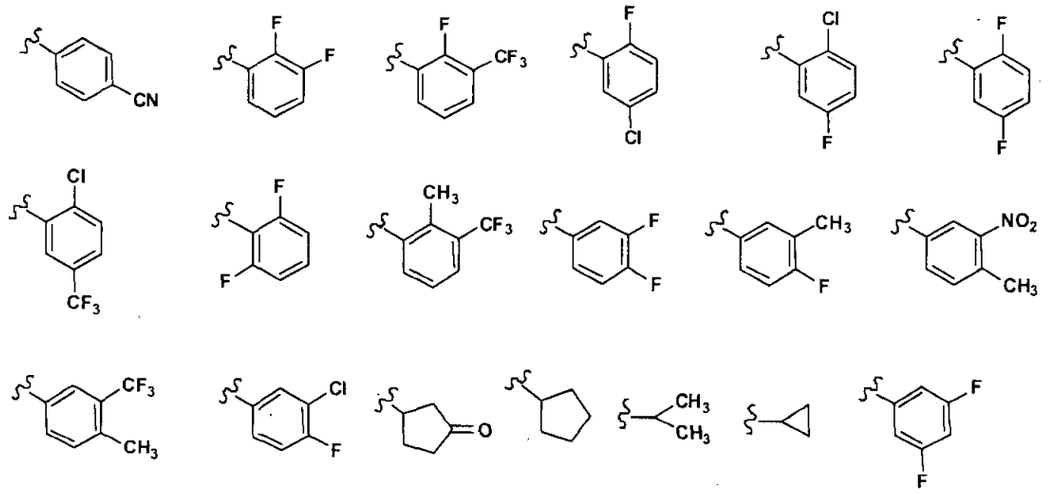


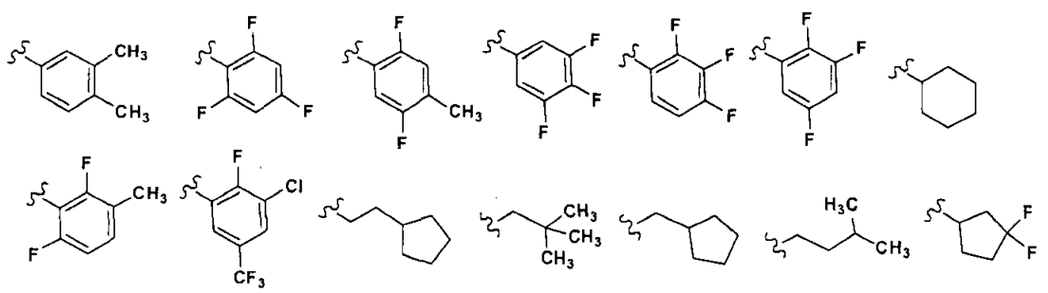
$R_1$ es H o:

(a) $-C(O)R_3$, en donde $R_3$:

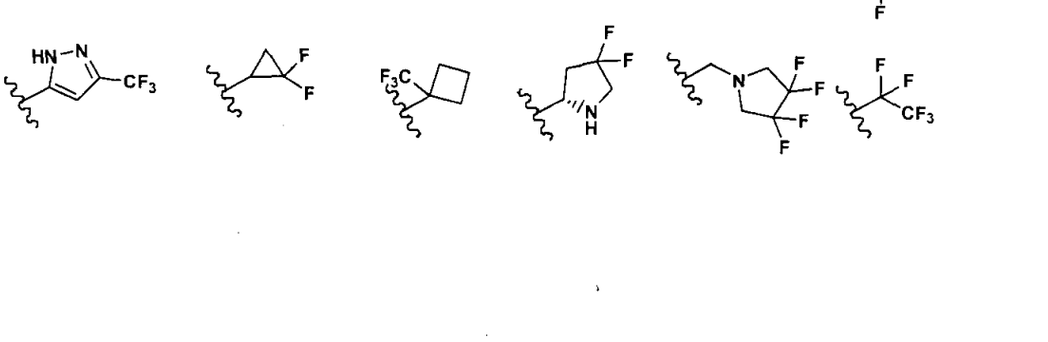


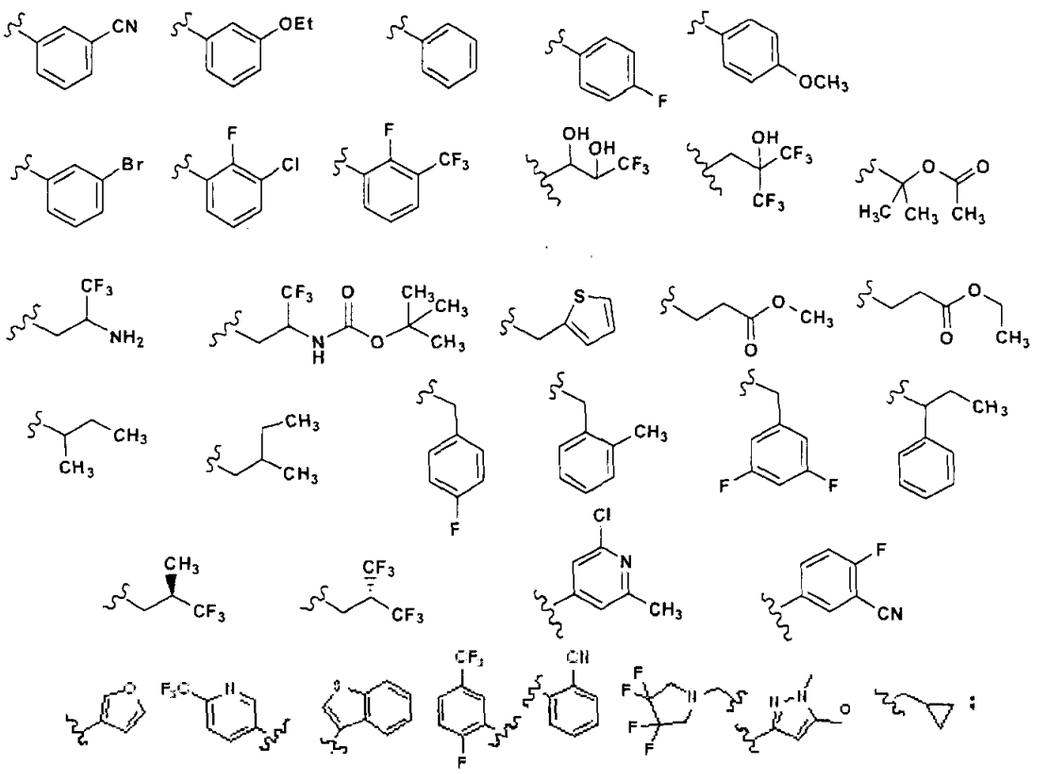




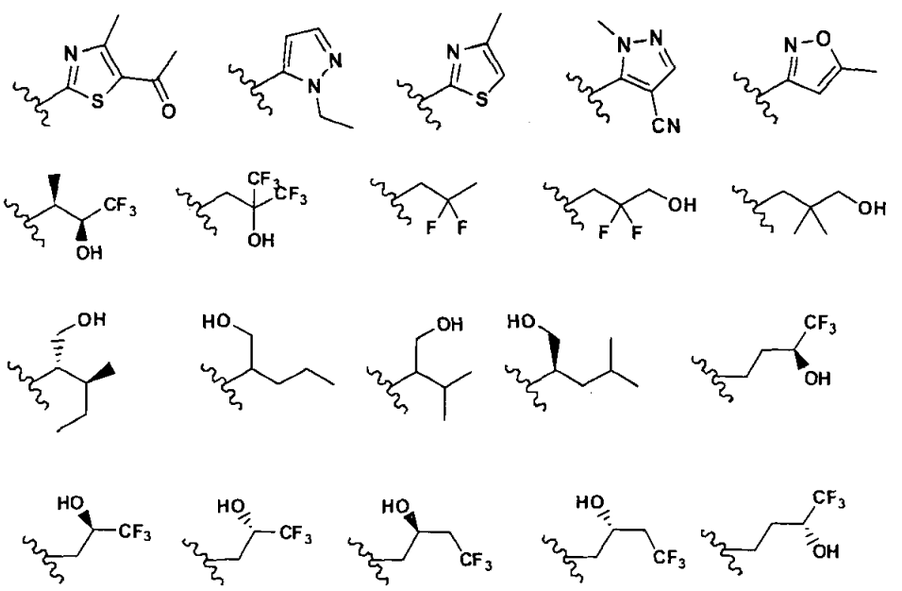


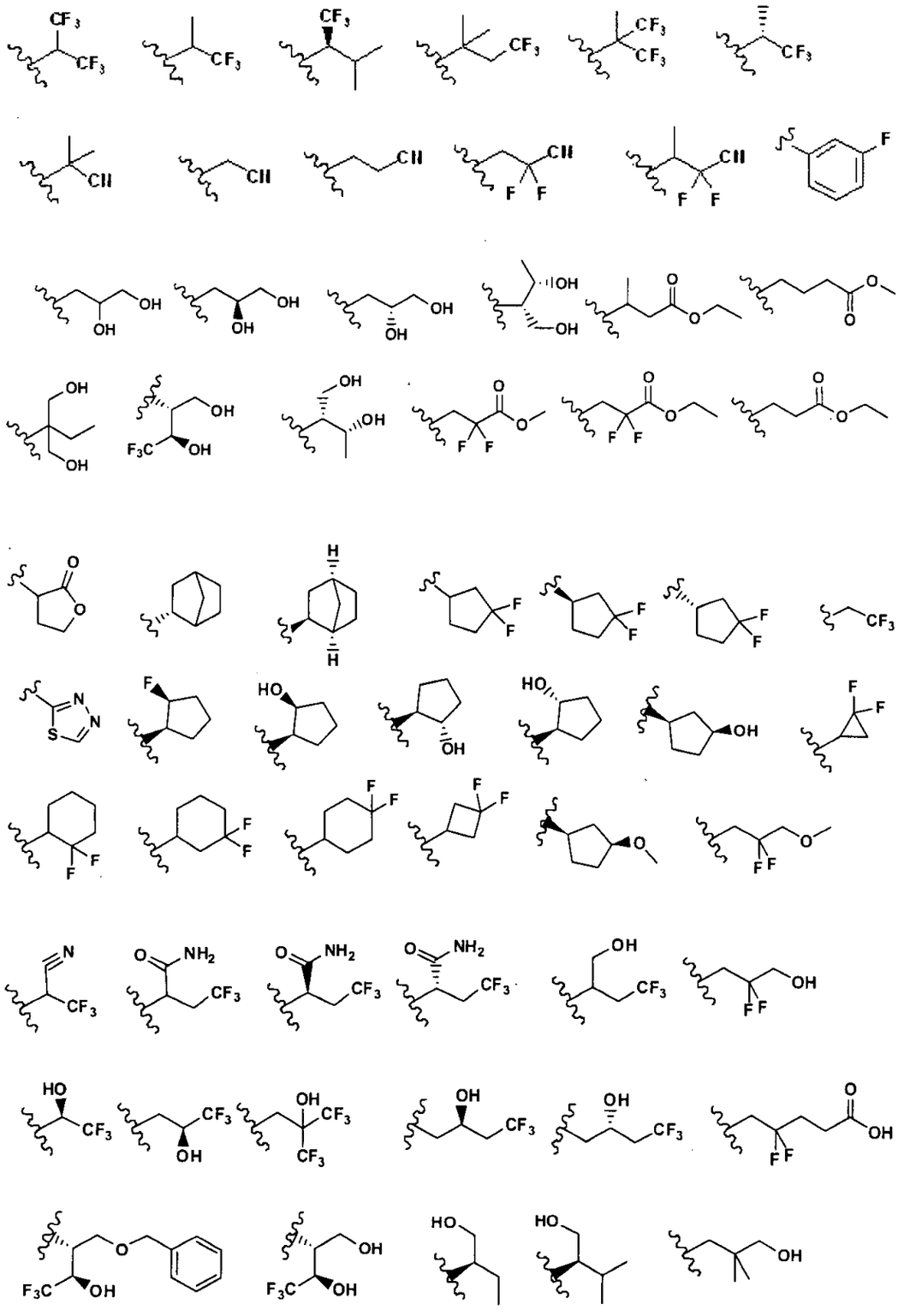


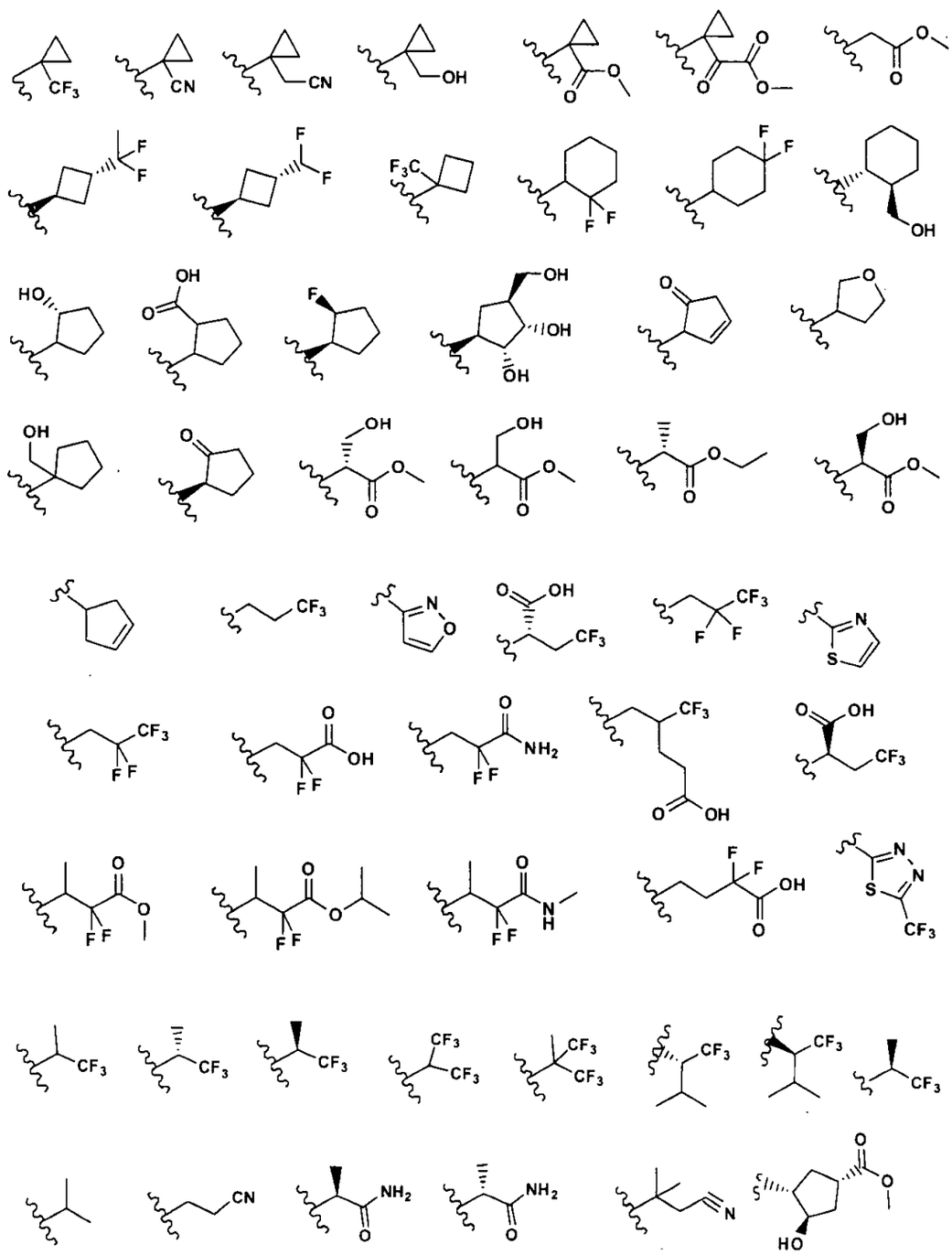


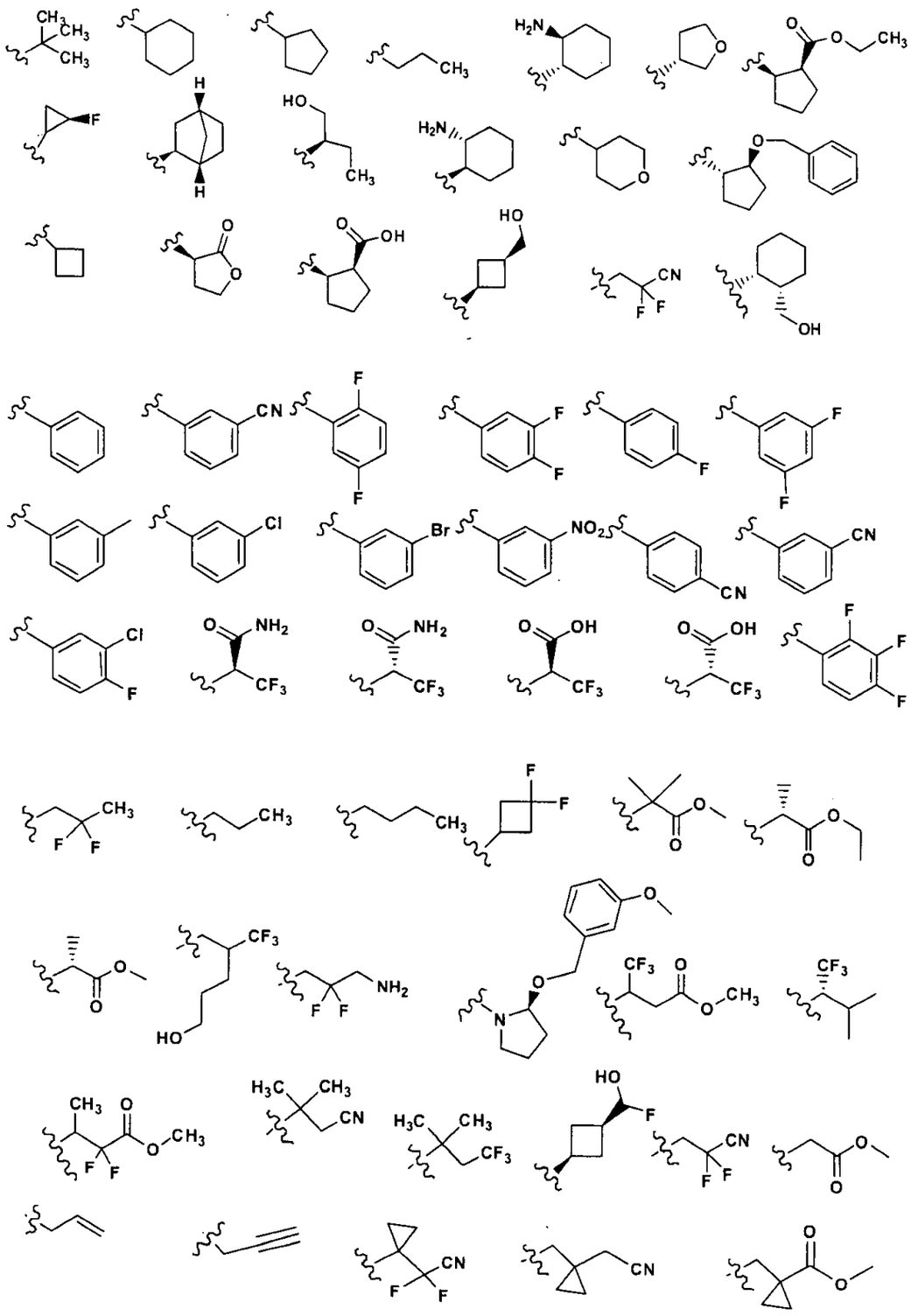


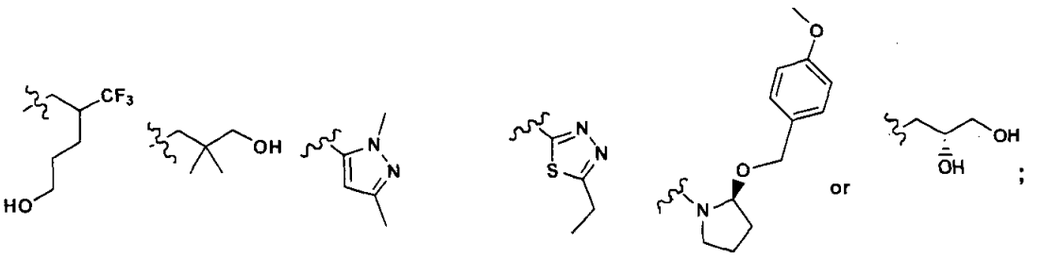
(b) $-C(O)NHR_3$, en donde el $R_3$ es:



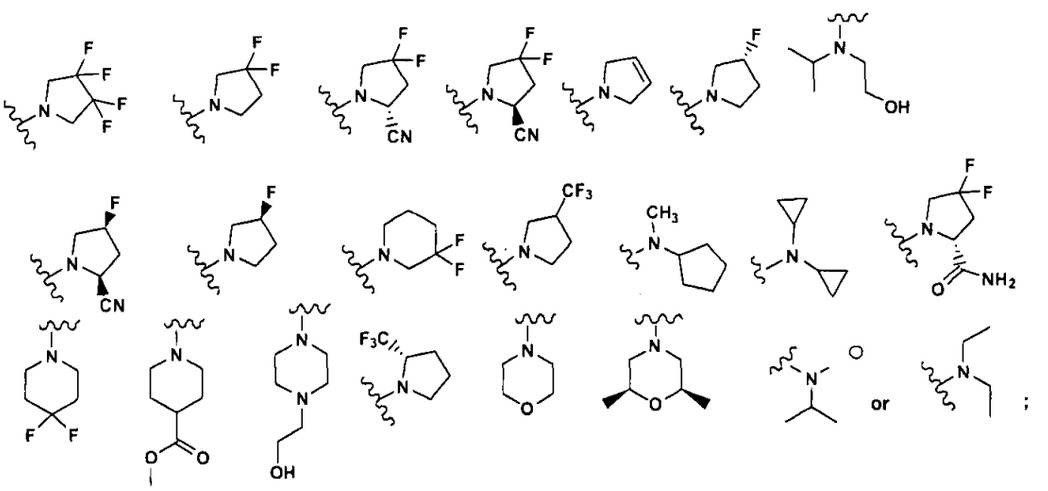




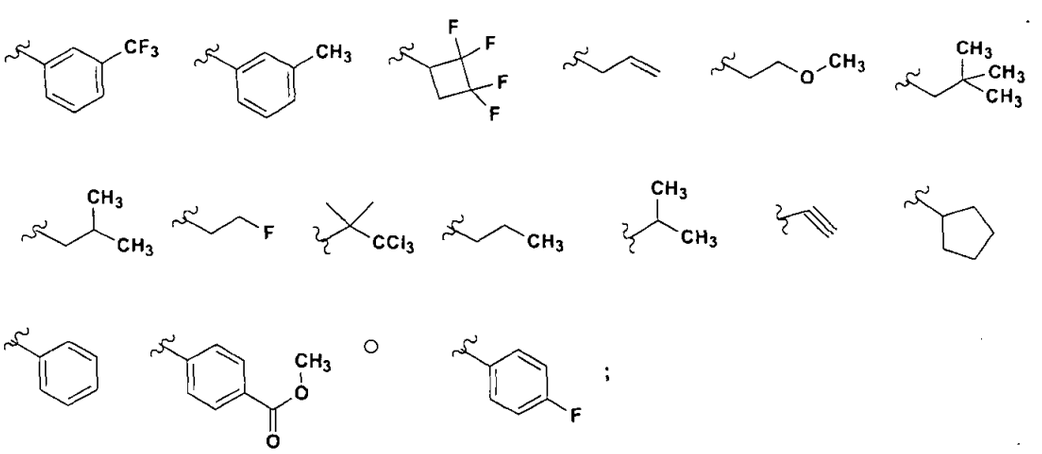




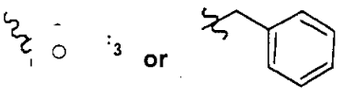
(c) $-C(O)NR_2R_3$, en donde el $NR_2R_3$ es:



(d) $-C(O)OR_4$ en donde el $R_4$ es:

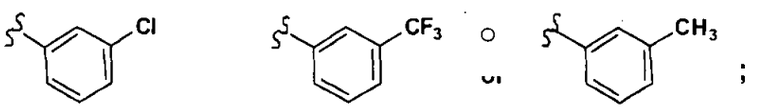


(e) $-SO_2R_5$ en donde el $R_5$ es:



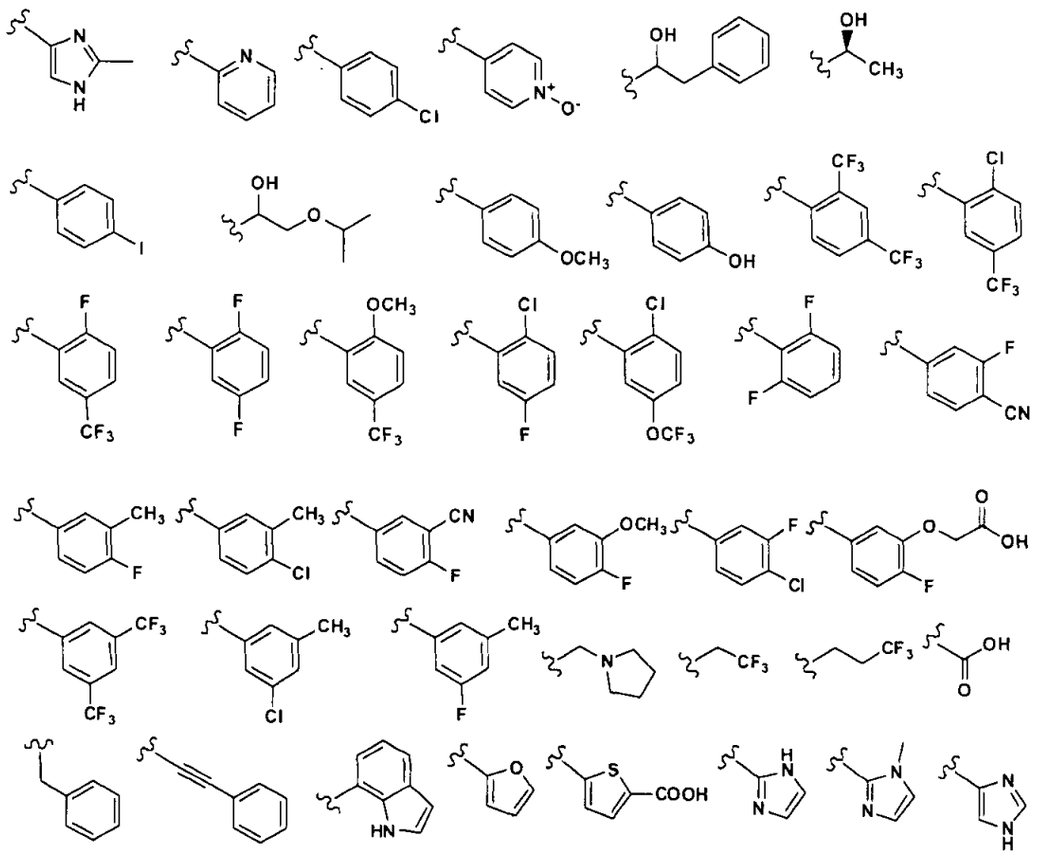

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(f) $-CSNHR_7$ en donde el $R_7$ es:

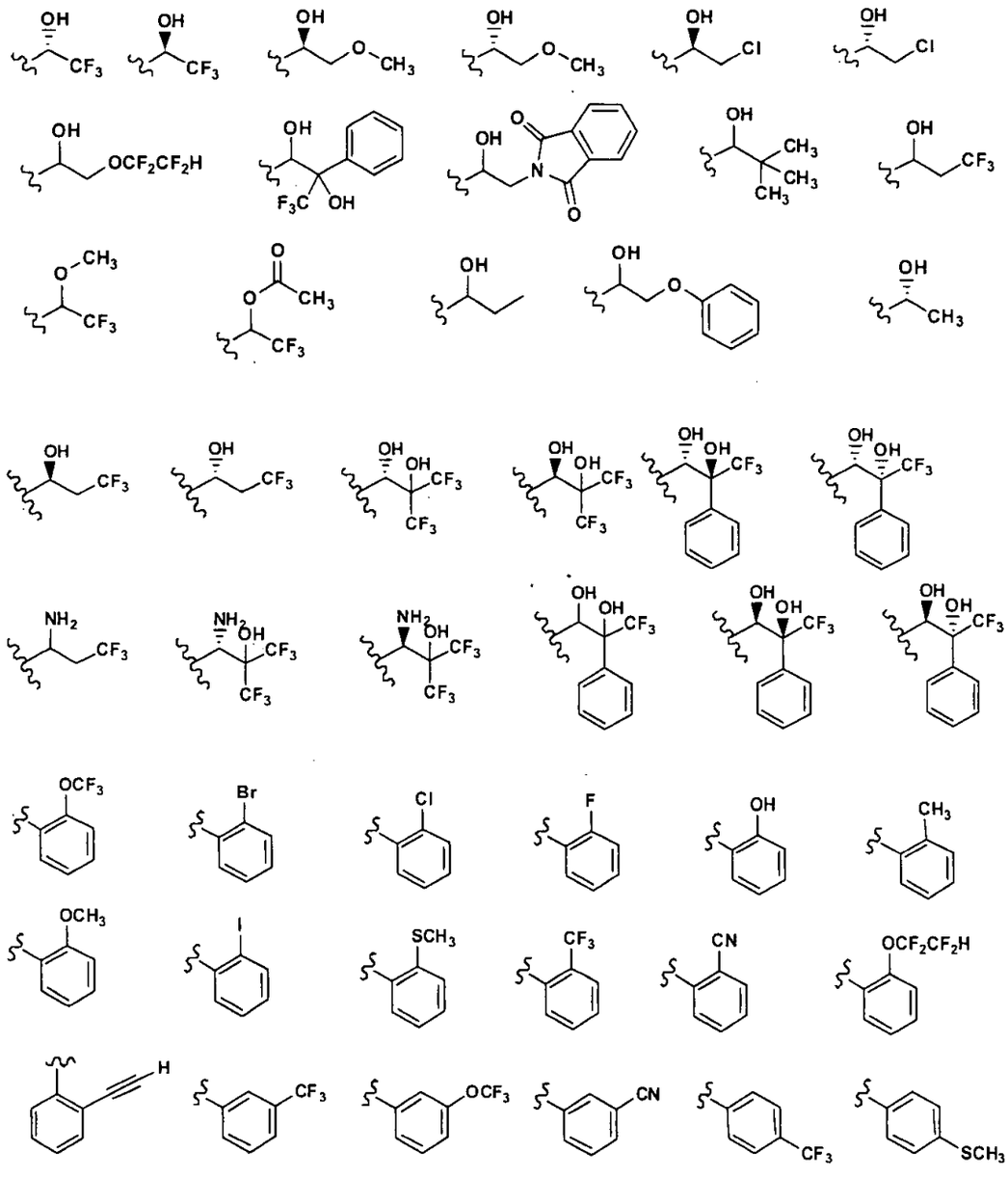


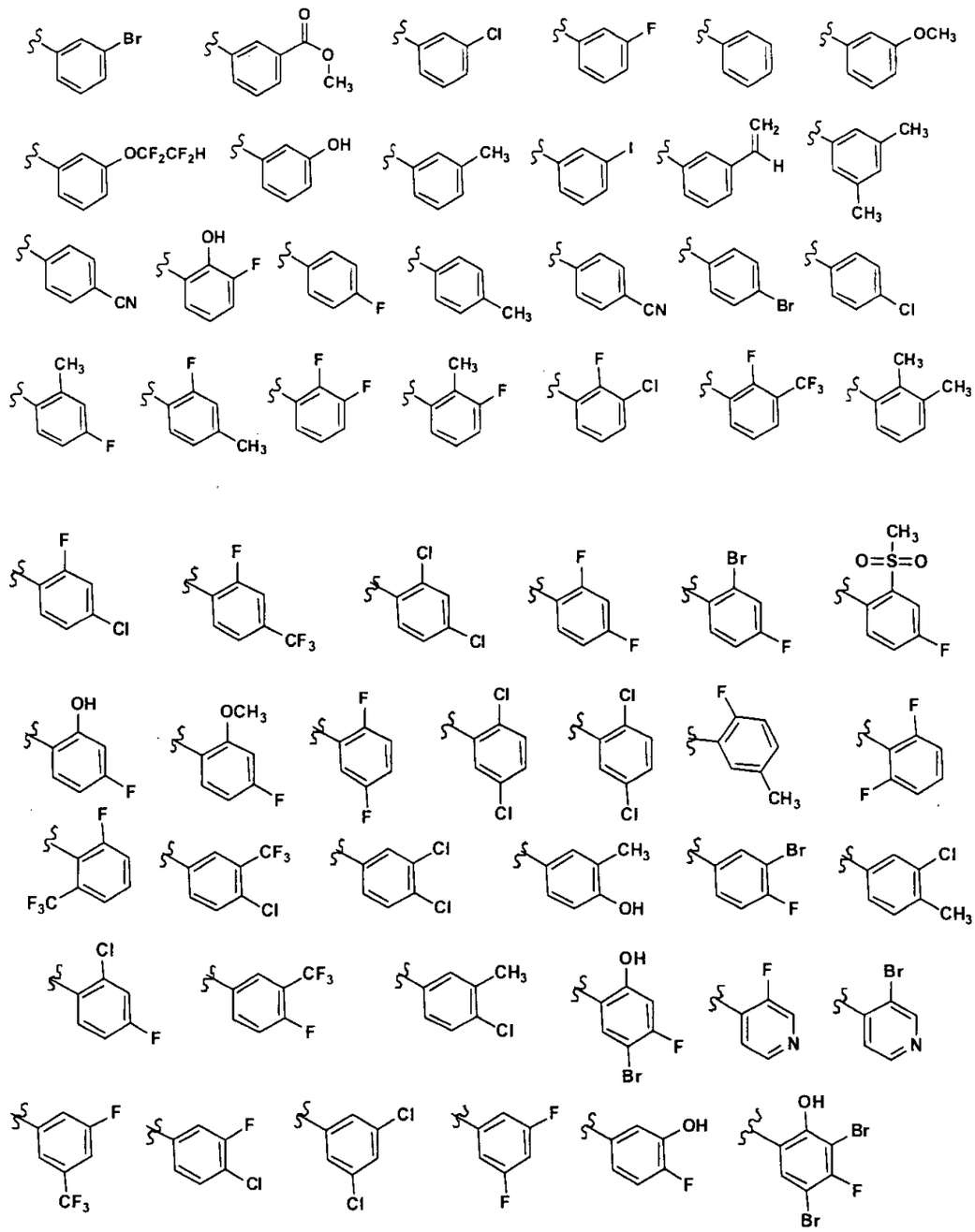
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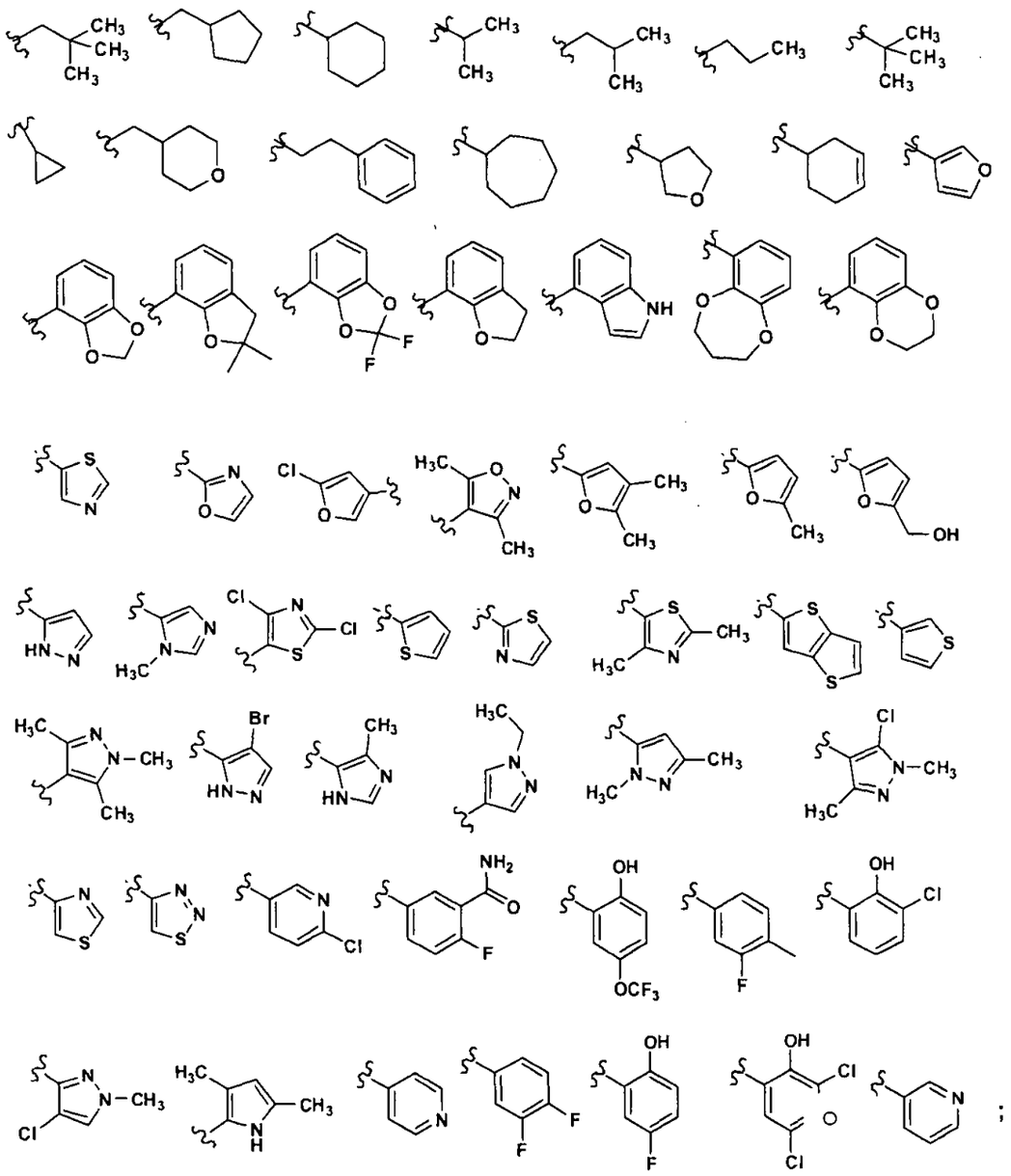
(g) $-CH_2R_8$ en donde el $R_8$ es:



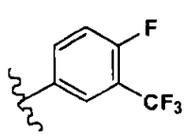
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(h) $-C(S)R_3$, en donde $R_3$:



En otra modalidad, los compuestos de la presente

invención se seleccionan de los compuestos ejemplificados en los ejemplos, por ejemplo, Ejemplos 273, 293, 305 y 337.

En todavía otra modalidad, composiciones farmacéuticas comprenden los compuestos de la presente invención solos o en combinación con un portador farmacéuticamente aceptable y/o al menos un agente terapéutico adicional.

En aún todavía otra modalidad, métodos para inhibir la proteína de transferencia de éster de colesterilo que comprende administrar a un mamífero que necesita del tratamiento un compuesto y/o composición farmacéutica de la presente invención se proporcionan.

En una modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de Alzheimer, ateroesclerosis, trombosis venosa, enfermedad arterial coronaria, enfermedad cardiaca coronaria, enfermedad vascular coronaria, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, trastornos cardiovasculares, angina, isquemia, isquemia cardiaca, apoplejía, infarto al miocardio, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de diabetes, obesidad o endotoxemia en un mamífero (incluyendo un humano siendo ya sea hombre o mujer) al administrar a un mamífero que necesita

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de tal tratamiento una cantidad, para tratar, prevenir o retardar la ateroesclerosis, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, trastornos cardiovasculares, angina, isquemia, isquemia cardiaca, apoplejía, infarto al miocardio, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de diabetes, obesidad o endotoxemia, de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de la ateroesclerosis en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la ateroesclerosis de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de la enfermedad vascular periférica en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la enfermedad vascular periférica de un compuesto y/o composición farmacéutica de la presente invención.

Aún en otra modalidad, se proporcionan métodos para

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tratar, prevenir o retardar el progreso de la dislipidemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la dislipidemia de un compuesto y/o composición farmacéutica de la presente invención.

Todavía en aún otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de la hiperbetalipoproteinemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la hiperbetalipoproteinemia de un compuesto y/o composición farmacéutica de la presente invención.

En una modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de hipoalfalipoproteinemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la hipoalfalipoproteinemia de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de hipercolesterolemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la hipercolesterolemia de un compuesto y/o composición farmacéutica de la presente

invención.

Aún en otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de hipertrigliceridemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la hipertrigliceridemia de un compuesto y/o composición farmacéutica de la presente invención.

Todavía en aún otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de la hipercolesterolemia familiar en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la hipercolesterolemia familiar de un compuesto y/o composición farmacéutica de la presente invención.

En una modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de trastornos cardiovasculares en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar un trastorno cardiovascular de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de angina en un mamífero al administrarle al mamífero que necesita de tal

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tratamiento, una cantidad para tratar, prevenir o retardar la angina de un compuesto y/o composición farmacéutica de la presente invención.

Aún en otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de isquemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la enfermedad isquémica de un compuesto y/o composición farmacéutica de la presente invención.

Todavía en aún otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de isquemia cardiaca en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la isquemia cardiaca de un compuesto y/o composición farmacéutica de la presente invención.

En una modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de apoplejía en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la apoplejía de un compuesto y/o composición farmacéutica de la presente invención.

En una modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de un infarto al miocardio en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar,

prevenir o retardar un infarto al miocardio de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de lesión por reperfusión en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la lesión por reperfusión de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de la restenosis angioplástica en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la restenosis angioplástica de un compuesto y/o composición farmacéutica de la presente invención.

Aún en otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de hipertensión en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la hipertensión de un compuesto y/o composición farmacéutica de la presente invención.

Aún en otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de las complicaciones vasculares de la diabetes en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para

tratar, prevenir o retardar las complicaciones vasculares de la diabetes de un compuesto y/o composición farmacéutica de la presente invención.

Todavía en aún otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de la obesidad en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la obesidad de un compuesto y/o composición farmacéutica de la presente invención.

En una modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de endotoxemia en un mamífero al administrarle al mamífero que necesita de tal tratamiento, una cantidad para tratar, prevenir o retardar la endotoxemia de un compuesto y/o composición farmacéutica de la presente invención.

En otra modalidad, se proporcionan métodos para tratar, prevenir o retardar el progreso de una enfermedad que requiere terapia de inhibidor de proteína de transferencia del éster de colesterilo, que comprende administrar, concurrentemente o secuencialmente, a un mamífero que necesita de tratamiento, prevención o retardo, una cantidad terapéuticamente efectiva de un compuesto de la presente invención y al menos un agente terapéutico adicional.

Aún en otra modalidad, se proporcionan métodos para inhibir la producción de lipoproteína remanente que

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comprenden administrar a un mamífero un compuesto y/o composición farmacéutica de la presente invención.

Todavía en aún otra modalidad, se proporcionan método para elevar el colesterol HDL en un mamífero, que comprende administrar a un mamífero que necesita de tratamiento, un compuesto y/o composición farmacéutica de la presente invención.

Se han usado ampliamente fenoles mono fluorizados como bloques sintéticos para muchos compuestos bioactivos. A la fecha, hay varios métodos reportador en la literatura para la síntesis de tales fenoles. Por ejemplo, tales fenoles pueden prepararse por: (i) fluorinación electrofílica de fenoles usando un rango de reactivos $F^+$; (ii) hidrólisis de bromofluorobenceno o clorofluorobenceno catalizado por un reactivo de cobre; (iii) diazotización de una correspondiente fluoroanilina; (iv) substitución hidroxi selectiva de ácido difluorobenzoico con hidróxido de sodio sólido en 1,3-dimetil-2-imidazolidinon (ver, Journal of Fluorine Chemistry, 121:97-99 (2003) y Bioorganic & Medicinal Chemistry, 12:5661-5675 (2004)); y (iv) el reemplazo de fluoroátomo de fluoruros de arilo activados tales como fluoroantracen-9,10-dionas, fluorobenz[g]isoquinolin-5,10-dionas y fluoronitrobencenos con trimetilsilanoato de sodio en solvente THF específico (ver Synthetic Communications, 28(18):3415-3422). Sin embargo, la mayoría de estos métodos usan reactivos que no

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son seguros, altamente peligrosos y/o aún no están disponibles. Además, estos métodos sólo pueden ser apropiados para la síntesis de 2 ó 4-fluorofenoles, y/o producen los compuestos deseados en bajos rendimientos.

De esta manera, no obstante que hay una variedad de métodos usados para producir fenoles mono fluorizados, hay una necesidad continua y una búsqueda continuada en este campo de la técnica para métodos alternativos para producir fenoles mono fluorizados bajo condiciones seguras y en rendimientos mayores.

En una modalidad, se proporcionan procesos para la preparación de principalmente un compuesto de la fórmula WW, B-$OCF_2CF_2H$, que comprende reducir una mezcla comprendida de un compuesto de la fórmula WW y un compuesto de la fórmula YY, B-$OCF_2CF_2Br$, con polvo de zinc bajo condiciones ácidas, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 9) arilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 10) heteroarilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 11) heteroarilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 12) heterociclilo, que puede

opcionalmente substituirse con uno o más $R_{20}$, 13) heterociclilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, y 20) $-CONR_6R_6$ y $R_6$, $R_9$ y $R_{10}$ son como se establece arriba.

En una modalidad, se proporcionan procesos para la preparación de una mezcla comprendida de un compuesto de la fórmula WW y un compuesto de la fórmula YY, $B-OCF_2CF_2Br$, que comprende hacer reaccionar un compuesto de la fórmula ZZ, B-OH, con 1,2-dibromotetrafluoroetano bajo condiciones básicas, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 9) arilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 10) heteroarilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 11) heteroarilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 12) heterociclilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 13) heterociclilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, y 20) $-CONR_6R_6$ y $R_6$, $R_9$ y $R_{10}$ son como se

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establece arriba.

En una modalidad, se proporcionan procesos para la preparación de un compuesto de la fórmula ZZ que comprende hacer reaccionar un compuesto de la fórmula AAA, B-F, con trimetilsilanoato de potasio en un solvente diferente a THF, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 9) arilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 10) heteroarilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 11) heteroarilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 12) heterociclilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 13) heterociclilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, y 20) $-CONR_6R_6$ y $R_6$, $R_9$ y $R_{10}$ son como se establece arriba.

En otra modalidad, se proporcionan procesos para la preparación de un compuesto de la fórmula WW, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1)

halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) -Oalquilo, y 4) ciano. Las presentes invenciones proporcionan tales métodos.

En una modalidad, se proporcionan procesos para la preparación de principalmente un compuesto de la fórmula WW, en donde el ácido es ácido trifluoroacético, ácido acético, ácido fórmico y otros solventes ácidos conocidos en la técnica, preferiblemente ácido acético.

En otra modalidad, se proporcionan procesos para la preparación de principalmente un compuesto de la fórmula WW, en donde la etapa de reducir la mezcla de un compuesto de la fórmula WW y un compuesto de la fórmula YY para formar principalmente un compuesto de la fórmula WW que comprende calentar la mezcla de reacción a alrededor de 50°C durante alrededor de una hasta alrededor de 15 horas, preferiblemente durante alrededor de cinco (5) horas.

Aún en otra modalidad, se proporcionan procesos para la preparación de una mezcla de un compuesto de la fórmula WW y un compuesto de la fórmula YY, en donde la base es hidruro de sodio, metóxido de sodio, metóxido de potasio, carbonato de potasio, carbonato de sodio, carbonato de cesio, carbonato de litio, y carbonato de amonio, preferiblemente carbonato de cesio.

Todavía en aún otra modalidad, se proporcionan procesos para la preparación de una mezcla de un compuesto de

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la fórmula WW y un compuesto de la fórmula YY, en donde la etapa de hacer reaccionar un compuesto de la fórmula ZZ con 1,2-dibromotetrafluoroetano se lleva a cabo en un solvente.

En otra modalidad, se proporcionan procesos para la preparación de una mezcla de un compuesto de la fórmula WW y un compuesto de la fórmula YY, en donde el solvente es diglima, DMSO, DMF o NMP, preferiblemente, DMSO.

En una modalidad, se proporcionan procesos para la preparación de una mezcla de un compuesto de la fórmula WW y un compuesto de la fórmula YY, en donde la etapa de hacer reaccionar un compuesto de la fórmula ZZ con 1,2-dibromotetrafluoroetano que comprende calentar la mezcla de reacción a alrededor de 50° alrededor de 140°C, preferiblemente a alrededor de 50°C, durante alrededor de diez (10) minutos hasta alrededor de 15 horas, preferiblemente alrededor de cinco (5) horas.

En otra modalidad, se proporcionan procesos para la preparación de un compuesto de la fórmula ZZ, en donde el solvente es diglima, dioxano, DMF o dietoxietano, preferiblemente diglima o dietoxietano.

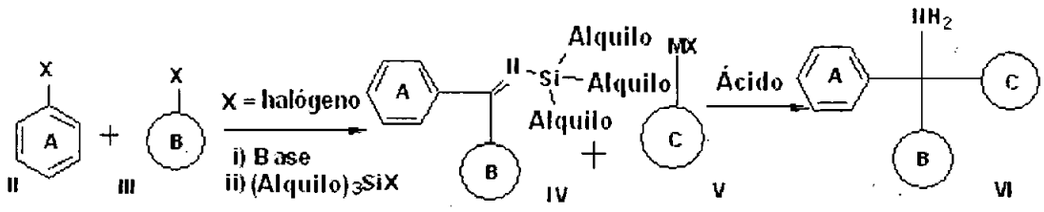
Aún en otra modalidad, se proporcionan procesos para la preparación de un compuesto de la fórmula ZZ, en donde la etapa de hacer reaccionar un compuesto de la fórmula AAA con trimetilsilanoato de potasio en un solvente diferente a THF que comprende calentar la mezcla de reacción a

alrededor de 100° alrededor de 140°C, preferiblemente a alrededor de 120°C, durante alrededor de tres (3) horas hasta alrededor de tres (3) días, preferiblemente, durante alrededor de cinco (5) horas.

**SINTESIS**

Generalmente, los compuestos de la presente invención pueden prepararse por métodos tales como aquellos ilustrado en los siguientes Esquemas de reacción A hasta W. Los compuestos ejemplares de la presente invención se preparan por los métodos ilustrados en los ejemplos establecidos más adelante. Los solventes, temperaturas, presiones, y otras condiciones de reacción pueden seleccionarse fácilmente por alguien de habilidad ordinaria en la técnica. Los materiales de partida están comercialmente disponibles o se preparan fácilmente por alguien de habilidad ordinaria en la técnica. Las técnicas de combinación pueden emplearse en la preparación de compuestos, por ejemplo, donde los interiomediarios poseen grupos apropiados para estas técnicas.

**Esquema de reacción A**

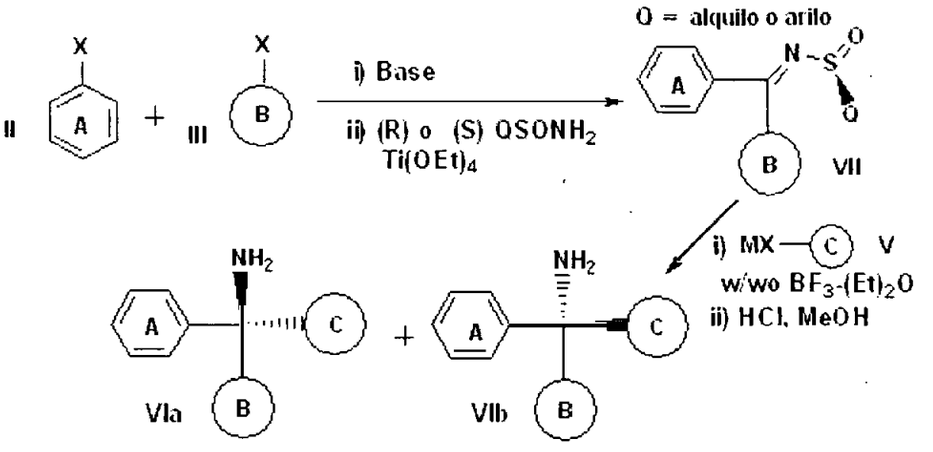



Como se ilustra en el Esquema de reacción A, el

reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula II es un grupo nitrilo o un grupo halógeno, tal como bromo, pueden combinarse con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo haluro, tal como bromo, o un grupo nitrilo, seguido por el tratamiento con una base, tal como nBuLi. Alternativamente, un reactivo fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula II es un grupo aldehído o un grupo halógeno, tal como bromuro, puede combinarse con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo haluro, tal como bromuro, o un grupo aldehído, seguido por tratamiento con una base, tal como nBuli, seguido por tratamiento con un agente oxidante tal como $MnO_4$ o reactivo Jone. La mezcla resultante puede entonces tratarse con un reactivo de tri-alquil silil haluro, tal como cloruro

de trimetilsililo, para proporcionar un intermediario de trimetilsilil imida de la Fórmula IV. Al intermediario de imida de la Fórmula IV puede agregársele un reactivo de metal de haluro, tal como un complejo de litio alquilo, un complejo de bromuro de magnesio o un complejo de cloruro de magnesio, o un complejo de bromuro de zinc o cloruro de zinc, de la Fórmula V, donde el complejo de haluro de metal se hace de un reactivo en donde la composición de C es como se describe bajo la Fórmula Ia y Ib, seguido por el tratamiento con ácido, tal como HCl, para remover el grupo sililo, para proporcionar el intermediario racémico de la Fórmula VI. Como se describe en los esquemas de reacción que proceden, el intermediario racémico de la Fórmula VI permitirá la generación de los compuestos de la Fórmula Ia o Ib por medio de las rutas a describirse.

**Esquema de reacción B**

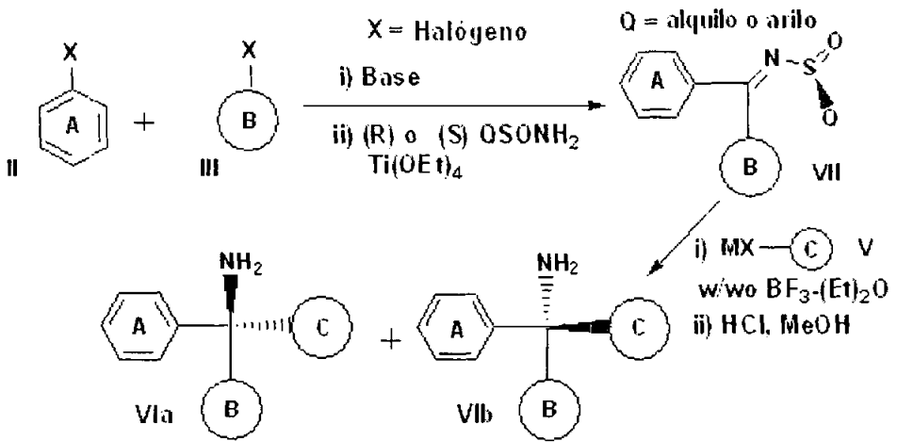



Como se ilustra en el Esquema de reacción B, el

reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula II es un grupo nitrilo o un grupo halógeno, tal como bromo, pueden combinarse con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo haluro, tal como bromo, o un grupo nitrilo, seguido por el tratamiento con una base, tal como nBuLi. Alternativamente, un reactivo fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula II es un grupo aldehído o un grupo halógeno, tal como bromuro, puede combinarse con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo haluro, tal como bromuro, o un grupo aldehído, seguido por tratamiento con una base, tal como nBuli, seguido por tratamiento con un agente oxidante tal como $MnO_4$ o reactivo Jone. La mezcla resultante puede entonces tratarse con un reactivo de sulfinamida substituido, tal como 4-

metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropan-2-sulfinamida o (R)-2-metilpropan-2-sulfinamida, junto con $Ti(OEt)_4$, para proporcionar el intermediario de sulfinil imida de la Fórmula VII. Al intermediario de sulfinil imida de la Fórmula VII puede agregársele un reactivo de metal de haluro, tal como un complejo de bromuro de magnesio o un complejo de cloruro de magnesio, o un complejo de bromuro de zinc o cloruro de zinc, de la Fórmula V, donde el complejo de haluro de metal se hace de un reactivo en donde la composición de C es como se describe bajo la Fórmula Ia y Ib, con o sin un ácido Lewis, tal como $BF_3 \cdot (Et)_2O$, seguido por el tratamiento con ácido, tal como HCl, para hidrolizar la sulfinamida, para proporcionar el intermediario de la Fórmula VIa y VIb. Por la aplicación de reactivo sulfinamida substituida, tal como (R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropan-2-sulfinamida o (R)-2-metilpropan-2-sulfinamida un experto en la técnica puede enriquecer la formación del antípoda (R) (Fórmula VIa) contra el antípoda (S) (Fórmula VIb) o el antípoda (S) (Fórmula VIb) contra el antípoda (R) (Fórmula VIa), respectivamente. Como se describe en los esquemas de reacción que proceden, el intermediario de la Fórmula VIa y VIb permitirá la generación de los compuestos de la Fórmula Ia o Ib por medio de las rutas a describirse.

**Esquema de reacción C**



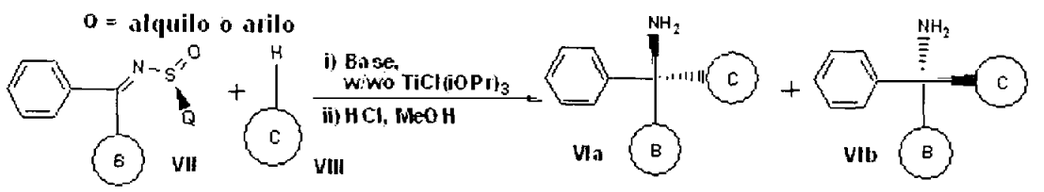

Como se ilustra en el Esquema de reacción C, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo éster de alquilo, tal como un metilo o un éster de etilo, pueden combinarse con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo haluro, tal como bromo, seguido por el tratamiento con una base, tal como nBuLi. La mezcla resultante puede entonces tratarse con un reactivo de sulfinamida substituido, tal como (R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropan-2-sulfinamida o (R)-2-metilpropan-2-sulfinamida, junto con $Ti(OEt)_4$, para

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proporcionar el intermediario de sulfonilimida de la Fórmula VII. Además, como se ilustra en el Esquema de reacción C, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula II es un grupo haluro, tal como bromo, pueden combinarse con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula III es un grupo éster de alquilo, tal como un metilo o un éster de etilo, seguido por el tratamiento con una base, tal como nBuLi. La mezcla resultante puede entonces tratarse con un reactivo de sulfinamida substituido, tal como (R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropan-2-sulfinamida o (R)-2-metilpropan-2-sulfinamida, junto con $Ti(OEt)_4$, para proporcionar el intermediario de sulfinil imida de la Fórmula VII. Al intermediario de sulfinil imida de la Fórmula VII puede agregársele un reactivo de metal de haluro, tal como un complejo de litio alquilo, un bromuro de magnesio o un complejo de cloruro de magnesio, o un complejo de bromuro de zinc o cloruro de zinc, de la Fórmula V, donde el complejo de haluro de metal se hace de un reactivo en donde la

composición de C es como se describe bajo la Fórmula Ia y Ib, con o sin un ácido Lewis, tal como $BF_3 \cdot (Et)_2O$, seguido por el tratamiento con ácido, tal como HCl, para hidrolizar la sulfinamida, para proporcionar los intermediarios de la Fórmula VIa y VIb. Por la aplicación de reactivo sulfinamida substituido, tal como (R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropan-2-sulfinamida o (R)-2-metilpropan-2-sulfinamida un experto en la técnica puede enriquecer la formación del antípoda (R) (Fórmula VIa) contra el antípoda (S) (Fórmula VIb) o el antípoda (S) (Fórmula VIb) contra el antípoda (R) (Fórmula VIa), respectivamente. Como se describe en los esquemas de reacción que proceden, el penúltimo intermediario de la Fórmula VIa y VIb permitirá la generación de los compuestos de la Fórmula Ia o Ib por medio de las rutas a describirse.

**Esquema de reacción D**

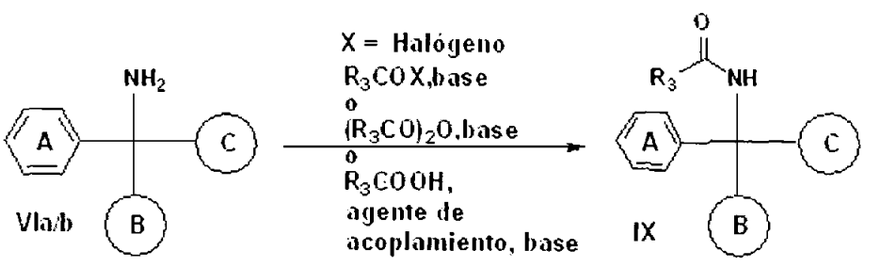



Como se ilustra en el Esquema de reacción D, al intermediario de sulfinil imida de la Fórmula VII puede agregársele una base, tal como LDA o nBuLi, con o sin la adición de $TiCl(iOPr)_3$, y un reactivo de la Fórmula VIII, en donde la composición de C es como se describe bajo la Fórmula

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Ia y Ib, con el requerimiento de que al menos uno de los substituyentes enlazados al reactivo de la Fórmula VIII es un hidrógeno que puede desprotonarse para proporcionar una especie de anión reactivo, seguido por el tratamiento con ácido, tal como HCl, para hidrolizar la sulfinamida, para proporcionar los intermediarios de la Fórmula VIa y VIb. Por la aplicación del reactivo sulfinamida substituido, tal como (R)-4-metilbencensulfiinamida o (R)-4-metilbencesulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropan-2-sulfinamida o (R)-2-metilpropan-2-sulfinamida un experto en la técnica puede enriquecer la formación del antípoda (R) (Fórmula VIa) contra el antípoda (S) (Fórmula VIb) o el antípoda (S) (Fórmula VIb) contra el antípoda (R) (Fórmula VIa), respectivamente. Como se describe en los esquemas de reacción que proceden, el penúltimo intermediario de la Fórmula VIa y VIb permitirá la generación de los compuestos de la Fórmula Ia o Ib por medio de las rutas a describirse.

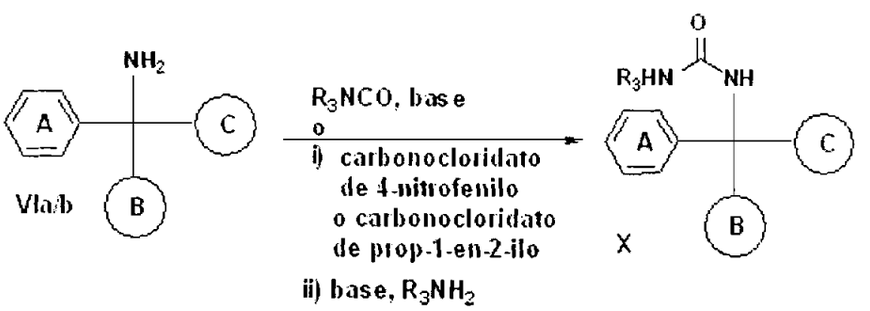
**Esquema de reacción E**




Como se ilustra en el Esquema de reacción E, un intermediario avanzado de la Fórmula VIa/b puede tratarse con un agente acilante, tal como un haluro ácido de la Fórmula

$R_3COX$, donde X = un halógeno, tal como cloro o bromo, o un anhídrido de la Fórmula $(R_3CO)_2O$, con o sin la presencia de una base, tal como trietilamina, piridina o N-etil-N-isopropilpropan-2-amina, para generar un derivado amida de la Fórmula XI, donde $R_3$ se deriva del agente o anhídrido acilante antes mencionado y es como se describe por la Fórmula Ia y Ib. Alternativamente, puede utilizarse un intermediario avanzado de la Fórmula VIa/b con un intermediario carboxilato de la Fórmula $R_3COOH$, junto con un agente de acoplamiento, tal como EDCI, DCC u otros agentes conocidos por un experto en la técnica para facilitar la formación de enlace amida, junto con o sin una base, tal como trietilamina, piridina o N-etil-N-isopropilpropan-2-amina, para generar un derivado amida de la Fórmula IX, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_3$ es como se describe por la Fórmula Ia y Ib

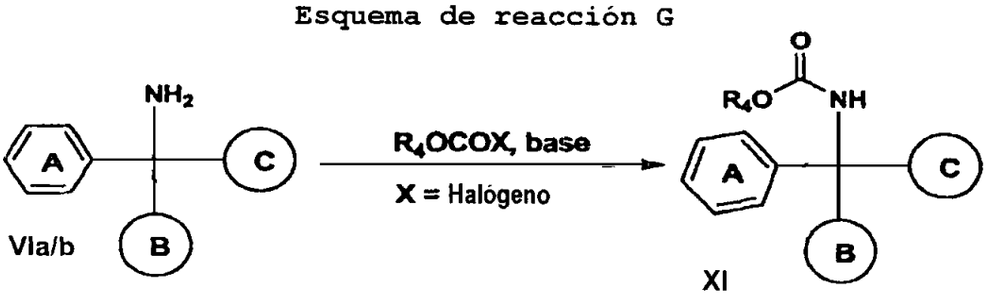
**Esquema de reacción F**




Como se ilustra en el Esquema de reacción F, un intermediario avanzado de la Fórmula Via/b puede tratarse con un isocianato de la Fórmula $R_3NCO$, con o sin la presencia de

una base, tal como trietilamina, piridina o N-etil-N-isopropilpropan-2-amina, para generar un derivado de urea de la Fórmula X, donde $R_3$ se deriva de los reactivos de isocianato antes mencionados y es como se describe por la Fórmula Ia y Ib. Alternativamente, puede hacerse reaccionar un intermediario avanzado de la Fórmula VIa/b con un agente tal como clorhidrato de 4-nitrofenil carbono o clorhidrato de prop-1-en-2-il carbono, para crear un intermediario de carbamato reactivo que puede entonces hacerse reaccionar con una amina o intermediario de sal de amina de la Fórmula $R_3NH_2$, con o sin la presencia de una base, tal como trietilamina, piridina o N-etil-N-isopropilpropan-2-amina, para generar un derivado de urea de la Fórmula X, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_3$ es como se describe por la Fórmula Ia y Ib.

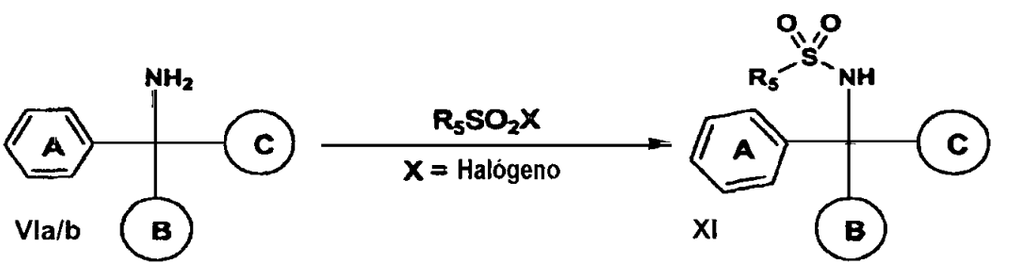
**Esquema de reacción G**




Como se ilustra en el Esquema de reacción G, un intermediario avanzado de la Fórmula VIa/b puede tratarse con un clorhidrato de carbono de la Fórmula $R_4OCOCl$, en la presencia de una base, tal como carbonato de potasio, para generar un derivado de carbamato de la Fórmula XI, el cual es

un compuesto de la Fórmula Ia y Ib, donde $R_4$ se deriva de los reactivos de clorhidrato de carbono antes mencionados y es como se describe por la Fórmula Ia y Ib.

**Esquema de reacción H**




Como se ilustra en el Esquema de reacción H, un intermediario avanzado de la Fórmula VIa/b puede tratarse con un cloruro de sulfonilo de la Fórmula $R_5SO_2Cl$, en la presencia de una base, tal como trietilamina, piridina o N-etil-N-isopropilpropan-2-amina, para generar un derivado de sulfonamida de la Fórmula XII, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_5$ se deriva de los reactivos de cloruro de sulfonilo antes mencionados y es como se describe por la Fórmula Ia y Ib.

**Esquema de reacción I**

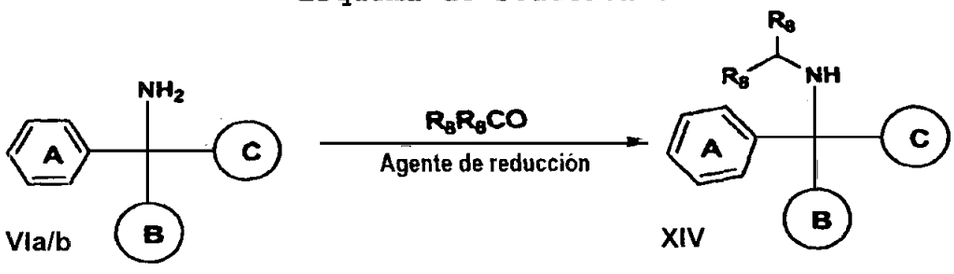



Como se ilustra en el Esquema de reacción I, un intermediario avanzado de la Fórmula VIa/b puede tratarse con un aldehído de la Fórmula $R_8CHO$, con o sin una cantidad

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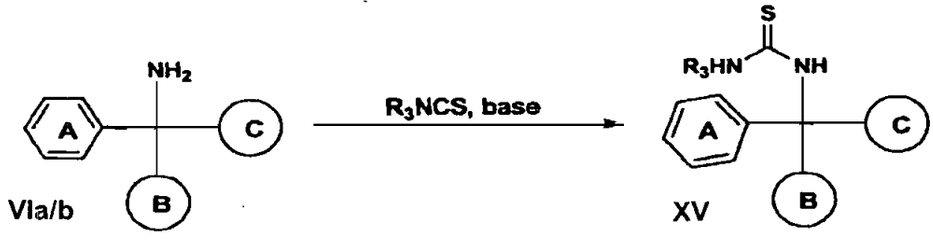
catalítica de un ácido, tal como ácido acético, seguido por el tratamiento con un agente reductor, tal como $NaBH(OAc)_3$, para generar un derivado de alquil amina de la Fórmula XIII, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_8$ se deriva de los reactivos de aldehído antes mencionados y es como se describe por la Fórmula Ia y Ib.

**Esquema de reacción J**




Como se ilustra en el Esquema de reacción J, un intermediario avanzado de la Fórmula VI puede tratarse con cetona de la Fórmula $R_8R_8CO$, con o sin una cantidad catalítica de un ácido, tal como ácido acético, seguido por el tratamiento con un agente reductor, tal como $NaBH(OAc)_3$, para generar un derivado de alquil amina de la Fórmula XIV, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_8$ se deriva de los reactivos de cetona antes mencionados y es como se describe por la Fórmula Ia y Ib.

**Esquema de reacción K**

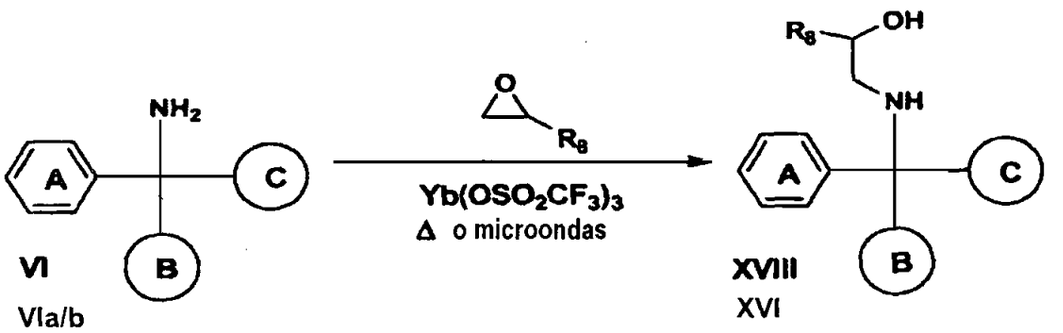



Como se ilustra en el Esquema de reacción K, un

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intermediario avanzado de la Fórmula VIa/b puede tratarse con un isotiocianato de la Fórmula $R_3NCS$, con o sin una base, tal como trietilamina, piridina o N-etil-N-isopropilpropan-2-amina, para generar un derivado de tiourea de la Fórmula XV, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_3$ se deriva de los reactivos de isotiocianato antes mencionados y es como se describe por la Fórmula Ia y Ib.

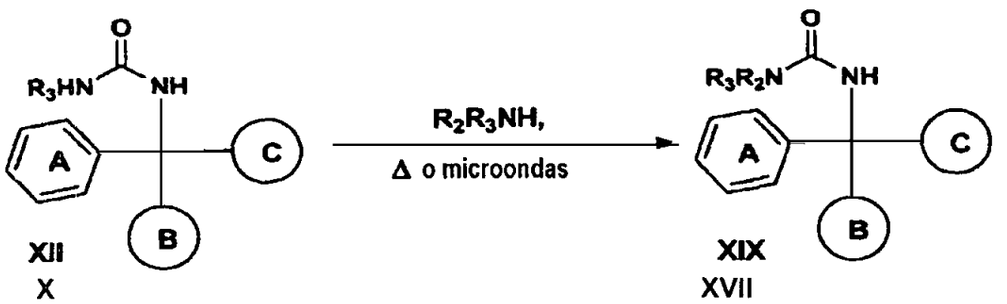
**Esquema de reacción L**




Como se ilustra en el Esquema de reacción L, un intermediario avanzado de la Fórmula VIa/b puede tratarse con un reactivo de oxirano, de la Fórmula $CH_2OCHR_8$, en la presencia de un catalizador, tal como $Sc(OSO_2CF_3)_3$ o $Yb(OSO_2CF_3)_3$, con calentamiento estándar o por medio de irradiación con un microondas, para generar un derivado de alquil hidroxi amina de la Fórmula XVI, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_8$ se deriva de los reactivos de oxirano antes mencionados y es como se describe por la Fórmula Ia y Ib.

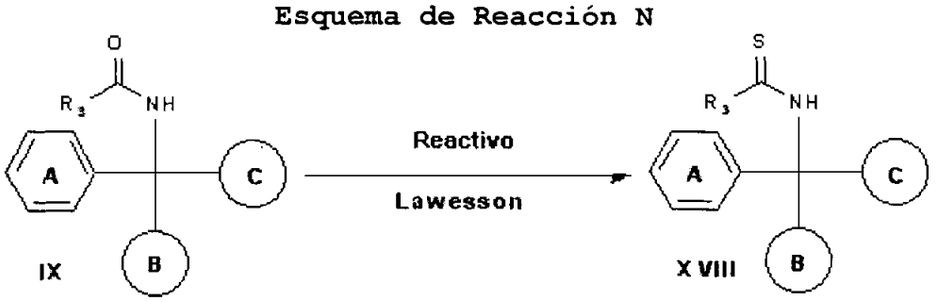
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**Esquema de reacción M**




Como se ilustra en el Esquema de reacción M, un reactivo de la Fórmula X, el cual es un compuesto de la Fórmula Ia y Ib, puede tratarse con un reactivo de amina disustituido de la Fórmula $R_2R_3NH$, con calentamiento o por medio de irradiación en un microondas, para obtener el derivado de urea disustituido de la Fórmula XVII, el cual es un compuesto de la Fórmula Ia y Ib, donde $R_2$ y $R_3$ se deriva del reactivo de amina disustituido antes mencionado y es como se describe por la Fórmula Ia y Ib.

**Esquema de Reacción N**

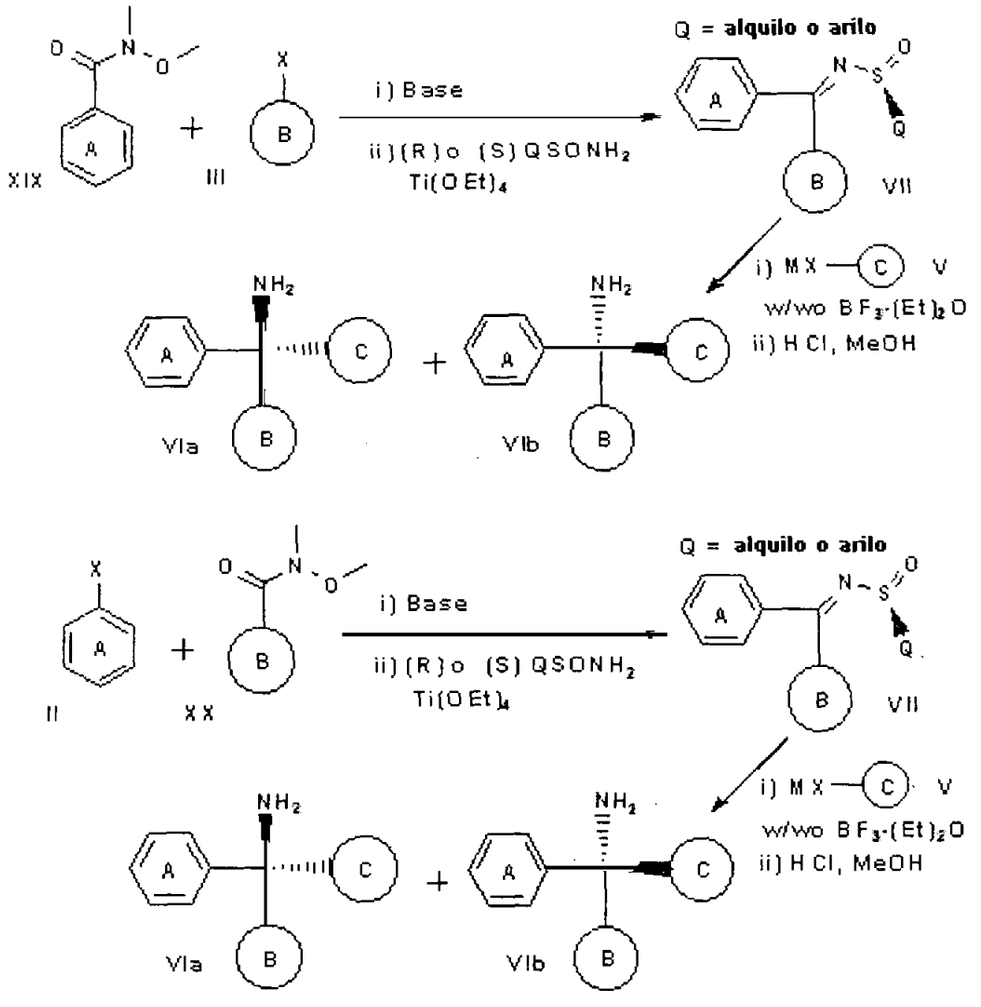



Como se ilustra en el Esquema de Reacción N, un reactivo de la Fórmula IX, el cual es un compuesto de Fórmula Ia y Ib, se puede tratar con un agente, tal como reactivo de Lawesson o cualquier otro reactivo conocido por un experto en la técnica para la conversión de un grupo funcional amida a

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un grupo funcional tioamida, para obtener un derivado de tioamida de la Fórmula XVIII, el cual es un compuesto de Fórmula Ia y Ib, donde $R_3$ se deriva como se describe por la fórmula Ia y Ib.

**Esquema de Reacción O**




Como se ilustra en el Esquema de Reacción O, un reactivo de fenilo substituido de la Fórmula XIX, en donde la composición de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los

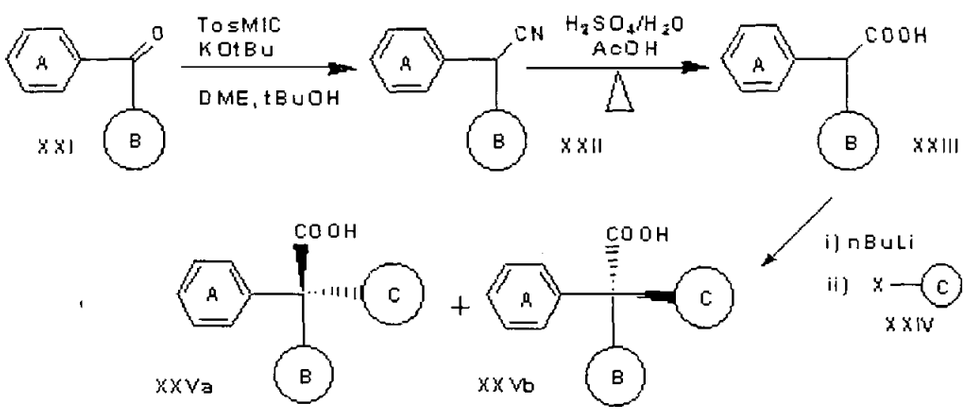
substituyentes unidos al reactivo de la Fórmula XIX es un grupo N-metoxi-N-metilacetamida, se puede combinar con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula III es un grupo haluro, tal como bromo, seguido por tratamiento con una base, tal como nBuLi. La mezcla resultante luego se puede tratar con un reactivo de sulfinamida substituido, tal como (R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropano-2-sulfinamida o (R)-2-metilpropano-2-sulfinamida, a lo largo con $Ti(OEt)_4$, para producir el intermediario de sulfinil amida de la Fórmula VII. Al intermediario de sulfinil amida de la Fórmula VII puede agregarse un reactivo de haluro de metal (MX), tal como un complejo de bromuro de magnesio o un complejo de cloruro de magnesio, o un complejo de bromuro de zinc o cloruro de zinc, de la Fórmula V, donde el complejo de haluro de metal se hace a partir de un reactivo en donde la composición de C es como se describe bajo la Fórmula Ia e Ib, con o sin un ácido Lewis, tal como $BF_3 \cdot (Et)_2O$, seguido por tratamiento con ácido, tal como HCl, para hidrolizar la sulfinamida, para producir los penúltimos intermediarios de la Fórmula VIa y VIb. además, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la

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Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes unidos al reactivo de la Fórmula II es un grupo haluro, tal como bromo, se puede combinar con un reactivo de la Fórmula XX, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula XX, es un grupo N-metoxi-N-metilacetamida, seguido por tratamiento con una base, tal como nBuLi. La mezcla resultante luego se puede tratar con un reactivo de sulfinamida substituido, tal como (R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropano-2-sulfinamida o (R)-2-metilpropano-2-sulfinamida, a lo largo con $Ti(OEt)_4$, para producir el intermediario de sulfinil amida de la Fórmula VII. Al intermediario de sulfinil amida de la Fórmula VII puede agregarse un reactivo de haluro de metal (MX), tal como un complejo de bromuro de magnesio o un complejo de cloruro de magnesio, o un complejo de bromuro de zinc o cloruro de zinc, de la Fórmula V, donde el complejo de haluro de metal se hace a partir de un reactivo en donde la composición de C es como se describe bajo la Fórmula Ia e Ib, con o sin un ácido de Lewis, tal como $BF_3 \cdot (Et)_2O$, seguido por tratamiento con ácido, tal como HCl, para hidrolizar la sulfinamida, para producir los penúltimos intermediarios de la Fórmula VIa y VIb. Por la aplicación del reactivo de sulfinamida substituido, tal como

(R)-4-metilbencensulfinamida o (R)-4-metilbencensulfinamida o (S)-2-metilpropano-2-sulfinamida o (R)-2-metilpropano-2-sulfinamida un experto en la técnica puede enriquecer la formación del (R) antípoda (Fórmula VIa) contra el (S) antípoda (Fórmula VIb) o el (S) antípoda (Fórmula VIb) contra el (R) antípoda (Fórmula VIa), respectivamente. Como se describe en los procedimientos de los esquemas, el penúltimo intermediario de la Fórmula VIa y VIb permitirá la generación de compuestos de la Fórmula Ia ó Ib por medio de las rutas descritas.

**Esquema de Reacción P**




Como se ilustra en el Esquema de Reacción A y Esquema de Reacción P, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula II es un grupo nitrilo o un grupo halógeno, tal como bromo, se puede combinar con un reactivo de la Fórmula

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III, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula III es un grupo haluro, tal como bromo, o un grupo nitrilo, seguido por tratamiento con una base, tal como nBuLi, seguido por tratamiento con ácido acuoso, tal como HCl 1N, para formar un intermediario de benzofenona de la Fórmula XXI. Alternativamente, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula II es un grupo aldehído o un grupo halógeno, tal como bromo, se puede combinar con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula III es un grupo haluro, tal como bromo, o un grupo aldehído, seguido por tratamiento con una base, tal como nBuLi, seguido por tratamiento con ácido acuoso, tal como HCl 1N, para formar un intermediario de benzofenona de la Fórmula XXI. Alternativamente, como se ilustra en el Esquema de Reacción C y Esquema de Reacción P, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de

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la Fórmula II es un grupo éster de alquilo, tal como a metil o un éster de etilo, se puede combinar con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula III es un grupo haluro, tal como bromo, seguido por tratamiento con una base, tal como nBuLi, seguido por tratamiento con ácido acuoso, para producir un intermediario de benzofenona de la Fórmula XXI. Además, como se ilustra en el Esquema de Reacción C y Esquema de Reacción P, un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula II es un grupo haluro, tal como bromo, se puede combinar con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula III es un grupo éster de alquilo, tal como a metil o un éster de etilo, seguido por tratamiento con una base, tal como nBuLi, seguido por tratamiento con ácido acuoso, para producir un intermediario de benzofenona de la Fórmula XXI. Como se ilustra en el Esquema de Reacción O y Esquema de Reacción P, un reactivo de fenilo substituido de la Fórmula XIX, en donde la composición

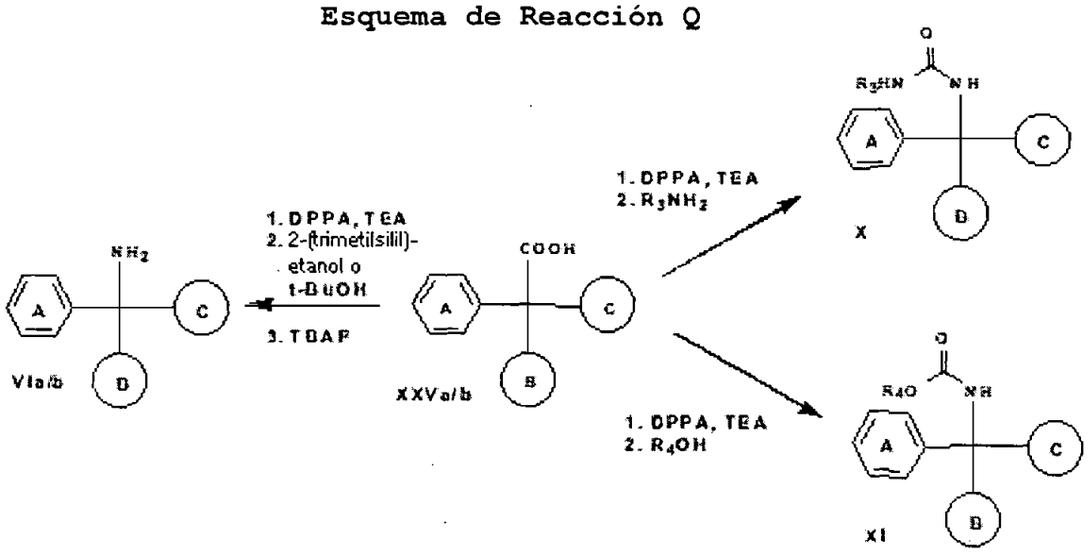
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de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes unidos al reactivo de la Fórmula XIX es un grupo N-metoxi-N-metilacetamida, se puede combinar con un reactivo de la Fórmula III, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula III es un grupo haluro, seguido por tratamiento con una base, tal como nBuLi, seguido por tratamiento con ácido acuoso, para producir un intermediario de benzofenona de la Fórmula XXI, o un reactivo de fenilo substituido de la Fórmula II, en donde la composición de A es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes unidos al reactivo de la Fórmula II es un grupo haluro, tal como bromo, se puede combinar con un reactivo de la Fórmula XX, en donde la composición de B es como se describe bajo la Fórmula Ia e Ib, con el requerimiento de que al menos uno de los substituyentes (X) unidos al reactivo de la Fórmula XX, es un grupo N-metoxi-N-metilacetamida, seguido por tratamiento con una base, tal como nBuLi, seguido por tratamiento con ácido acuoso, para producir un intermediario de benzofenona de la Fórmula XXI. Numerosos enfoques alternativos conocidos por un experto en la técnica pueden también emplearse para generar un intermediario de benzofenona de la Fórmula XXI.

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Como se ilustra en el Esquema de Reacción P, un intermediario de benzofenona de la Fórmula XXI se puede tratar con un agente tal como 1-(isocianometilsulfonil)-4-metilbenceno (TosMIC) y una base, tal como ter-butóxido de potasio, para producir un intermediario de la Fórmula XXII. La hidrólisis de un intermediario de la Fórmula XXII puede completarse por tratamiento con un ácido, tal como $H_2SO_4$ acuoso y ácido acético, para producir un intermediario de la Fórmula XXIII. Un intermediario de la Fórmula XXIII se puede tratar con una base, tal como n-butil litio, seguido por un reactivo de haluro de alquilo de la Fórmula XXIV, donde X es un haluro, tal como cloro, bromo o yodo y la composición de C es como se describe bajo la Fórmula Ia y Ib, para producir un intermediario de la Fórmula XXVa y XXVb, los cuales son intermediarios claves para la síntesis de compuestos de la Fórmula Ia y Ib.

**Esquema de Reacción Q**



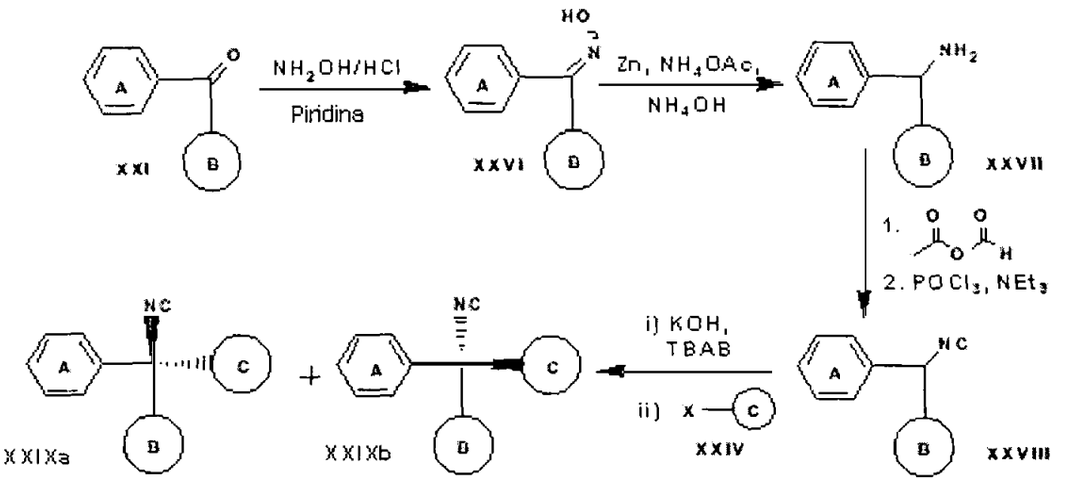

Como se ilustra en el Esquema de Reacción Q, un

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intermediario de la Fórmula XXVa/b se puede tratar con un agente tal como azida de fenilfosforilo (DPPA) en la presencia de una base, tal como trietilamina (TEA), seguido por tratamiento con un agente, tal como 2-(trimetilsilil)etanol o alcohol ter-butílico y desdoblamiento eventual del carbamato intermediario resultante por tratamiento con agentes tales como fluoruro de tetrabutilamonio (TBAF) o ácido trifluoroacético, para producir el intermediario avanzado de la Fórmula VIa/b, el cual es un intermediario clave para la síntesis de compuestos de la Fórmula Ia y Ib. Un intermediario de la Fórmula XXVa/b se puede tratar con un agente tal como azida de fenilfosforilo (DPPA) en la presencia de una base, tal como trietilamina (TEA), seguido por tratamiento con un agente de la fórmula $R_3NH_2$, donde $R_3$ se define como se describe bajo la Fórmula Ia y Ib, para dar compuestos de la Fórmula X, los cuales son compuestos de la Fórmula Ia y Ib. Además, un intermediario de la Fórmula XXVa/b se puede tratar con un agente tal como azida de fenilfosforilo (DPPA) en la presencia de una base, tal como trietilamina (TEA), seguido por tratamiento con un agente de la fórmula $R_4OH$, donde $R_4$ se define como se describe bajo la Fórmula Ia y Ib, para dar compuestos de la Fórmula XI, los cuales son compuestos de la Fórmula Ia y Ib.

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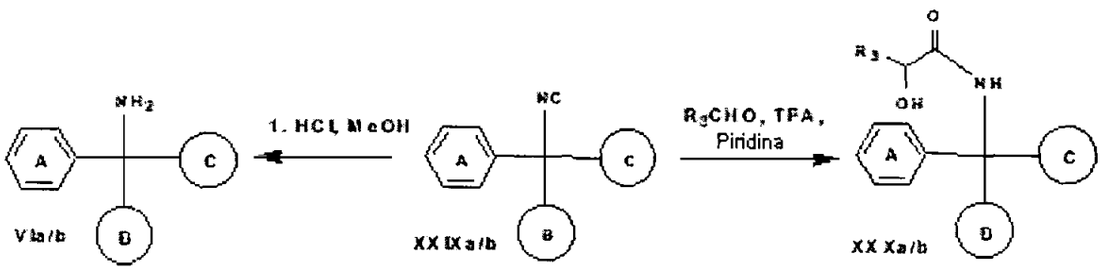
**Esquema de Reacción R**




Como se ilustra en el Esquema de Reacción R, un intermediario de la Fórmula XXI, se hace como se describe en Esquema de Reacción P, se puede tratar con un reactivo tal como $NH_2OH$, en la presencia de un ácido tal como HCl, seguido por tratamiento con una base tal como piridina, para producir un intermediario de la Fórmula XXVI. Un intermediario de la Fórmula XXVI se puede tratar con un agente reductor tal como zinc, a lo largo con $NH_4OAc$ y $NH_4OH$, para producir un intermediario de la Fórmula XXVII. Un intermediario de la Fórmula XXVII se puede tratar con un agente formilante, tal como anhídrido fórmico acético, seguido por deshidratación a través del tratamiento con un agente tal como $POCl_3$, para producir el intermediario de isonitrilo de la Fórmula XXVIII. El intermediario de isonitrilo de la Fórmula XXVIII se puede tratar con una base, tal como KOH acuoso, a lo largo con bromuro de tetrabutilamonio, seguido por un reactivo de

haluro de alquilo de la Fórmula XXIV donde la composición de C es como se describe bajo la Fórmula Ia y Ib, y X puede ser un haluro, tal como cloro, bromo o yodo, para producir los intermediarios de la Fórmula XXIXa y XXIXb, los cuales son intermediarios claves para la síntesis de compuestos de la Fórmula Ia y Ib. La formación de un intermediario de la Fórmula XXIXa ó XXIXb a partir de un intermediario de la Fórmula XXVIII, como se describe arriba, también puede llevarse a cabo en la presencia de un catalizador quiral tal como, pero no se limita a, Cloruro de N-bencilcinconinio o N-cloruro de bencilcinconidio, para enriquecer la formación del intermediario de la Fórmula XXIXa sobre el intermediario de la Fórmula XXIXb o para enriquecer la formación del intermediario de la Fórmula XXIXb sobre el intermediario de la Fórmula XXIXa como sea necesario para hacer los compuestos de la Fórmula Ia y Ib.

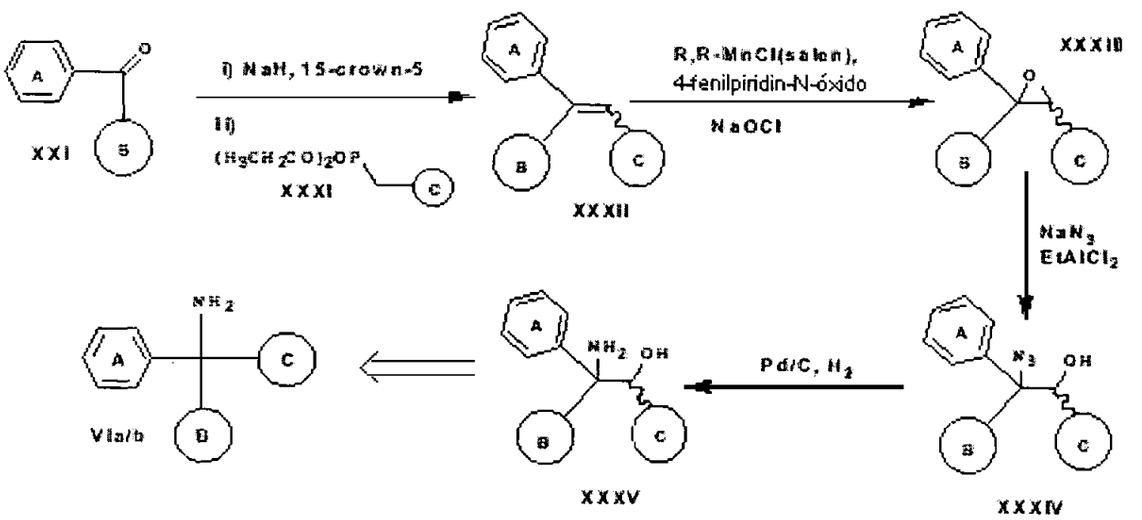
**Esquema de Reacción S**




Como se ilustra en el Esquema de Reacción S, un intermediario de la Fórmula XXIXa/b se puede convertir a un intermediario de la Fórmula VIa/b por tratamiento con un

ácido tal como HCl en metanol. Como se describe en los esquemas de reacción previos, y el intermediario de la Fórmula VIa/b es un intermediario clave para la síntesis de compuestos de la Fórmula Ia y Ib. Además, un intermediario de la Fórmula XXIXa/b puede tratarse directamente con un aldehído de la Fórmula $R_3CHO$, donde la definición de $R_3$ es como se describe bajo la Fórmula Ia y Ib, y un ácido, tal como ácido trifluoroacético, en la presencia de una base, tal como piridina, para producir compuestos de la Fórmula XXXa/b, los cuales son compuestos de la Fórmula Ia y Ib.

**Esquema de Reacción T**

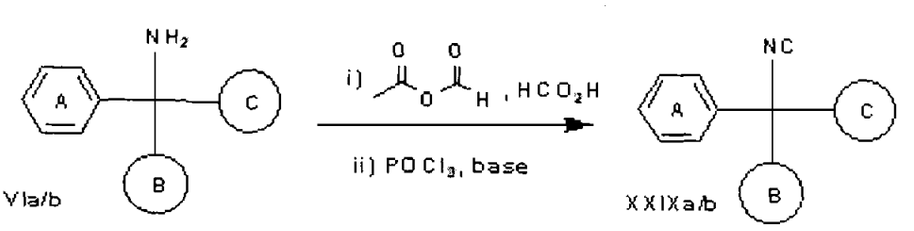



Como se ilustra en el Esquema de Reacción T, un intermediario de la Fórmula XXI, se hace como se describe en los Esquemas de Reacción P, puede hacerse reaccionar con un reactivo de la Fórmula XXXI, donde la composición de C es como se describe bajo la Fórmula Ia y Ib, para producir un intermediario de estireno de la Fórmula XXXII. Un reactivo de

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la Fórmula XXXII puede derivarse de una variedad de intermediarios comercialmente disponibles o puede fácilmente hacerse por un experto en la técnica. Un intermediario de estireno de la Fórmula XXXII se puede tratar con un agente epoxidante, tal como clorito de sodio en la presencia de 4-fenilpiridina-N-óxido, con o sin un catalizador quiral tal como, cloruro de(1R,2R)-(-)-[1,2-ciclo-hexanodiamino-N,N'-bis(3,5-di-t-butil-saliciliden)]manganeso (III), (R,R-MnCl (salen)), para obtener un intermediario de oxirano de la Fórmula XXXIII. El tratamiento del intermediario de oxirano de la Fórmula XXXIII con un agente tal como $NaN_3$, en la presencia de un ácido de Lewis tal como dicloruro de etilaluminio, proporciona el intermediario de azida de la Fórmula XXXIV. La reducción del intermediario de azida de la Fórmula XXXIV puede llevarse a cabo sobre paladio en carbón vegetal en la presencia de $H_2$ gas para generar el intermediario avanzado de la Fórmula XXXIV. Un intermediario de la Fórmula XXXV se divisa por el intermediario de la Fórmula VIa/b el cual es un intermediario clave en la ruta para la síntesis de compuestos de la Fórmula Ia y Ib.

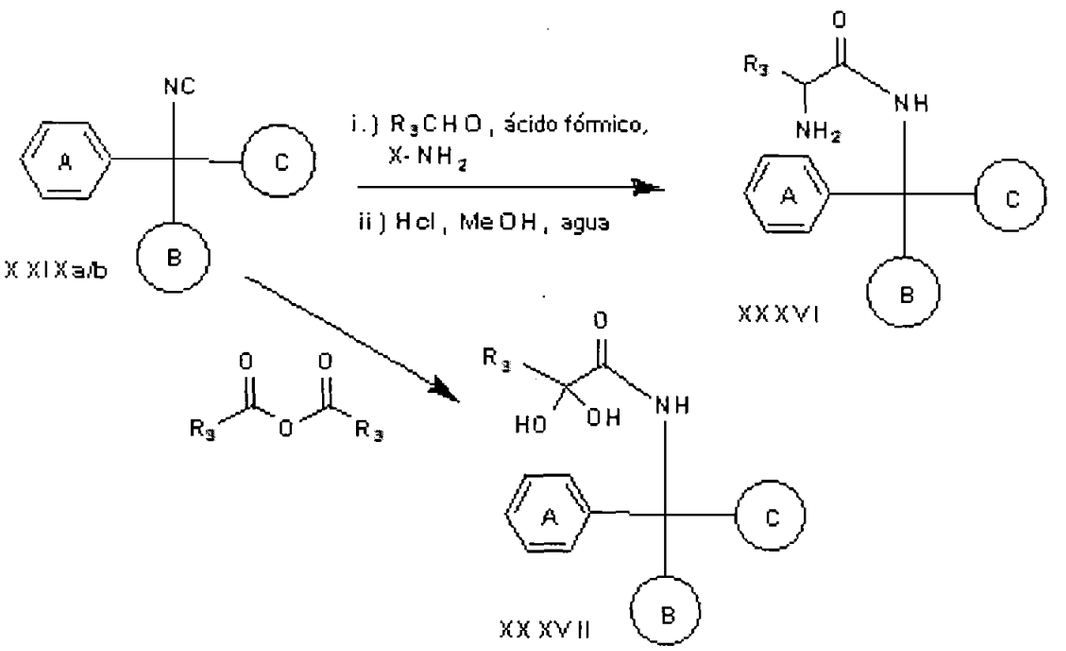
**Esquema de Reacción U**



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Como se ilustra en el Esquema de Reacción U, un intermediario de la Fórmula VIa/b, se puede convertir en un intermediario del compuesto XXXIIIa/b por tratamiento con un agente formilante, tal como, anhídrido fórmico acético, seguido por un agente deshidratante, tal como oxicloruro de fósforo, a lo largo con una base, tal como trietilamina. Como se describe en el Esquemas de Reacción S, un intermediario de la Fórmula XXIXa/b puede utilizarse para hacer compuestos de la Fórmula Ia y Ib.

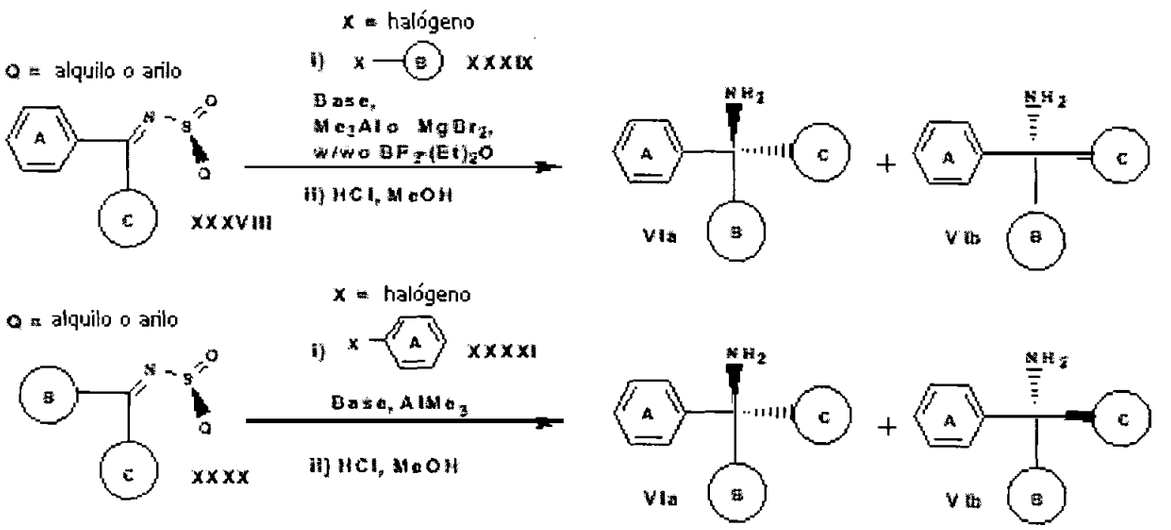
**Esquema de Reacción V**




Como se ilustra en el Esquema de Reacción V, un intermediario de la Fórmula XXIXa/b, se puede tratar con un reactivo aldehído de la Fórmula $R_3CHO$, donde $R_3$ es como se describe por la fórmula Ia y Ib, a lo largo con un ácido, tal

como ácido fórmico, y un reactivo de amina, de la fórmula general $X-NH_2$, donde X representa un desdoblamiento del grupo de protección seleccionado fácilmente por un experto en la técnica, seguido por tratamiento con y ácido, tal como HCl, en la presencia de un alcohol y agua, para producir un compuesto de la Fórmula XXXVI, el cual es un compuesto de la Fórmula Ia y Ib. Alternativamente un reactivo de la Fórmula XXIXa/b se puede tratar con un reactivo anhídrido de la Fórmula $(R_3CO)_2O$, donde $R_3$ es como se describe por la fórmula Ia y Ib, para producir un compuesto de la Fórmula XXXVII, el cual es un compuesto de Fórmula Ia y Ib.

**Esquema de Reacción W**




Como se ilustra en el Esquema de Reacción W, por las aplicaciones de las rutas descritas en los Esquemas de Reacción A, B, C y O para la síntesis de un intermediario de la Fórmula VII, un experto en la técnica puede hacer

intermediarios de la Fórmula XXXVII y XXXX, donde la definición de A, B y C son como se definen por la fórmula Ia y Ib. Un intermediario de la Fórmula XXXVIII puede reaccionar con un intermediario de la Fórmula XXXIX, donde X es un halógeno, tal como bromo, yodo o cloro, y la definición de C es como se describe por la fórmula Ia y Ib, en la presencia de una base, tal como n-butil litio o ter-butil litio, a lo largo con un agente metilante tal como, $CH_3Al$ o $MgBr_2$, seguido por la hidrólisis de la sulfinamida, para producir el intermediario de la Fórmula VIa y VIb, el cual es un intermediario clave en la ruta para los compuestos de la Fórmula Ia y Ib. Un intermediario de la Fórmula XXXX puede reaccionar con un intermediario de la Fórmula XXXXI, donde X es un halógeno, tal como bromo, yodo o cloro, y la definición de A es como se describe por la fórmula Ia y Ib, en la presencia de una base, tal como n-butil litio o ter-butil litio, a lo largo con un agente metilante tal como, $CH_3Al$, seguido por la hidrólisis de la sulfinamida, para producir el intermediario de la Fórmula VIa y VIb, el cual es un intermediario clave en la ruta para los compuestos de la Fórmula Ia y Ib.

Los esquemas de reacción anteriores dan una revisión de varios procesos generales para la síntesis de compuestos de la Fórmula Ia y Ib. Los compuestos adicionales de la Fórmula Ia y Ib pueden hacerse fácilmente por un

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experto en la técnica por modificaciones adicionales de grupos funcionales en las posiciones A, B, C o $R_1$ de los compuestos de la Fórmula Ia y Ib hechas por los procesos ilustrados en los esquemas incluidos. Los ejemplos que siguen describen numerosas aplicaciones de las rutas descritas en los esquemas de reacción A-W así como rutas adicionales para compuestos de la fórmula Ia y Ib se llevan cabo a través de la modificación de grupos funcionales en las posiciones A, B, C ó $R_1$ de los compuestos de la fórmula Ia y Ib.

**UTILIDAD**

Los compuestos de la presente invención han mostrado que inhiben la proteína de transferencia del éster de colesterol (CETP) por más del 30% a dos diferentes concentraciones de menos de 100 uM, preferiblemente con una potencia de menos de 5 uM, más preferiblemente con una potencia de menos de 500 nM. Los compuestos de la invención también se encuentran que inhiben la actividad de transferencia del éster de colesterol usando ensayos in vitro que contienen hasta 96% de plasma, y para inhibir la actividad de transferencia del éster de colesterol en plasma en animales. En consecuencia, los compuestos dentro del alcance de la presente invención inhiben la proteína CETP, y como tal se espera que sean útiles en el tratamiento, prevención, y/o retardo del progreso de varios trastornos.

Por ejemplo, los compuestos de la presente

invención, sus profármacos y las sales de tales compuestos y profármacos pueden adaptarse al uso terapéutico como agentes que inhiben la actividad de proteína de transferencia del éster de colesterol en mamíferos, particularmente humanos. De esta manera, los compuestos de la presente invención se espera que sean útiles para elevar el colesterol HDL en el plasma, sus componentes asociados, y las funciones realizadas por estos en mamíferos, particularmente humanos. En virtud de su actividad esperada, estos agentes también se espera que reduzcan los niveles de plasma de triglicéridos, colesterol VLDL, colesterol LDL y sus componentes asociados en mamíferos, particularmente humanos. Por lo tanto, estos compuestos se esperan que sean útiles para el tratamiento y corrección de las diversas dislipidemias observadas que están asociada con el desarrollo e incidencia de ateroesclerosis y enfermedad cardiovascular, incluyendo hipoalfalipoproteinemia, hiperbetalipoproteinemia, hipertrigliceridemia, e hipercolesterolemia familiar (ver Patente E.U.A. No. 6,489,478, incorporada en la presente para referencia).

Adicionalmente, la introducción de un gen CETP funcional en un animal que carece de CETP (ratón) resulta en niveles de HDL reducidos (Agellon, L.B., y col.: Biol. Chem. 266: 10796-10801 (1991)), y, susceptibilidad incrementada a la ateroesclerosis (Marotti, K. R., y col.: Nature 364: 73-75

(1993)). También, la inhibición de la actividad CETP con un anticuerpo inhibidor contra colesterol HDL en hámster (Evans, G. F., y col.: J. of Lipid Research 35: 1634-1645 (1994)) y conejo (Whitlock, M. E., y col.: J. Clin. Invest. 84: 129-137 (1989)). La supresión de CETP en plasma incrementado por inyección intravenosa con oligodesoxinucleótidos antisentido contra ARNm CETP reducen la ateroesclerosis en conejos alimentados con colesterol (Sugano, M., y col.: J. of Biol. Chem. 273: 5033-5036 (1998)). De forma importante, los sujetos humanos deficientes en CETP de plasma, debido a la mutación genética poseen niveles de colesterol HDL en el plasma marcadamente elevados y apolipoproteína A-I, el componente de apoproteína principal de HDL. Además, la mayoría demuestra colesterol LDL en plasma marcadamente reducido y apolipoproteína B (el componente de apolipoproteína principal del LDL (Inazu, A., Brown, M. L., Hesler, C. B., y col.: N. Engl. J. Med. 323: 1234-1238 (1990)).

Dada la correlación negativa entre los niveles de colesterol HDL y lipoproteínas asociadas con HDL, y la correlación positiva entre triglicéridos, colesterol LDL, y sus apolipoproteínas asociadas en la sangre con el desarrollo de enfermedades cardiovasculares, vasculares cerebrales y vasculares periféricas, los compuestos de la presente invención, sus profármacos y las sales de tales compuestos y

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profármacos, en virtud de su acción farmacológica, se espera que sean útiles para el tratamiento, prevención, la detención y/o regresión de ateroesclerosis y sus estados de enfermedad asociados. Estos trastornos cardiovasculares incluyen (por ejemplo, angina, isquemia cardiaca e infarto al miocardio), complicaciones debidas a terapias de enfermedad cardiovascular (por ejemplo, lesión por reperfusión y restenosis angioplástica), hipertensión, apoplejía, y ateroesclerosis asociada con trasplante de órgano.

Debido a los efectos benéficos ampliamente asociados con los niveles de HDL elevados, un agente que inhibe la actividad CETP en humanos, en virtud de su capacidad para incrementar el HDL, también proporciona avenidas valiosas para la terapia en un número de otras áreas de enfermedad como tal.

En consecuencia, dada la capacidad de los compuestos de la presente invención, sus profármacos y las sales de tales compuestos y profármacos para alterar la composición de lipoproteína por medio de la inhibición de la transferencia del éster de colesterilo, se espera que sean útiles en el tratamiento, prevención y/o retardo del progreso de complicaciones vasculares asociadas con la diabetes. La hiperlipidemia está presente en la mayoría de los sujetos con diabetes mellitus (Howard, B. V., J. Lipid Res. 28, 613 (1987)). Aún en presencia de niveles de lípidos normales, los

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sujetos diabéticos experimentan un riesgo mayor de enfermedad cardiovascular (Kannel, W. B. and McGee, D. L., Diabetes care 2, 120 (1979)). La transferencia de éster de colesterilo mediada por CETP se conoce que se incrementa anormalmente en la diabetes tanto dependiente de la insulina (Bagdade, J. D., Subbaiah, P. V. and Ritter, M. C, Eur. J. Clin. Invest. 21, 161 (1991)) como no dependiente de insulina (Bagdade, J. D., y col., Atherosclerosis 104, 69 (1993)). Esto sugiere que el incremento anormal en la transferencia de colesterol resulta en cambio en la composición de lipoproteína, particularmente para VLDL y LDL, que son más aterogénicos (Bagdade, J. D., y col., Lipid Res. 36, 759 (1995)). Estos cambios no se observarán necesariamente durante la separación por exclusión de lípidos de rutina. De esta manera, se espera que la presente invención sea útil para reducir el riesgo de complicaciones vasculares como resultado de la condición diabética.

Además, los compuestos de la presente invención se espera que sean útiles en el tratamiento de la obesidad. Tanto en humanos (Radeau, T., y col., Lipid Research. 36 (12):2552-61 (1995)) y primates no humanos (Quinet, E., y col., Clinical Investigation. 87 (5): 1559-66 (1991)) el ARNm para CETP se expresa a altos niveles en tejido adiposo. El mensaje adiposo se incrementa con la alimentación grasa (Martin, L. J., y col., Lipid Research. 34 (3):437-46

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(1993)), y su traducción en proteína de transferencia funcional y a través de la secreción contribuye significativamente a los niveles de CETP en plasma. En adipocitos humanos, el volumen del colesterol se proporciona por el LDL y HDL de plasma (Fong, B. S., y col., Biochimica et Biophysica Acta. 1004 (1):53-60 (1989)). La absorción de éster de colesterilo HDL depende en gran parte de CETP (Benoist, F., y col., Journal of Biological Chemistry. 272 (38):23572-23577 (1997)). Esta capacidad de CETP para estimular la absorción de colesterilo HDL, acoplado con el enlace aumentado de HDL a adipocitos en sujetos obesos (Jimenez, J. G., y col., International Journal of Obesity. 13 (5):699-709 (1989)), sugiere un papel para el CETP, no sólo para generar el fenotipo HDL inferior para estos sujetos, sino también en el desarrollo de la obesidad por sí misma al promover la acumulación de colesterol. Los inhibidores de la actividad CETP que bloquean este proceso, por lo tanto, sirven como adyuvantes útiles para la terapia dietética al causar la reducción de peso.

Los inhibidores CETP son útiles en el tratamiento de la inflamación debido a la asepsia de Gram negativo y choque séptico. Por ejemplo, la toxicidad sistémica de asepsia de Gram negativa es en gran parte debido a la endotoxina, un lipopolisacárido (LPS) liberado de la superficie exterior de la bacteria, que causa una respuesta

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inflamatoria extensiva. El lipopolisacárido puede formar complejos con lipoproteínas (Ulevitch, R. J., y col., J. Clin. Invest. 67, 827-837 (1981)). Los estudios *in vitro* han demostrado que el enlace de LPS a HDL reduce substancialmente la producción y liberación de mediadores de la inflamación (Ulevitch, R. J., y col., J. Clin. Invest. 62, 1313-24 (1978)). Los estudios *in vivo* muestran que los ratones transgénicos que expresan apo-A1 humano y niveles HDL elevados se protegen del choque séptico (Levine, D. M., y col., Proc. Natl. Acad. Sci. 90, 12040-44 (1993)). De forma importante, la administración de HDL reconstituido a humanos enfrentados con endotoxina, resulta en una respuesta inflamatoria reducida (Pajkrt, D., y col., J. Exp. Med. 184, 1601-08 (1996)). Los inhibidores CETP, en virtud del hecho de que elevan los niveles de HDL, aligeran el desarrollo de la inflamación y choque séptico.

De esta manera, la presente invención proporciona métodos para la prevención o tratamiento de uno o más de los trastornos anteriormente mencionados, que comprende la etapa de administrar a un sujeto que necesita del mismo, una cantidad efectiva de al menos un compuesto de la presente invención, su profármaco y la sal de tal compuesto y profármacos. Otros agentes terapéuticos tales como aquellos descritos más adelante pueden emplearse con los compuestos inventivos en los métodos presentes. En los métodos de la

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presente invención, tales otros agentes terapéuticos pueden administrarse antes de, simultáneamente con o después de la administración de los compuestos de la presente invención.

Además, los compuestos de la presente invención se espera que sean útiles en la inhibición de la producción de lipoproteína remanente (Okamoto y col., WO 2005/030185).

Ensayo CETP

La inhibición CETP puede determinarse a una concentración específica de compuesto de prueba en cualquiera de los ensayos descritos en la presente. Las potencia se calculan más generalmente al determinar los valores $IC_{50}$ usando estos ensayos.

Ensayo de Proximidad de Centelleo CETP

Los compuestos de la presente invención inhiben la transferencia del éster de colesterol dependiente de CETP de HDL a LDL como se describe aquí. Las diluciones de compuestos en DMSO (1 µl) se agregan a placas BD (#353232). A esto se le agrega 20 µl de una mezcla que contiene $^3$H-CE/HDL (0.15 µl), LDL biotinilinado (concentración final ~5 ug de proteína/ml) y HDL deshabilitado (concentración final 16 ug/ml) en una solución reguladora de pH que contiene HEPES 50 mM, pH 7.4, NaCl 150 mM y azida de sodio al 0.05%. Las reacciones se iniciaron por la adición de 10 ul de solución reguladora de pH que contiene CETP recombinante humano purificado, y se incuba a 37°C. Al final de la reacción, se agregan 60 ul de

perlas LEADseeker (#RPNQ0261, 2 mg/ml en solución reguladora de pH que contiene 1 mg/ml de BSA y 0.05 mg de proteína/ml de HDL), y las placas se cubren y se leen posteriormente. La actividad de respaldo se determina en un conjunto de cavidades que reciben solución reguladora de pH pero no CETP. El nivel de inhibición se determina al comparar las lecturas en las cavidades que contienen el compuesto con las lecturas en las cavidades de control que contienen DMSO.

Ensayo de Transferencia del Éster de Colesterol en Plasma

Los compuestos de la presente invención también se probaron para su capacidad para inhibir la actividad de transferencia del éster de colesterol en el plasma como se describe aquí. Las diluciones de los compuestos en DMSO (1 µl) se agregan a placas de polipropileno de 384 cavidades. A cada cavidad se le agregan 29 ul de plasma humano que contiene 0.15 ul de $^{3}$H-CE/HDL. La reacción se incuba a 37°C y se finaliza por la adición de 6 ul de reactivo de precipitación (2:1:1 de agua:$MgCl_2$ 1M:Dextralip 50 al 2%), para precipitar el LDL y VLDL. Después de 10 minutos a temperatura ambiente, se transfieren 15 ul de la reacción a placas filtro (Millipore, #MHVBN45) previamente humedecidas con 100 ul de solución salina regulada en pH en fosfato. Las placas se centrifugan (1800 rpm) a temperatura ambiente durante 10 minutos, y se agrega 50 ul de Microscint-20. Las placas se sellan entonces y se leen. La actividad de respaldo

se determina con las muestras de plasma incubadas a 4°C. El nivel de inhibición se determina al comparar las lecturas en las cavidades que contienen el compuesto con las lecturas en las cavidades de control que contiene DMSO.

Actividad de Transferencia del éster de Colesterol *In Vivo*

Los compuestos de la presente invención muestran además que inhiben la actividad de transferencia del éster de colesterol en el plasma en ratones que son dualmente transgénicos para CETP humano y apoB-100 (hCETP/apoB-100) como se describe aquí.

Los ratones (comercialmente disponibles de Taconic) se hicieron ayunar durante dos horas y se obtiene el plasma antes de la dosis. Los animales se dosificaron con vehículo o compuestos (p.o.). El vehículo puede variar como sea necesario para disolver el compuesto, mientras al mismo tiempo no tiene, o es mínima, actividad en la actividad de transferencia del éster de colesterol en el plasma. Las muestras de plasma se colectan nuevamente en varios momentos después de dosificar y se evalúan para actividad de transferencia del éster de colesterol.

Para medir la actividad CETP en muestras de plasma obtenidas de animales tratados con compuestos, se emplea la siguiente metodología. A una muestra de plasma (típicamente entre 9 y 30 ul), se le agrega 1 µl de $^{3}$H-CE/HDL diluido (0.15 ul $^{3}$H-CE/HDL y 85 ul de solución reguladora de pH de

ensayo) para etiquetar el HDL endógeno. La solución reguladora de pH de ensayo contiene HEPES 50 mM, pH 7.4, Y NaCl 150 mM. La reacción se incuba a 37°C, y el LDL/VLDL se precipita con 3 ul de reactivo de precipitación (4:1:1 de agua:$MgCl_2$ 0.5M:Dextralip 50 al 1%). Los tubos se centrifugaron durante 15-30 minutos a 10,000 x g (10°C), los sobrenadantes se descartan, y los gránulos se disuelven en 140 ul de SDS al 2%. La mitad de la solución SDS (70 ul) se transfiere a tubos de centelleo, se agrega fluido de centelleo, y se mide la radioactividad en un contador de centelleo. La actividad de respaldo se determina para cada muestra con una alícuota incubada a 4°C. La inhibición de transferencia del éster de colesterol en el plasma se calcula al comparar la actividad de transferencia en una muestra de plasma obtenida después de dosificar a la actividad de transferencia en la muestra de plasma obtenida del mismo animal antes de dosificar. Todos los datos se substraen del respaldo.

El ensayo *in vivo* descrito antes (con modificaciones apropiadas dentro de la experiencia en la técnica) puede usarse para determinar la actividad de otros agentes que controlan los lípidos o triglicéridos así como los compuestos de esta invención. Los ensayos establecidos antes también proporcionan un medio por el cual las actividades de los compuestos de la presente invención, sus

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profármacos y las sales de tales compuestos y profármacos (u otros agentes descritos en la presente) pueden compararse uno con el otro y con las actividades de otros compuestos conocidos. Los resultados de estas comparaciones son útiles para determinar los niveles de dosis en mamíferos, incluyendo humanos, para el tratamiento de las enfermedades/condiciones descritas arriba.

Protocolo de Colesterol HDL

La capacidad de los inhibidores de CETP para incrementar el colesterol HDL (HDL-C) se puede mostrar en sujetos mamíferos a través métodos conocidos para un experto en la técnica (ver Evans, G.F. y colaboradores, J. Lipid Research, 35:1634-1645 (1994)). Por ejemplo, los compuestos de la presente invención se han mostrado para ser benéficos en la elevación del HDL-C en hámsteres sirios dorados. Los hámsteres se alimentan con una dieta grasa moderada que contienen cantidades variables de aceite de coco y colesterol para alterar sus niveles de HDL-C y LDL-C. Los hámsteres alimentados con grasa moderadamente se dejan en ayuno y se les extrae sangre para determinar los niveles de HDL-C de línea base, luego se les da la dosis oralmente con compuesto por tres días en un vehículo apropiado. Los animales se dejan en ayuno y se les extrae sangre nuevamente en el tercer día de dosificación, y los resultados se comparan con los niveles de HDL-C de línea base. Los compuestos aumentan el HDL-C en

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este modelo en una manera dependiente de la dosis, demostrando su utilidad para alterar los lípidos del plasma.

Protocolo Anti-obesidad

La capacidad de los inhibidores para provocar pérdida de peso se puede evaluar en sujetos humano obesos con índice de masa corporal (BMI) ≥ 30 $Kg/m^2$. Las dosis de inhibidor se administran suficientes para resultar en un incremento de ≥ 25% en niveles de colesterol HDL. La BMI y la distribución de grasa del cuerpo, definida como relación de cintura (W) a cadera (H) (WHR), se monitorean durante el curso de los estudios de 3 a 6 meses, y los resultados para los grupos de tratamiento se comparan con aquellos que reciben placebo.

Los ensayos anteriores pueden, por supuesto, variarse por aquellos expertos en la técnica.

La presente invención también provee composiciones farmacéuticas que comprenden al menos uno de los compuestos de la presente invención, sus profármacos y las sales de tales compuestos y profármacos capaces de prevenir, tratar, y/o reducir el progreso de uno o más de los trastornos antes mencionados en una cantidad efectiva del mismo, y un vehículo o diluyente farmacéuticamente aceptable. La composiciones de la presente invención pueden contener otros agentes terapéuticos como se describe más adelante, y pueden ser formuladas, por ejemplo, al emplear diluentes o vehículos

sólidos o líquidos convencionales, así como aditivos farmacéuticos de un tipo apropiado para el modo de administración deseado (por ejemplo, excipientes, aglutinantes, conservadores, estabilizantes, saborizantes, etc.) de acuerdo con las técnicas tales como aquellas bien conocidas en la técnica de la formulación farmacéutica.

Los compuestos de la presente invención pueden ser administrados por cualquier medio apropiado, por ejemplo, oralmente, tal como en la forma de tabletas, cápsulas, gránulos, o polvos; sublingualmente; bucalmente; parenteralmente, como por inyección subcutánea, intravenosa, intramuscular o intraesternal o técnicas de infusión (por ejemplo, como soluciones o suspensiones acuosas o no acuosas inyectables estériles); nasalmente como por un rocío de inhalación; tópicamente, también en la forma de una crema o ungüento; o rectalmente como en la forma de supositorios; en formulaciones de dosis unitaria que contienen vehículo o diluyentes farmacéuticamente aceptables, no tóxicos. Los compuestos presentes pueden, por ejemplo, ser administrados en una forma apropiada para liberación inmediata o liberación prolongada. La liberación inmediata o la liberación prolongada pueden ser logradas por el uso de composiciones farmacéuticas apropiadas que comprenden los compuestos presentes, o, particularmente en el caso de liberación prolongada, por el uso de dispositivos tales como implantes

subcutáneos o bombas osmóticas.

Las composiciones ejemplares para administración oral incluyen suspensiones las cuàles pueden contener, por ejemplo, celulosa microcristalina para dar volumen, ácido algínico o alginato de sodio como un agente de suspensión, metilcelulosa como un mejorador de viscosidad, y agentes edulcorantes o saborizantes tales como aquellos conocidos en la técnica; y tabletas de liberación inmediata las cuales pueden contener, por ejemplo, celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y/o lactosa y/u otros excipientes, aglutinantes, prolongadores, disgregantes, diluyentes y lubricantes tales como aquellos conocidos en la técnica. Los compuestos de la presente invención también pueden ser suministrados a través de la cavidad oral por administración sublingual y/o bucal. Las tabletas moldeadas, tabletas comprimidas o tabletas liofilizadas son formas ejemplares que pueden usarse. Las composiciones ejemplares incluyen aquellas que formulan los compuestos presentes con diluentes de rápida disolución tales como manitol, lactosa, sacarosa, y/o ciclodextrinas. También pueden estar incluidos en tales formulaciones excipientes de alto peso molecular, tales como celulosas (avicel) o polietilenglicoles (PEG). Tales formulaciones también pueden incluir un excipiente para ayudar a la adhesión de mucosa tal como celulosa de hidroxipropilo (HPC), celulosa de

hidroxipropil metilo (HPMC), celulosa de carboximetilo de sodio (SCMC), copolímero de anhídrido maleico (por ejemplo, Gantrez); y agentes para controlar la liberación tales como copolímero poliacrílico (por ejemplo, Carbopol 934). También pueden ser agregados agentes lubricantes, agentes mejoradores de flujo, saborizantes, colorantes y estabilizadores para facilidad de la fabricación y uso.

Las composiciones ejemplares para aerosol nasal o administración por inhalación incluyen soluciones salinas que pueden contener, por ejemplo, alcohol bencílico u otros conservadores apropiados, promotores de absorción para mejorar biodisponibilidad, y/u otros agentes solubilizantes o dispersantes tales como aquellos conocidos en la técnica.

Las composiciones ejemplares para administración parenteral incluyen soluciones o suspensiones inyectables que pueden contener, por ejemplo, diluyentes o solventes parenteralmente aceptables, no tóxicos, tales como manitol, 1,3 butanodiol, agua, solución de Ringer, una solución de cloruro de sodio isotónica, u otros agentes dispersantes o humectantes y de suspensión adecuados, incluyendo mono- o diglicéridos sintéticos, y ácidos grasos, incluyendo ácido oleico.

Las composiciones ejemplares para administración rectal incluyen supositorios los cuales pueden contener, por ejemplo, excipientes no irritantes apropiados, tales como

manteca de cacao, ésteres glicéridos sintéticos o polietilenglicoles, los cuales son sólidos a temperaturas ordinarias, pero se licuan y/o disuelven en la cavidad rectal para liberar el fármaco.

Las composiciones ejemplares para administración tópica incluyen un portador tópico tal como Plastibase (aceite mineral gelificado con polietileno).

La cantidad efectiva de un compuesto de la presente invención puede ser determinada por alguien de habilidad ordinaria en la técnica, e incluye cantidades de dosis ejemplares para un humano adulto desde alrededor de 0.001 hasta 100 mg/Kg de peso corporal de compuesto activo por día, el cual puede ser administrado en una sola dosis o en la forma de dosis individuales divididas, tal como desde 1 hasta 4 veces por día. Se entenderá que el nivel de dosis específico y la frecuencia de dosificación para cualquier sujeto particular puede variar y dependerá de una variedad de factores que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y duración de la acción de tal compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y tiempo de administración, velocidad de excreción, combinación del fármaco, y severidad de la condición particular. Los sujetos preferidos para tratamiento incluyen animales, más preferiblemente especies mamíferas tales como humanos, y

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animales domésticos tales como perros, gatos, y similares, sujetó a los trastornos anteriormente mencionados.

Los compuestos de la presente invención pueden emplearse solos o en combinación con cada uno y/u otro agente terapéuticos adecuado útil en el tratamiento de los trastornos antes mencionados u otros trastornos.

Por ejemplo, se podrían usar en combinación con un inhibidor de reductasa HMG-CoA, un inhibidor de síntesis de colesterol, un inhibidor de absorción de colesterol, otro inhibidor de CETP, un inhibidor de secreción de MTP/Apo B, un modulador PPAR y otros agentes que disminuyen el colesterol tales como un fibrato, niacina, una resina de intercambio iónico, un antioxidante, un inhibidor de ACAT, y un secuestrante de ácido biliar. Otros agentes farmacéuticos también podrían incluir los siguientes: inhibidor de reabsorción de ácido biliar, un inhibidor de transportador de ácido biliar ileal, un inhibidor de ACC, un antihipertensivo (tal como NORVASC®), un modulador de receptor de estrógeno selectivo, un modulador de receptor de andrógeno selectivo, un antibiótico, un antidiabético (tal como metformina, un activador de PPARγ, una sulfonilurea, insulina, un inhibidor de reductasa de aldosa (ARI) y un inhibidor de deshidrogenasa de sorbitol (SDI), aspirina (ácido acetilsalicílico) y niacina y combinaciones de estos.

Cualquier inhibidor de reductasa HMG-CoA se puede

usar en el aspecto de combinación de esta invención. El término inhibidor de reductasa de HMG-CoA se refiere a compuestos los cuales inhiben la bioconversión de la coenzima A de hidroximetilglutarilo a ácido mevalónico catalizado por la enzima reductasa HMG-CoA. Tal inhibición se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Meth. Enzymol., 71:455-509 (1981) y referencias citadas en ella). Una variedad de estos compuestos se describen y se hace referencia posteriormente sin embargo, otros inhibidores de reductasa HMG-CoA serán conocidos por aquellos expertos en la técnica. La Patente de EUA No. 4,231,938 (la descripción de la cual está incorporada de esa manera por referencia) describe ciertos compuestos aislados después de cultivo de un microorganismo que pertenece al género *Aspergillus*, tal como lovastatina. También, la Patente de EUA No. 4,444,784 (la descripción de la cual está incorporada de esa manera por referencia) describe derivados sintéticos de los compuestos antes mencionados, tales como simvastatina. También, la Patente de EUA No. 4,739,073 (la descripción de la cual está incorporada por referencia) describe ciertos indoles substituidos, tales como fuvastatina. También, la Patente de EUA No. 4,346,227 (la descripción de la cual está incorporada por referencia) describe derivados de ML-236B, tales como pravastatina. También, la EP-491226A (la descripción de la cual está

incorporada por referencia) describe ciertos ácidos piridildihidroxiheptenoicos, tales como cerivastatina. Además, la Patente de EUA No. 5,273,995 (la descripción de la cual está incorporada por referencia) describe ciertas 6-[2-( -pirrol-1-il substituidos)alquil]piran-2-onas tales como atorvastatina y cualquier forma farmacéuticamente aceptable de estas (esto es LIPITOR®). Inhibidores de reductasa HMG-CoA adicionales incluyen rosuvastatina y pitavastatina. Las estatinas también incluyen los compuestos como rosuvastatina descrita en U.S. RE37,314 E, pitavastatina descrita en EP 304063 B1 y U.S. 5,011,930; mevastatina, descrita en U.S. 3,983,140; velostatina, descrita en U.S. 4,448,784 y U.S. 4,450,171; compactina, descrita en U.S. 4,804,770; dalvastatina, descrita en la Publicación de Solicitud de Patente Europea No. 738510 A2; fluindostatina, descrita en Publicación de Solicitud de Patente Europea No. 363934 A1; y dihidrocompactina, descrita en U.S. 4,450,171.

Cualquier modulador de PPAR se puede usar en el aspecto de combinación de esta invención. El término modulador de PPAR se refiere a compuestos los cuales modulan la actividad del receptor de activador proliferador de peroxisoma (PPAR) en mamíferos, particularmente humanos. Tal modulación se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar conocidos en la literatura. Se cree que los compuestos, por modulación del

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receptor PPAR, regulan la transcripción de genes claves involucrados en el metabolismo de lípidos y glucosa así como aquellos en oxidación de ácido graso y también aquellos involucrados en asimilación de lipoproteína de alta densidad (HDL) (por ejemplo, transcripción de gen AI de apolipoproteína), en consecuencia la reducción de toda la grasa corporal y el aumento de colesterol HDL. Por virtud de su actividad, estos compuestos también reducen los niveles de plasma de triglicéridos, colesterol VLDL, colesterol LDL y sus componentes asociados tales como polipoproteína B en mamíferos, particularmente humanos, en tanto que aumenta el colesterol HDL y la apolipoproteína AI. De ahí, estos compuestos son útiles para el tratamiento y corrección de varias dislipidemias observadas para ser asociadas con el desarrollo e incidencia de ateroesclerosis y enfermedad cardiovascular, incluyendo hipoalfalipoproteinemia e hipertrigliceridemia. Una variedad de estos compuestos se describen y se hace referencia posteriormente, sin embargo, ostro serán conocidos por aquellos expertos en la técnica. Las Publicaciones Internacionales WO 02/064549 y WO 02/064130, la solicitud de Patente de EUA No. 10/720,942, y la solicitud de Patente de EUA No. 60/552,114 describen ciertos productos los cuales son activadores PPARα.

Cualquier otro modulador de PPAR se puede usar en el aspecto de combinación de esta invención. En particular,

los moduladores PPARβ y/o PPARγ pueden ser útiles en combinación con compuestos de la presente invención. Un ejemplo de inhibidor PPAR se describe en US 2003/0225158 como ácido {5-Metoxi-2-metil-4-[4-(4-trifluoromethil-benci]oxi)-benzilsulfani]-fenoxi}-acético.

Cualquier inhibidor de secreción de MTP/Apo B (proteína de transferencia de triglicérido microsomal y o apolipoproteína B) se puede usar en el aspecto de combinación de esta invención. El término inhibidor de secreción de MTP/Apo B se refiere a compuestos los cuales inhiben la secreción de triglicéridos, éster de colesterilo, y fosfolípidos. Tal inhibición se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Wetterau, J.R., Science, 258:999 (1992)). Una variedad de estos compuestos se describen y se hace referencia posteriormente, sin embargo otros inhibidores de secreción de MTP/Apo B serán conocidos para aquellos expertos en la técnica, que incluyen implitapride (Bayer) y compuestos adicionales tales como aquellos descritos en WO 96/40640 y WO 98/23593, (dos publicaciones ejemplares). Por ejemplo, los siguientes inhibidores de secreción de MTP/Apo B son particularmente útiles: [2-(1H-[1,2,4,]triazol-3-ilmetil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida de ácido 4'-trifluorometil-bifenil-2-carboxílico; [2-(2-acetilamino-etil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida de ácido 4'-

trifluorometil-bifenil-2-carboxílico; éster de metilo de ácido (2-{6-[(4'-trifiuorometil-bifenil-2-carbonil)-amino]-3,4-dihidro-1H-isoquinolin-2-il}-etil)-carbámico; [2-(1H-imidazol-2-ilmetil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida de ácido 4'-trifluorometil-bifenil-2-carboxílico; [2-(2,2-difenil-etil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida de ácido 4'-trifluorometil-bifenil-2-carboxílico; [2-(2-etoxi-etil)-1,2,3,4-tetrahidro-isoquinolin-6-il]-amida de ácido 4'-trifluorometil-bifenil-2-carboxílico; (S)-N-{2-[bencil(metil)amino]-2-oxo-1-feniletil}-1-metil-5-[4'-(trifluorometil)[1,1'-bifenil]-2-carboxamido]-1H-indol-2-carboxamida; (pentilcarbamoil-fenil-metil)-amida de ácido (S)-2-[(4'-trifluorometil-bifenil-2-carbonil)-amino]-quinoline-6-carboxílico; 1H-indol-2-carboxamida,1-metil-N-[(1S)-2-[metil(fenilmetil)amino]-2-oxo-1-feniletil]-5-[[[4'-(trifluorometil)[1,1'-bifenil]-2-il]carbonil]amino]; y N-[(1S)-2-(bencilmetilamino)-2-oxo-1-feniletil]-1-metil-5-[[[4'-(thfluorometil)[1,1'-bifenil]-2-il]carbonil]amino]-1H-indol-2-carboxamida.

Cualquier inhibidor de sintasa HMG-CoA se puede usar en el aspecto de combinación de esta invención. El término inhibidor de sintasa HMG-CoA se refiere a compuestos los cuales inhiben la biosíntesis de coenzima A de hidroximetilglutarilo de coenzima A de acetilo y coenzima A de acetoacetilo, catalizada por la sintetasa de enzima HMG-

CoA. La inhibición se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (Meth. Enzymol., 35:155-160 (1975); Meth. Enzymol., 110:19-26 (1985) y referencias citadas en ellos). Una variedad de compuestos se describen y se hace referencia posteriormente, sin embargo otros inhibidores de sintasa HMG-CoA serán conocidos para aquellos expertos en la técnica. La Patente de EUA No. 5,120,729 describe ciertos derivados de beta-lactama. La Patente de EUA No. 5,064,856 describe ciertos derivados de espiro-lactona preparados por cultivo de un microorganismo (MF5253). La Patente de EUA No. 4,847,271 describe ciertos compuestos de oxetano tales como derivados de ácido 11-(3-hidroximetil-4-oxo-2-oxetail)-3,5,7-trimetil-2,4-undecadienóico.

Cualquier compuesto que disminuya la expresión del gen de reductasa de HMG-CoA se puede usar en el aspecto de combinación de esta invención. Estos agentes pueden ser inhibidores de transcripción de reductasa de HMG-CoA que bloquean la transcripción de ADN o inhibidores de traducción que previenen o disminuyen la traducción de codificación de ARNm para reductasa de HMG-CoA dentro de proteína. Los compuestos pueden afectar ya sea la transcripción o la traducción directamente, o pueden ser biotransformados a compuestos que tienen las actividades antes mencionadas por una o más enzimas en la cascada biosintética de colesterol o

pueden llevar a la acumulación de un metabolito de isopreno que tiene las actividades antes mencionadas. Los compuestos pueden provocar este efecto por disminución de los niveles de SREBP (proteína que enlaza al receptor de esterol) por inhibición de la actividad de la proteasa del sitio 1 (SIP) o agonizando el receptor de oxiesterol o SCAP. La regulación se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (Meth. Enzymol., 110:9-19 (1985)). Varios compuestos se describen y se hacen referencia posteriormente, sin embargo otros inhibidores de la expresión del gen de reductasa HMG-CoA serán conocidos para aquellos expertos en la técnica. La Patente de EUA No. 5,041,432 describe ciertos derivados de lanoesterol 15-sustituido. Otros esteroles oxigenados que suprimen la síntesis de reductasa de HMG-CoA se describen por E.I. Mercer (Prog. Lip. Res., 32:357-416 (1993)).

Cualquier compuesto que tiene actividad como un inhibidor de CETP puede servir como el segundo compuesto en el aspecto de terapia de combinación de la presente invención. El término inhibidor de CETP se refiere a compuestos que inhiben el transporte mediado por la proteína de transferencia de éster de colesterilo (CETP) y triglicéridos de HDL a LDL y VLDL. La actividad de inhibición de CETP se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, la

Patente de EUA No. 6,140,343). Una variedad de inhibidores de CETP serán conocidos para aquellos expertos en la técnica, por ejemplo, aquellos descritos en las Patente de EUA Nos. 6,140,343 y 6,197,786. Los inhibidores de CETP descritos en estas patentes incluyen compuestos, tales como éster de etilo de ácido [2R,4S] 4-[(3,5-bis-trifluorometilbencil)metoxicarbonilamino]-2-etil-6-trifluorometil-3,4-dihidro-2H-quinolina-1-carboxílico (torcetrapib). Los inhibidores de CETP también se describen en la Patente de EUA No. 6,723,752, la cual incluye un sinnúmero de inhibidores de CETP que incluyen (2R)-3-{[3-(4-cloro-3-etil-fenoxi)-fenil]-[[3-(1,1,2,2-tetrafluoroetoxi)fenil]metil]amino}-1,1,1-trifluoro-2-propanol. Más aún, los inhibidores de CETP incluidos en la presente también se describen en la Solicitud de Patente de EUA No. 10/807,838 y Publicación PCT No. WO 2006/090250. La Patente de EUA No. 5,512,548 describe ciertos derivados de polipéptido que tienen actividad como inhibidores, mientras que ciertos derivados de rosenonolactona inhibidora de CETP y análogos que contienen fosfato de éster de colesterilo se describen en J. Antibiot., 49(8):815-816 (1996), y Bioorg. Med. Chem. Lett., 6:1951-1954 (1996), respectivamente.

Cualquier inhibidor de sintetasa de escualeno se puede usar en el aspecto de combinación de esta invención. El término inhibidor de sintetasa de escualeno se refiere a

compuestos los cuales inhiben la condensación de 2 moléculas de farnesilpirofosfato para formar escualeno, catalizado por la sintetasa de escualeno de enzima. La inhibición se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (Meth. Enzymol., 15:393-454 (1969) y Meth. Enzymol., 110:359-373 (1985) y referencias contenidas en ellas). Una variedad de estos compuestos se describen y se hace referencia posteriormente, sin embargo otros inhibidores de sintetasa de escualeno serán conocidos por aquellos expertos en la técnica. La Patente de EUA No. 5,026,554 describe los productos de fermentación del microorganismo MF5465 (ATCC 74011) que incluyen ácido zaragózico. Se ha acumulado un resumen de otros inhibidores de sintetasa de escualeno patentados (Curr. Op. Ther. Patents, 861-864 (1993)).

Cualquier inhibidor de epoxidasa de escualeno se puede usar en el aspecto de combinación de esta invención. El término inhibidor de epoxidasa de escualeno se refiere a compuestos los cuales inhiben la bioconversión de escualeno y oxígeno molecular en escualeno-2,3-epóxido, catalizado por la epoxidasa de escualeno de enzima. La inhibición se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (Biochim. Biophys. Acta, 794:466-471 (1984)). Una variedad de estos compuestos se describen y se hace referencia posteriormente, sin embargo otros inhibidores

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de exposidasa serán conocidos por aquellos expertos en la técnica. Las Patentes de EUA Nos. 5,011,859 y 5,064,864 describen ciertos análogos de flúor de escualeno. La publicación de EP 395,768 A describe ciertos derivados de alilamina sustituidos. La publicación de PCT WO 93/12069 A describe ciertos derivados de alcohol amino. La Patente de EUA No. 5,051,534 describe ciertos derivados de escualeno de ciclopropiloxi.

Cualquier inhibidor de ciclasa de escualeno se puede usar como el segundo componente en el aspecto de combinación de esta invención. El término inhibidor de ciclasa de escualeno se refiere a compuestos los cuales inhiben la bioconversión de escuelen-2,3-epóxido a lanosterol, catalizada por la ciclasa de escualeno de enzima. La inhibición se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (FEBS Lett., 244:347-350 (1989)). Además, los compuestos descritos y a los que se hace referencia posteriormente son inhibidores de ciclasa de escualeno, sin embargo otros inhibidores de ciclasa de escualeno también serán conocidos por aquellos expertos en la técnica. La Publicación PCT WO 94/10150 describe ciertos derivados de 1,2,3,5,6,7,8,8a-octahidro-5,5,8(beta)-trimetil-6-isoquinolineamina, tales como N-trifluoroacetil-1,2,3,5,6,7,8,8a-octahidro-2-allil-5,5,8(beta)-trimetil-6(beta)-isoquinolineamina. La

Publicación de Patente Francesa 2697250 describe ciertos derivados de etanol de beta, beta-dimetil-4-piperidina tales como 1-(1,5,9-trimetildecil)-beta, beta-dimetil-4-piperidinetanol.

Cualquier inhibidor de epoxidasa de escualeno/ciclasa de escualeno combinado se puede usar como el segundo componente en el aspecto de combinación de esta invención. El término inhibidor de epoxidasa de escualeno/ciclasa de escualeno combinado se refiere a compuestos que inhiben la bioconversión de escualeno a lanosterol a través de un intermediario de escualeno-2,3-epóxido. En algunos ensayos es posible distinguir entre inhibidores de epoxidasa de escualeno e inhibidores de ciclasa de escualeno, sin embargo, estos ensayos son reconocidos por aquellos expertos en la técnica. Así la inhibición por inhibidores de epoxidasa de escualeno/ciclasa de escualeno combinados se determina fácilmente por aquellos expertos en la técnica de acuerdo con los ensayos estándar antes mencionada para inhibidores de ciclasa de escualeno o epoxidasa de escualeno. Una variedad de estos compuestos se describen y se hace referencia posteriormente, sin embargo otros inhibidores de epoxidasa de escualeno/ciclasa de escualeno serán conocidos para aquellos expertos en la técnica. Las Patentes de EUA Nos. 5,084,461 y 5,278,171 describen ciertos derivados de azadecalin. La Publicación de

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EP 468,434 describe ciertos derivados de éter de piperidilo y tio-éter tales como sulfóxido de 2-(1-piperidil)pentil isopentil y sulfuro de etilo de 2-(1-piperidil)etilo. La Publicación de PCT WO 94/01404 describe ciertas piperidinas de acilo tal como 1-(1-oxopentil-5-feniltio)-4-(2-hidroxi-1-metil)-etil)piperidina. La Patente de EUA No. 5,102,915 describe ciertos derivados de escualeno de ciclopropiloxi.

Los compuestos de la presente invención también se pueden administrar en combinación con compuestos que ocurren naturalmente que actúan para disminuir los niveles de colesterol de LDL en plasma o aumentar los niveles de HDL en plasma vía una ruta distinta de los inhibidores de CETP. Estos compuestos que ocurren naturalmente comúnmente se llaman nutracéuticos e incluyen, por ejemplo, extracto de ajo y niacina. La niacina es un agente secundario particularmente atractivo para combinación con un inhibidor de CETP como conforme este también eleva los niveles de colesterol HDL. Más aún, la niacina disminuye el colesterol LDL y triglicéridos. Por lo tanto, una combinación de niacina y un inhibidor de CETP podrían no solamente proporcionar la potencia para la eficacia de aumento de HDL mejorado, sino que podría producir un cambio muy favorable en el perfil de riesgo cardiovascular general por disminución de colesterol LDL y triglicéridos. La niacina está disponible comercialmente en varias formas de dosificación. La niacina

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de liberación inmediata se puede comprar en mercado no oficial en farmacias o en tiendas de alimentos para la salud. Una forma de liberación lenta de niacina está disponible y se conoce como Niaspan. La niacina también se puede combinar con otros agentes terapéuticos tales como iovastatina, un inhibidor de reductasa HMG-CoA. Esta terapia de combinación con iovastatina se conoce como ADVICOR™ (Kos Pharmaceuticals Inc.). En pruebas clínicas a largo plazo, la niacina ya sea como monoterapia o en combinación con inhibidores de reductasa HMG-CoA han demostrado que reducen los eventos cardiovasculares, muertes cardiovasculares y toda causa de mortalidad.

Cualquier inhibidor de absorción de colesterol se puede usar como un componente adicional en el aspecto de combinación de la presente invención. El término inhibición de absorción de colesterol se refiere a la capacidad de un compuesto para prevenir el colesterol contenido dentro del espacio del intestino desde que entra dentro de las células intestinales y/o el paso desde dentro de las células intestinales hacia el sistema de linfoide y/o en la corriente sanguínea. La actividad de inhibición de absorción de colesterol se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, J. Lipid Res., 34:377-395 (1993)). Los inhibidores de absorción de colesterol son conocidos por aquellos expertos en la

técnica y se describen, por ejemplo, en PCT WO 94/00480. Un ejemplo de un inhibidor de absorción de colesterol recientemente aprobado es el ZETIA™ (ezetimibe) (Schering-Plough/Merck).

Cualquier inhibidor de ACAT se puede usar en el aspecto de terapia de combinación de la presente invención. El término inhibidor de ACAT se refiere a compuestos que inhiben la esterificación intracelular de colesterol de dieta por la enzima acilo CoA:colesterol aciltransferasa. Tal inhibición se puede determinar fácilmente por uno de experiencia en la técnica de acuerdo con ensayos estándar, tales como el método de Heider y colaboradores, descrito en J. Lipid Res., 24:1127 (1983). Una variedad de estos compuestos son conocidos por aquellos expertos en la técnica, por ejemplo, la Patente de EUA No. 5,510,379 describe ciertos carboxisulfonatos, mientras que WO 96/26948 y WO 96/10559 ambas describen derivados de urea que tienen actividad inhibidora de ACAT. Ejemplos de inhibidores de ACAT incluyen compuestos tales como Avasimibe (Pfizer), CS-505 (Sankyo) y Eflucimibe (Ell Lilly y Pierre Fabre).

Un inhibidor de lipasa se puede usar en el aspecto de terapia de combinación de la presente invención. Un inhibidor de lipasa es un compuesto que inhibe el desdoblamiento metabólico de triglicéridos de dieta o fosfolípidos de plasma en ácidos grasos libres y los

glicéridos que corresponden (por ejemplo, EL, HL, etc.). Bajo condiciones fisiológicas normales, la lipólisis ocurre vía un proceso de dos pasos que involucra la acilación de una porción de serina activada de la enzima de lipasa. Esto lleva a la producción de un intermediario hemiacetal de lipasa de ácido graso, el cual se desdoble luego para liberar un diglicérido. Después de más desacilación, el intermediario de ácido graso de lipasa se desdobla, resultando en lipasa libre, un glicérido y ácido graso. En el intestino, los ácidos grasos libres resultantes y los monoglicéridos se incorporan en las micelas de fosfolípido de ácido biliar, los cuales se absorben subsiguientemente en el nivel del límite de cepillo del intestino delgado. Las micelas eventualmente entran la circulación periférica como cilomicrones. La actividad de inhibición de lipasa se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Meth. Enzymol. 286:190-231). La lipasa pancreática media el desdoblamiento metabólico de ácidos grasos de triglicéridos en las posiciones de carbono 1- y 3-. El sitio primario del metabolismo de grasas ingeridas están en el duodeno y yeyuno proximal por la lipasa pancreática, la cual usualmente se secreta en bastante exceso de las cantidades necesarias del rompimiento de grasas en el intestino delgado superior. Debido a que la lipasa pancreática es la enzima primaria requerida para la absorción

de triglicéridos dietéticos, los inhibidores tienen utilidad en el tratamiento de obesidad y las otras condiciones relacionadas. La actividad de inhibición de lipasa pancreática se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Meth. Enzymol. 286:190-231).

La lipasa gástrica es una lipasa distinta inmunológicamente que es responsable para aproximadamente 10 a 40% de la digestión de grasas dietéticas. La lipasa gástrica se secreta en respuesta a estimulación mecánica, la ingestión de alimento, la presencia de un alimento graso o por agentes simpáticos. La lipólisis gástrica de grasas ingeridas es de importancia fisiológica en la provisión de ácidos grasos necesarios para provocar actividad de lipasa pancreática en el intestino y también es de importancia para la absorción de grasa en una variedad de condiciones fisiológicas y patológicas asociadas con insuficiencia pancreática. Ver, por ejemplo, Abrams, C.K. y colaboradores, Gastroenterology, 92:125 (1987). La actividad de inhibición de lipasa pancreática se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Meth. Enzymol. 286:190-231).

Una variedad de inhibidores de lipasa gástrica y/o pancreática se conocen por un experto en la técnica. Los inhibidores de lipasa preferidos son aquellos inhibidores que

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se seleccionan del grupo que consiste de lipstatina, tetrahidrolipstatina (orlistat), valilactona, esterastina, ebelactona A, y ebelactona B. El compuesto de tetrahidrolipstatina es especialmente preferido. El inhibidor de lipasa, N-3-trifluorometilfenil-N'-3-cloro-4'-trifluorometilfenilurea, y los diferentes derivados de urea relacionados con este se describen en la Patente de EUA No. 4,405,644. El inhibidor de lipasa, esteracina, se describe en las Patentes de EUA Nos. 4,189,438 y 4,242,453. El inhibidor de lipasa, ciclo-O,O'-[(1,6-hexanediil)-bis-(iminocarbonil)]dioxima, y las diferentes bis(iminocarbonil)dioxinas relacionadas con esta se pueden preparar como se describe en Petersen y colaboradores, Liebig's Annalen, 562:205-229 (1949).

Una variedad de inhibidores de lipasa pancreática se describen en la presente a continuación. Los inhibidores de lipasa pancreática lipstatina, lactona de ácido (2S, 3S, 5S, 7Z, 10Z)-5-[(S)-2-formamido-4-metil-valeriloxi]-2-hexil-3-hidroxi-7,10-hexadecanóico, y tetrahidrolipstatina (orlistat), lactona de ácido (2S, 3S, 5S)-5-[(S)-2-formamido-4-metil-valeriloxi]-2-hexil-3-hidroxi-hexadecanóico 1,3, y la variedad de derivados de N-formileucina sustituidos y estereoisómeros de estos, se describen en la Patente de EUA No. 4,598,089. Por ejemplo, la tetrahidrolipstatina se prepara como se describe en, por ejemplo, las Patentes de EUA

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Nos. 5,274,143; 5,420,305; 5,540,917; y 5,643,874. El inhibidor de lipasa pancreática, FL-386, 1-[4-(2-metilpropil)ciclohexil]-2-[(fenilsulfonil)oxi]etanona, y las variedades de derivados de sulfonato sustituidos relacionados con éste, se describen en la Patente de EUA No. 4,452,813. El inhibidor de lipasa pancreático, WAY-121898, 4-fenoxifenil-4-metilpiperidin-1-il-carboxilato, y los diferentes ésteres de carbamato y sales farmacéuticamente aceptables relacionadas con estos, se describen en las Patente de EUA Nos. 5,512,565; 5,391,571 y 5,602,151. El inhibidor de lipasa pancreática, valilactona, y un proceso para la preparación de este por el cultivo microbial de la cepa *Actinomycetes* MG147-CF2, se describe en Kitahara, y colaboradores, J. Antibiotics, 40(11):1647-1650 (1987). Los inhibidores de lipasa pancreática, ebelactona A y ebelactona B, y un proceso para la preparación de estos por el cultivo microbial de la cepa *Actinomycetes* MG7-G1, se describe en Umezawa y colaboradores, J. Antibiotics, 33:1594-1596 (1980). El uso de las ebelactonas A y B en la supresión de formación de monoglicérido se describe en Japanese Kokai 08-143457, publicada en junio 4, 1996.

Otros compuestos que se comercializan para hiperlipidemia, que incluyen hipercolesterolemia y los cuales se pretende que ayuden a prevenir o tratar ateroesclerosis incluyen secuestrantes de ácido biliar, tales como Welchol®,

Colestid®, LoCholest® y Questran®; y derivado de ácido fíbrico, tales como Atromid®, Lopid® y Tricot®.

La diabetes se puede tratar por administración a un paciente que tiene diabetes (especialmente Tipo II), resistencia a insulina, tolerancia a glucosa dañada, síndrome metabólico, o lo similar, o cualquiera de las complicaciones diabéticas tales como neuropatía, neuropatía, retinopatía o cataratas, de una cantidad terapéuticamente efectiva de un compuesto de la presente invención en combinación con otros agentes (por ejemplo, insulina) que se pueden usar para tratar diabetes. Esto incluye las clases de agentes antidiabéticos (y agentes específicos) descritos en la presente.

Cualquier inhibidor de fosforilasa de glicógeno se puede usar como el segundo agente en combinación con un compuesto de la presente invención. El término inhibidor de fosforilasa de glicógeno se refiere a compuestos que inhiben la bioconversión de glicógeno a glucosa-1-fosfato la cual se cataliza par la enzima de fosforilasa de glicógeno. La actividad de inhibición de fosforilasa de glicógeno se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, J. Med. Chem. 41:2934-2938 (1998)). Una variedad de inhibidores de fosforilasa de glicógeno son conocidos por aquellos expertos en la técnica que incluyen aquellos descritos en WO 96/39384

y WO 96/39385.

Cualquier inhibidor de reductasa de aldosa se puede usar en combinación con un compuesto de la presente invención. El término inhibidor de reductasa de aldolasa se refiere a compuestos que inhiben la bioconversión de glucosa a sorbitol. La cual se cataliza por la enzima de reductasa de aldosa. La inhibición de reductasa de aldosa se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, J. Malone, "Red Celt Sorbitol, an Indicator of Diabetic Control", Diabetes, 29:861-864 (1980)). Una variedad de inhibidores de reductasa aldosa son conocidos para aquellos expertos en la técnica, tales como aquellos descritos en la Patente de EUA No. 6,579,879, la cual incluye 6-(5-cloro-3-metilbenzofuran-2-sulfonil)-2H-piridazin-3-ona.

Cualquier inhibidor de deshidrogenasa de sorbitol se puede usar en combinación con un compuesto de la presente invención. El término inhibidor de deshidrogenasa de sorbitol se refiere a compuestos que inhiben la bioconversión de sorbitol a fructosa la cual se cataliza por la enzima de deshidrogenasa de sorbitol. La actividad de inhibición de deshidrogenasa de sorbitol se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Analyt. Biochem., 280:329-331 (2000)). Una variedad de inhibidores de deshidrogenasa de sorbitol se

conocen, por ejemplo, las Patentes de EUA Nos. 5,728,704 y 5,866,578 describen compuestos y un método para tratar o prevenir complicaciones diabéticas por inhibición de la enzima de deshidrogenasa de sorbitol.

Cualquier inhibidor de glucosidasa se puede usar en combinación con un compuesto de la presente invención. Un inhibidor de glucosidasa inhibe la hidrólisis enzimática de carbohidratos de complejo por hidrolasas de glicosida, por ejemplo, amilasa o maltasa, en azúcares simples biodisponibles, por ejemplo, glucosa. La acción metabólica rápida de glucosidasas, particularmente después de consumo de niveles altos de carbohidratos, resulta en un estado de hiperglucemia alimentaria el cual, en sujetos adiposos o diabéticos, lleva a secreción mejorada de insulina, síntesis de grasa mejorada y una reducción en la degradación de grasa. Después de las hiperglucemias, la hiperglucemia ocurre frecuentemente, debido a los niveles aumentados de insulina presente. Adicionalmente, se sabe que el quimo que permanece en el estómago promueve la producción de jugo gástrico, el cual inicia o favorece el desarrollo de gastritis o úlceras duodenales. En consecuencia, los inhibidores de glucosidasa se sabe que tienen utilidad en la aceleración del paso de carbohidratos a través del estómago e inhiben la absorción de glucosa del intestino. Más aún, la conversión de carbohidratos en lípidos del tejido graso y la incorporación

subsiguiente de grasa alimentaria en los depósitos del tejido graso consecuentemente se reduce o retarda, con el beneficio consecuente de reducción o prevención de las anormalidades dañinas que resultan de esto. La actividad de inhibición de glucosidasa se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Biochemistry, 8:4214 (1969)). Un inhibidor de glucosidasa preferido generalmente incluye un inhibidor de amilasa. Un inhibidor de amilasa es un inhibidor de glucosidasa que inhibe la degradación enzimática de almidón o glicógeno en maltosa. La actividad de inhibición de amilasa se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Meth. Enzymol., 1:149 (1955)). La inhibición de la degradación enzimática es benéfica en la reducción de cantidades de azúcares biodisponibles, que incluyen glucosa y maltosa, y las condiciones dañinas consecuentes que resultan de esto.

Una variedad de inhibidores de glucosidasa son conocidos para un experto en la técnica y ejemplos se proporcionan posteriormente. Los inhibidores de glucosidasa preferidos son aquellos inhibidores que se seleccionan del grupo que consiste de acarbosa, adiposita, voglibosa, miglitol, emiglitato, camiglibosa, tendamistato, trestatina, pradimicina-Q y salbostatina. El inhibidor de glucosidasa, acarbosa, y los diferentes derivados de azúcar amino

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relacionados con este se describen en las Patentes de EUA Nos. 4,062,950 y 4,174,439 respectivamente. El inhibidor de glucosidasa, adiposita, se describe en la Patente de EUA No. 4,254,256. El inhibidor de glucosidasa, voglibosa, 3,4-dideoxi-4-[[2-hidroxi-1-(hidroximetil)etil]amino]-2-C-(hidroximetil)-D-epi-inositol y los diferentes pseudos-aminoazúcares N-sustituidos relacionados con estos, se describen en la Patente de EUA No. 4,701,559. El inhibidor de glucosidasa, miglitol, (2R,3R,4R,5S)-1-(2-hidroxietil)-2-(hidroximetil)-3,4,5-piperidinetriol, y las diferentes 3,4,5-trihidroxipiperidinas relacionadas con éste, se describen en la Patente de EUA No. 4,639,436. El inhibidor de glucosidasa, emiglitato, p-[2-[(2R,3R,4R,5S)-3,4,5-trihidroxi-2-(hidroximetil)piperidino]etoxi]-benzoato de etilo, los diferentes derivados relacionados con este y las sales de adición de ácido farmacéuticamente aceptables de éste, se describen en la Patente de EUA No. 5,192,772. El inhibidor de glucosidasa, MDL-25637, 2,6-dideoxi-7-O-β-D-glucopirano-sil-2,6-imino-D-glicero-L-gluco-heptitol, los diferentes homodisacáridos relacionados con este y las sales de adición de ácido farmacéuticamente aceptables de éste, se describen en la Patente de EUA No. 4,634,765. El inhibidor de glucosidasa, camiglibosa, metil 6-deoxi-6-[(2R,3R,4R,5S)-3,4,5-trihidroxi-2-(hidroximetil)piperidino]-(α-D-glucopiranosida sesquihidrato, los derivados de desoxi-

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nojirimicina relacionados con este, las diferentes sales farmacéuticamente aceptables de éste y los métodos sintéticos para la preparación de este, se describen en las Patentes de EUA Nos. 5,157,116 y 5,504,078. El inhibidor de glucosidasa, salbostatina los diferentes pseudosacáridos relacionados con éste, se describen en la Patente de EUA No. 5,091,524.

Una variedad de inhibidores de amilasa son conocidos por un experto en la técnica. El inhibidor de amilasa, tendamistat y los diferentes péptidos cíclicos relacionados con éste, se describen en la Patente de EUA No. 4,451,455. El inhibidor de amilasa AI-3688 y los diferentes péptidos cíclicos relacionados con éste se desglosan en la Patente de EUA No. 4,623,714. El inhibidor de amilasa, trestatina, que consiste de una mezcla de trestatina A, trestatina B y trestatina C y los diferentes aminoazúcares que contienen trehalosa relacionados con éste se describen en la Patente de EUA No. 4,273,765.

Los compuestos antidiabéticos adicionales, los cuales se pueden usar como el segundo agente en combinación con un compuesto de la presente invención, incluyen, por ejemplo, los siguientes: biguanidas (por ejemplo, metformina), insulina secretagogos (por ejemplo, sulfonilureas y glinidas), glitazonas, agonistas de PPARγ sin glitazona, agonistas de PPARβ, inhibidores de DPP-IV, inhibidores de PDE5, inhibidores de GSK-3, antagonistas de

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glucagón, inhibidores de f-1,6-BPase(Metabasis/Sankyo), GLP-1/análogos (AC 2993, también conocido como exendin-4), insulina e insulina mimética (productos naturales Merck). Otros ejemplos podrían incluir inhibidores PKC-β y anti AGE.

Los compuestos de la presente invención se pueden usar en combinación con agentes anti-obesidad. Cualquier agente anti-obesidad se puede usar como el segundo agente en las combinaciones y ejemplos que se proporcionan en la presente. La actividad anti-obesidad se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar conocidos en la técnica.

Los agentes anti-obesidad apropiados incluyen fenilpropanolamina, efedrina, pseudoefedrina, fentermina, agonistas de receptor adrenérgico $\beta_3$, inhibidores de proteína de transferencia de secreción de apolipoproteína-B /triglicérido microsomal (apo-B/MTP), agonistas de MCR-4-, agonistas de colecistoquinina-A (CCK-A), inhibidores de reabsorción de monoamina (por ejemplo, sibutramina), agentes simpatomiméticos, agentes serotoninérgicos, antagonistas de receptor de canabinoide (CB-1) (por ejemplo, rimonabant descrito en la Patente de EUA No. 5,624,941 (SR-141,716A), compuestos de purina, tales como aquellos descritos en la Publicación de Patente de EUA No. 2004/0092520; compuestos de pirazolo[1,5-a][1,3,5]triazina, tales como aquellos descritos en la Solicitud de Patente de EUA No Provisional No.

10/763,105; y compuestos de pirazolilo e imidazolilo bicíclicos, tales como aquellos descritos en la Solicitud de Patente de EUA No Provisional No. 60/518,280, agonistas de dopamina (por ejemplo, bromocriptina), análogos de receptor de hormona de estimulación de melanocito, agonistas de 5HT2c, antagonistas de hormona de concentración de melanina, leptina (la proteína OB), análogos de leptina, agonistas de receptor de leptina, antagonistas de galanina, inhibidores de lipasa (por ejemplo, tetrahidrolipstatina, esto es orlistat), agonistas de bombesina, agentes anoréxicos (por ejemplo, un agonista de bombesina), antagonistas de Neuropéptido-Y, tiroxina, agentes tiromiméticos, deshidroepiandroesteronas o análogos de estas, agonistas o antagonistas de receptor de glucocorticoide, antagonistas de receptor de orexin, antagonistas de proteína que enlaza urocortina, agonistas de receptor de péptido-1 similar a glucagón, factores neurotróficos filiares (por ejemplo, Axokine™), proteínas relacionadas con agutí humanas (AGRP), antagonistas de receptor de grelina, antagonistas o agonistas inversos de receptor de histamina 3, agonistas de receptor de neuromedin U, y similares. Rimonabant (SR-141,716A también conocidos bajo el nombre comercial de Acomplia™ disponibles de Sanofi-Aventis) se pueden preparar como se describe en la Patente de EUA No. 5,624,941. Otros antagonistas CB-1 apropiados incluyen aquellos descritos en las Patentes de EUA Nos.

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5,747,524, 6,432,984 y 6,518,264; Publicación de Patentes de EUA Nos. US2004/0092520, US2004/0157839, US2004/0214855, y US2004/0214838; Solicitud de Patente de EUA No. 10/971,599; y Publicación de Patentes PCT Nos. WO 02/076949, WO 031075660, WO 04/048317, WO 04/013120, y WO 04/012671.

Los inhibidores de secreción de apolipoproteína-B/proteína de transferencia de triglicérido microsomal (apo-B/MTP) para uso como agentes anti-obesidad son inhibidores MTP selectivos de intestino, tales como dilotapida descrita en la Patente de EUA No. 6,720,351; 4-(4-(4-(4-((2-((4-metil-4H-1,2,4-triazol-3-iltio)metil)-2-(4-clorofenil)-1,3-dioxolan-4-il)metoxi)fenil)piperazin-1-il)fenil)-2-sec-butil-2H-1,2,4-triazol-3(4H)-ona (R103757) descrita en las Patentes de EUA Nos. 5,521,186 y 5,929,075; e implitapida (BAY 13-9952) descrita en la Patente de EUA No. 6,265,431. Como se usa en la presente, el término "selectivo del intestino" significa que el inhibidor de MTP tiene una exposición mayor al tejido gastrointestinal contra la exposición sistémica.

Cualquier tiromimético se puede usar como el segundo agente en combinación con un compuesto de la presente invención. La actividad tiromimética se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, Atherosclerosis, 126: 53-63 (1996)). Una variedad de agentes tiromiméticos son conocidos por aquellos expertos en la técnica, por ejemplo aquellos

descritos en las Patentes de EUA Nos. 4,766,121; 4,826,876; 4,910,305; 5,061,798; 5,284,971; 5,401,772; 5,654,468; y 5,569,674. Otros agentes anti-obesidad incluyen sibutramina la cual se puede preparar como se describe en la Patente de EUA No. 4,929,629 y bromocriptina la cual se puede preparar como se describe en las Patentes de EUA Nos. 3,752,814 y 3,752,888.

Los compuestos de la presente invención también se pueden usar en combinación con otros agentes antihipertensivos. Cualquier agente antihipertensivo se puede usar como el segundo agente en tales combinaciones y ejemplos se proporcionan en la presente. La actividad antihipertensiva se determina fácilmente por aquellos expertos en la técnica de acuerdo con ensayos estándar (por ejemplo, mediciones de presión sanguínea).

Ejemplos de productos comercializados actualmente que contienen agentes antihipertensivos incluyen bloqueadores de canal de calcio, tales como Cardizem®, Adalat®, Calan®, Cardene®, Covera®, Dilacor®, DynaCirc®, Procardia XL®, Sular®, Tiazac®, Vascor®, Verelan®, Isoptin®, Nimotop®, Norvasc®, y Plendile; inhibidores de enzima que convierte angiotensina (ACE), tales como Accupril®, Altace®, Captopril®, Lotensin®, Mavik®, Monopril®, Prinivil®, Univasc®, Vasotec® y Zestril®.

La amlodipina y compuestos de dihidropiridina

relacionados se describen en la Patente de EUA No. 4,572,909, como agentes antiisquémicos y antihipertensivos potentes. La Patente de EUA No. 4,879,303 describe la sal de bencensulfonato de amlodipina (también denominada besilato de amlodipina). La amlodipina y el besilato de amlodipina son bloqueadores de canal de calcio de larga duración y potentes. Como tal, la amlodipina, besilato de amlodipina, maleato de amlodipina y otras sales de adición de ácido farmacéuticamente aceptables de amlodipina tienen utilidad como agentes antihipertensivos y como agentes antiisquémicos. El besilato de amlodipina actualmente se vende como Norvasc®.

Los bloqueadores de canal de calcio los cuales están dentro del alcance de esta invención incluyen, pero no se limitan a: bepridil, el cual se puede preparar como se desglosa en la Patente de EUA No. 3,962,238 o la Re-emisión de EUA No. 30,577; el clentiazem, el cual se puede preparar como se describe en la Patente de EUA No. 4,567,175; el diltiazem, fendilina, la cual se puede preparar como se describe en la Patente de EUA No. 3,262,977; galopamil, el cual se puede preparar como se describe en la Patente de EUA No. 3,261,859; mibefradil, el cual se puede preparar como se describe en la Patente de EUA No. 4,808,605; prenilamina, la cual se puede preparar como se describe en la Patente de EUA No. 3,152,173; semotiadil, el cual se puede preparar como se describe en la Patente de EUA No. 4,786,635; terodilina, la

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cual se puede preparar como se describe en la Patente de EUA No. 3,371,014; verapamil, el cual se puede preparar como se describe en la Patente de EUA No. 3,261,859; aranipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,572,909; barnidipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,220,649; benidipina, la cual se puede preparar como se describe en la Publicación de Solicitud de Patente Europea No. 106,275; cilnidipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,672,068; efonidipina, la cual se puede preparar como se describe en la Patente de EUA No.4,885,284; elgodipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,952,592; felodipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,264,611; isradipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,466,972; lacidipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,801,599; lercanidipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,705,797; manidipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,892,875; nicardipina, la cual se puede preparar como se describe en la Patente de EUA No. 3,985,758; nifedipina, el cual se puede preparar como se describe en la Patente de EUA No. 3,485,847; nilvadipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,338,322; nimodipina, la cual se puede preparar como

se describe en la Patente de EUA No. 3,799,934; nisoldipina, la cual se puede preparar como se describe en la Patente de EUA No. 4,154,839; nitrendipina, la cual se puede preparar como se describe en la Patente de EUA No. 3,799,934; cinarizina, la cual se puede preparar como se describe en la Patente de EUA No. 2,882,271; flunarizina, la cual se puede preparar como se describe en la Patente de EUA No. 3,773,939; lidoflazina, la cual se puede preparar como se describe en la Patente de EUA No. 3,267,104; Iomerizina, la cual se puede preparar como se describe en la Patente de EUA No. 4,663,325; benciclano, el cual se puede preparar como se describe en la Patente Húngara No. 151,865; etafenona, la cual se puede preparar como se describe en la Patente Alemana No. 1,265,758; y perhexilina, la cual se puede preparar como se describe en la Patente Inglesa No. 1,025,578.

Los Inhibidores de Enzima de Conversión de Angiotensina (Inhibidores de ACE) los cuales están dentro del alcance de esta invención incluyen, pero no se limitan a: alacepril, el cual se puede preparar como se describe en la Patente de EUA No. 4,248,883; benazepril, el cual se puede preparar como se describe en la Patente de EUA No. 4,410,520; captopril, el cual se puede preparar como se describe en las Patentes de EUA Nos. 4,046,889 y 4,105,776; ceronapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,462,790; delapril, el cual se puede preparar como se

describe en la Patente de EUA No. 4,385,051; enalapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,374,829; fosinopril, el cual se puede preparar como se describe en la Patente de EUA No. 4,337,201; imadapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,508,727; lisinopril, el cual se puede preparar como se describe en la Patente de EUA No. 4,555,502; moveltopril, el cual se puede preparar como se describe en la Patente Belga No. 893,553; perindopril, el cual se puede preparar como se describe en la Patente de EUA No. 4,508,729; quinapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,344,949; ramipril, el cual se puede preparar como se describe en la Patente de EUA No. 4,587,258; espirapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,470,972; temocapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,699,905; y trandolapril, el cual se puede preparar como se describe en la Patente de EUA No. 4,933,361.

Los antagonistas de receptor de Angiotensina II (antagonistas A-II) los cuales están dentro del alcance de esta invención incluyen, pero no se limitan a: candesartán, el cual se puede preparar como se describe en la Patente de EUA No. 5,196,444; eprosartán, el cual se puede preparar como se describe en la Patente de EUA No. 5,185,351; irbesartán, el cual se puede preparar como se describe en la Patente de

EUA No. 5,270,317; Iosartán, el cual se puede preparar como se describe en la Patente de EUA No. 5,138,069; y valsartán, el cual se puede preparar como se describe en la Patente de EUA No. 5,399,578.

Los bloqueadores de receptor Beta-adrenérgicos (beta- o β-bloqueadores) los cuales están dentro del alcance de esta invención incluyen, pero no se limitan a: acebutolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,857,952; alprenolol, el cual se puede preparar como se describe en la Solicitud de Patente Holandesa No. 6,605,692; amosulalol, el cual se puede preparar como se describe en la Patente de EUA No. 4,217,305; arotinolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,932,400; atenolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,663,607 o 3,836,671 ; befunolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,853,923; betaxolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,252,984; bevantolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,857,981; bisoprolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,171,370; bopindolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,340,541; bucumolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,663,570; bufetolol, el cual se puede preparar como se describe en la

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Patente de EUA No. 3,723,476; bufuralol, el cual se puede preparar como se describe en la Patente de EUA No. 3,929,836; bunitrolol, el cual se puede preparar como se describe en las Patentes de EUA Nos. 3,940,489 y 3,961,071; buprandolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,309,406; clorhidrato de butiridina, el cual se puede preparar como se describe en la Patente Francesa No. 1,390,056; butofilolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,252,825; carazolol, el cual se puede preparar como se describe en la Patente Alemana No. 2,240,599; carteolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,910,924; carvedilol, el cual se puede preparar como se describe en la Patente de EUA No. 4,503,067; celiprolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,034,009; cetamolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,059,622; cloranolol, el cual se puede preparar como se describe en la Patente Alemana No. 2,213,044; dilevalol, el cual se puede preparar como se describe en Clifton y colaboradores, J. Med. Chem., 25:670 (1982); epanolol, el cual se puede preparar como se describe en la Solicitud de Publicación de Patente Europea No. 41,491; indenolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,045,482; labetalol, el cual se puede preparar como se describe en la Patente de EUA No. 4,012,444; levobunolol, el

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cual se puede preparar como se describe en la Patente de EUA No. 4,463,176; mepindolol, el cual se puede preparar como se describe en Seeman y colaboradores, Heir. Chim. Acta, 54:241 (1971); metipranolol, el cual se puede preparar como se describe en la Solicitud de Patente Checoeslovaca No. 128,471; metoprolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,873,600; moprolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,501,7691; nadolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,935, 267; nadoxolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,819,702; nebivalol, el cual se puede preparar como se describe en la Patente de EUA No. 4,654,362; nipradilol, el cual se puede preparar como se describe en la Patente de EUA No. 4,394,382; oxprenolol, el cual se puede preparar como se describe en la Patente Inglesa No. 1,077,603; perbutolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,551,493; pindolol, el cual se puede preparar como se describe en las Patentes de Suiza Nos. 469,002 y 472,404; practolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,408,387; pronetalol, el cual se puede preparar como se describe en la Patente Inglesa No. 909,357; propranolol, el cual se puede preparar como se describe en las Patente de EUA Nos. 3,337,628 y 3,520,919; sotalol, el cual se puede preparar como se describe en Uloth y

colaboradores, J. Med. Chem., 9:88 (1966); sufinalol, el cual se puede preparar como se describe en la Patente Alemana No. 2,728,641; talindol, el cual se puede preparar como se describe en las Patentes de EUA Nos. 3,935,259 y 4,038,313; tertatolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,960,891; tilisolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,129,565; timolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,655,663; toliprolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,432,545; y xibenolol, el cual se puede preparar como se describe en la Patente de EUA No. 4,018,824.

Los bloqueadores de receptor alfa-adrenérgico (alfa- o α-bloqueadores) los cuales están dentro del alcance de esta invención incluyen, pero no se limitan a: amosulalol, el cual se puede preparar como se describe en la Patente de EUA No. 4,217,307; arotinolol, el cual se puede preparar como se describe en la Patente de EUA No. 3,932,400; dapiprazol, el cual se puede preparar como se describe en la Patente de EUA No. 4,252,721; doxazosina, la cual se puede preparar como se describe en la Patente de EUA No. 4,188,390; fenspirida, la cual se puede preparar como se describe en la Patente de EUA No. 3,399,192; indoramina, la cual se puede preparar como se describe en la Patente de EUA No. 3,527,761; labetolol; naftopidil, el cual se puede preparar como se describe en la

Patente de EUA No. 3,997,666; nicergolina, la cual se puede preparar como se describe en la Patente de EUA No. 3,228,943; prazosina, la cual se puede preparar como se describe en la Patente de EUA No. 3,511,836; tamsulosina, la cual se puede preparar como se describe en la Patente de EUA No. 4,703,063; tolazolina, la cual se puede preparar como se describe en la Patente de EUA No. 2,161,938; trimazosina, la cual se puede preparar como se describe en la Patente de EUA No. 3,669,968; e yohimbina, la cual se puede aislar de fuentes naturales de acuerdo con métodos bien conocidos para aquellos expertos en la técnica.

El término "vasodilatador", cuando se usa en la presente, se pretende que incluya vasodilatadores cerebrales, vasodilatadores coronarios y vasodilatadores periféricos. Los vasodilatadores cerebrales dentro del alcance de esta invención incluyen, pero no se limitan a: benciclano; cinarizina; citicolina, la cual se puede aislar de fuentes naturales como se describe en Kennedy y colaboradores, J. Am. Chem. Soc., 77:250 (1955) o se sintetiza como se describe en Kennedy, J. Biol. Chem., 222:185 (1956); ciclandelato, el cual se puede preparar como se describe en la Patente de EUA No. 3,663,597; ciclonicato, el cual se puede preparar como se describe en la Patente Alemana No. 1,910,481; dicloroacetato de diisopropilamina, el cual se puede preparar como se describe en la Patente Inglesa No. 862,248; eburnamonina, la

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cual se puede preparar como se describe en Hermann y colaboradores, J. Am. Chem. Soc., 101:1540 (1979); fasudilo, el cual se puede preparar como se describe en la Patente de EUA No. 4,678,783; fenoxedilo, el cual se puede preparar como se describe en la Patente de EUA No. 3,818,021; flunarizina, la cual se puede preparar como se describe en la Patente de EUA No. 3,773,939; ibudilast, el cual se puede preparar como se describe en la Patente de EUA No. 3,850,941; ifenprodilo, el cual se puede preparar como se describe en la Patente de EUA No. 3,509,164; Iomerizina, la cual se puede preparar como se describe en la Patente de EUA No. 4,663,325; nafronilo, el cual se puede preparar como se describe en la Patente de EUA No. 3,334,096; nicametato, el cual se puede preparar como se describe en Blicke y colaboradores, J. Am. Chem. Soc., 64:1722 (1942); nicergolina, la cual se puede preparar como se describe anteriormente; nimodipina, la cual se puede preparar como se describe en la Patente de EUA No. 3,799,934; papaverina, la cual se puede preparar como se revisó en Goldberg, Chem. Prod. Chem. News, 17:371 (1954); pentifilina, la cual se puede preparar como se describe en la Patente Alemana No. 860,217; tinofedrina, la cual se puede preparar como se describe en la Patente de EUA No. 3,563,997; vincamina, la cual se puede preparar como se describe en la Patente de EUA No. 3,770,724; vinpocetina, la cual se puede preparar como se describe en la Patente de EUA No. 4,035,750;

y viquidilo, el cual se puede preparar como se describe en la Patente de EUA No. 2,500,444.

Los vasodilatadores coronarios dentro del alcance de esta invención incluyen, pero no se limitan a: amotrifeno, el cual se puede preparar como se describe en la Patente de EUA No. 3,010,965; bendazol, el cual se puede preparar como se describe en J. Chem. Soc., 2426 (1958); hemisuccinato de benfurodil, el cual se puede preparar como se describe en la Patente de EUA No. 3,355,463; benziodarona, la cual se puede preparar como se describe en la Patente de EUA No. 3,012,042; cloracizina, la cual se puede preparar como se describe en la Patente Inglesa No. 740,932; cromonar, el cual se puede preparar como se describe en la Patente de EUA No. 3,282,938; clobenfural, el cual se puede preparar como se describe en la Patente Inglesa No. 1,160,925; clonitrato, el cual se puede preparar a partir de propanediol de acuerdo a métodos bien conocidos para aquellos expertos en la técnica, por ejemplo, ver Annalen, 1870, 155, 165; cloricromen, el cual se puede preparar como se describe en la Patente de EUA No. 4,452,811; dilazep, el cual se puede preparar como se describe en la Patente de EUA No. 3,532,685; dipiridamol, el cual se puede preparar como se describe en la Patente Inglesa No. 807,826; droprenilamina, la cual se puede preparar como se describe en la Patente de Alemania No. 2,521,113; efloxato, el cual se puede preparar como se describe en las Patentes de Inglaterra

Nos. 803,372 y 824,547; tetranitrato de eritritilo, la cual se puede preparar por nitración de eritritol de acuerdo a métodos bien conocidos para aquellos expertos en la técnica; etafenona, la cual se puede preparar como se describe en la Patente de Alemania No. 1,265,758; fendilina, la cual se puede preparar como se describe en la Patente de EUA No. 3,262,977; floredilo, el cual se puede preparar como se describe en la Patente de Alemania No. 2,020,464; ganglefeno, el cual se puede preparar como se describe en la Patente de U.S.S.R. No. 115,905; hexestrol, el cual se puede preparar como se describe en la Patente de EUA No. 2,357,985; hexobendina, la cual se puede preparar como se describe en la Patente de EUA No. 3,267,103; tosilato de itramina, el cual se puede preparar como se describe en la Patente Sueca No. 168,308; khellin (biznaga), el cual se puede preparar como se describe en Baxter y colaboradores, J. Chem. Soc., 1949, S 30; lidoflazina, la cual se puede preparar como se describe en la Patente de EUA No. 3,267,104; hexanitrato de manitol, el cual se puede preparar por la nitración de manitol de acuerdo con los métodos bien conocidos para aquellos expertos en la técnica;; medibazina, la cual se puede preparar como se describe en la Patente de EUA No. 3,119,826; nitroglicerina; tetranitrato de pentaeritritol, el cual se puede preparar por la nitración de pentaeritritol de acuerdo con los métodos bien conocidos para aquellos expertos en la técnica;

pentrinitrol, el cual se puede preparar como se describe en la Patente de Alemania No. 638,422-3; perhexilina, la cual se puede preparar como se describe anteriormente; pimefilina, la cual se puede preparar como se describe en la Patente de EUA No. 3,350,400; prenilamina, la cual se puede preparar como se describe en la Patente de EUA No. 3,152,173; nitrato de propatilo, el cual se puede preparar como se describe en la Patente Francesa No. 1,103,113; trapidil, el cual se puede preparar como se describe en la Patente de Alemania del Este No. 55,956; tricromilo, el cual se puede preparar como se describe en la Patente de EUA No. 2,769,015; trimetazidina, la cual se puede preparar como se describe en la Patente de EUA No. 3,262,852; fosfato de trolnitrato, el cual se puede preparar por nitración de trietanolamina seguida por precipitación con ácido fosfórico de acuerdo con los métodos bien conocidos para aquellos expertos en la técnica; visnadina, la cual se puede preparar como se describe en las Patentes de EUA Nos. 2,816,118 y 2,980,699.

Los vasodilatadores periféricos dentro del alcance de esta invención incluyen, pero no se limitan a: nicotinato de aluminio, el cual se puede preparar como se describe en la Patente de EUA No. 2,970,082; bametán, el cual se puede preparar como se describe en Corrigan y colaboradores, J. Am. Chem. Soc., 67:1894 (1945); benciclano, el cual se puede preparar como se describe anteriormente; betahistina, la cual

se puede preparar como se describe en Walter y colaboradores, J. Am. Chem. Soc., 63:2771 (1941); bradiquinina, el cual se puede preparar como se describe en Hamburg y colaboradores, Arch. Biochem. Biophys., 76:252 (1958); brovincamina, la cual se puede preparar como se describe en la Patente de EUA No. 4,146,643; bufeniodo, el cual se puede preparar como se describe en la Patente de EUA No. 3,542,870; buflomedilo, el cual se puede preparar como se describe en la Patente de EUA No. 3,895,030; butalamina, la cual se puede preparar como se describe en la Patente de EUA No. 3,338,899; cetiedil, el cual se puede preparar como se describe en la Patente de Francia No. 1,460,571; ciclonicato, el cual se puede preparar como se describe en la Patente de Alemania No. 1,910,481; cinepazida, la cual se puede preparar como se describe en la Patente Belga No. 730,345; cinarizina, la cual se puede preparar como se describe anteriormente; ciclandelato, el cual se puede preparar como se describe anteriormente; dicloroacetato de diisopropilamina, el cual se puede preparar como se describe anteriormente; eledoisina, la cual se puede preparar como se describe en la Patente de Inglaterra No. 984,810; fenoxedil, el cual se puede preparar como se describe anteriormente; flunarizina, la cual se puede preparar como se describe anteriormente; hepronicato, el cual se puede preparar como se describe en la Patente de EUA No. 3,384,642; ifenprodil, el cual se puede preparar como se

describe anteriormente; iloprost, el cual se puede preparar como se describe en la Patente de EUA No. 4,692,464; niacinato de inositol, el cual se puede preparar como se describe en Badgett y colaboradores, J. Am. Chem. Soc., 69:2907 (1947); isoxsuprina, la cual se puede preparar como se describe en la Patente de EUA No. 3,056,836; calidin, el cual se puede preparar como se describe en Biochem. Biophys. Res. Commun., 6:210 (1961); calicreina, el cual se puede preparar como se describe en la Patente de Alemania No. 1,102,973; moxisilito, el cual se puede preparar como se describe en la Patente de Alemania No. 905,738; nafronilo, el cual se puede preparar como se describe anteriormente; nicametato, el cual se puede preparar como se describe anteriormente; nicergolina, la cual se puede preparar como se describe anteriormente; nicofuranosa, la cual se puede preparar como se describe en la Patente Suiza No. 366,523; nilidrin, el cual se puede preparar como se describe en las Patentes de EUA Nos. 2,661,372 y 2,661,373; pentifilina, la cual se puede preparar como se describe anteriormente; pentoxifilina, la cual se puede preparar como se describe en la Patente de EUA No. 3,422,107; piribedil, el cual se puede preparar como se describe en la Patente de EUA No. 3,299,067; prostaglandina $E_1$, el cual se puede preparar por cualquiera de los métodos referenciados en el Merck Index, Doceava Edición, Budaveri, Ed., New Jersey, p. 1353 (1996);

suloctidilo, el cual se puede preparar como se describe en la Patente de Alemania No. 2,334,404; tolazolina, la cual se puede preparar como se describe en la Patente de EUA No. 2,161,938; y niacinato de xantinol, el cual se puede preparar como se describe en la Patente de Alemania No. 1,102,750.

El término "diurético", dentro del alcance de esta invención, se pretende que incluya derivados de benzotiadiazina diuréticos, organomercuriales diuréticos, purinas diuréticas, esteroides diuréticos, derivados de sulfonamida diuréticos, uracilos diuréticos y otros diuréticos tales como amanozina, la cual se puede preparar como se describe en la Patente de Austria No. 168,063; amilorida, la cual se puede preparar como se describe en la Patente de Bélgica No. 639,386; arbutina, la cual se puede preparar como se describe en Tschitschibabin, Annalen, 1930, 479, 303; clorazanilo, el cual se puede preparar como se describe en la Patente de Austria No. 168,063; ácido etacrínico, el cual se puede preparar como se describe en la Patente de EUA No. 3,255,241; etozolin, el cual se puede preparar como se describe en la Patente de EUA No. 3,072,653; hidracarbazina, la cual se puede preparar como se describe en la Patente de Inglaterra No. 856,409; isosorbida, la cual se puede preparar como se describe en la Patente de EUA No. 3,160,641; manitol; metocalcona, la cual se puede preparar como se describe en Freudenberg y colaboradores, Ber., 1957,

90, 957; muzolimina, la cual se puede preparar como se describe en la Patente de EUA No. 4,018,890; perhexilina, la cual se puede preparar como se describe anteriormente; ticrinafen, el cual se puede preparar como se describe en la Patente de EUA No. 3,758,506; triamtereno el cual se puede preparar como se describe en la Patente de EUA No. 3,051,230; y urea.

Los derivados de benzotiadiazina diuréticos dentro del alcance de esta invención incluyen, pero no se limitan a: altiazida, la cual se puede preparar como se describe en la Patente de Inglaterra No. 902,658; bendroflumetiazida, la cual se puede preparar como se describe en la Patente de EUA No. 3,265,573; benztiazida, McManus y colaboradores, 136th Am. Soc. Meeting (Atlantic City, September 1959), Abstract of papers, pp 13-O; bencilhidroclorotiazida, la cual se puede preparar como se describe en la Patente de EUA No. 3,108,097; butiazida, la cual se puede preparar como se describe en las Patentes de Inglaterra Nos. 861,367 y 885,078; clorotiazida, la cual se puede preparar como se describe en las Patentes de EUA Nos. 2,809,194 y 2,937,169; clortalidona, la cual se puede preparar como se describe en la Patente de EUA No. 3,055,904; ciclopentiazida, la cual se puede preparar como se describe en la Patente de Bélgica No. 587,225; ciclotiazida, la cual se puede preparar como se describe en Whitehead y colaboradores, J. Org. Chem., 26:2814 (1961); epitiazida, la

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cual se puede preparar como se describe en la Patente de EUA No. 3,009,911; etiazida, la cual se puede preparar como se describe en la Patente de Inglaterra No. 861,367; fenquizona, el cual se puede preparar como se describe en la Patente de EUA No. 3,870,720; indapamida, la cual se puede preparar como se describe en la Patente de EUA No. 3,565,911; hidroclorotiazida, la cual se puede preparar como se describe en la Patente de EUA No. 3,164,588; hidroflumetiazida, la cual se puede preparar como se describe en la Patente de EUA No. 3,254,076; meticlotiazida, la cual se puede preparar como se describe en Close y colaboradores, J. Am. Chem. Soc., 82:1132 (1960); meticrano, el cual se puede preparar como se describe en las Patentes de Francia Nos. M2790 y 1,365,504; metolazona, la cual se puede preparar como se describe en la Patente de EUA No. 3,360,518; paraflutizida, la cual se puede preparar como se describe en la Patente de Bélgica No. 620,829; politiazida, la cual se puede preparar como se describe en la Patente de EUA No. 3,009,911; quinetazona, la cual se puede preparar como se describe en la Patente de EUA No. 2,976,289; teclotiazida, la cual se puede preparar como se describe en Close y colaboradores, J. Am. Chem. Soc., 82:1132 (1960); y triclormetiazida, la cual se puede preparar como se describe en de Stevens y colaboradores, Experientia, 16:113 (1960).

Los derivados de sulfonamida diuréticos dentro del

alcance de esta invención incluyen, pero no se limitan a: acetazolamida, la cual se puede preparar como se describe en la Patente de EUA No. 2,980,679; ambusida, la cual se puede preparar como se describe en la Patente de EUA No. 3,188,329; azosemida, la cual se puede preparar como se describe en la Patente de EUA No. 3,665,002; bumetanida, la cual se puede preparar como se describe en la Patente de EUA No. 3,634,583; butazolamida, la cual se puede preparar como se describe en la Patente de Inglaterra No. 769,757; cloraminofenamida, la cual se puede preparar como se describe en las Patentes de EUA Nos. 2,809,194, 2,965,655 y 2,965,656; clofenamida, la cual se puede preparar como se describe en Olivier, Rec. Trav. Chim., 1918, 37, 307; clopamida, la cual se puede preparar como se describe en la Patente de EUA No. 3,459,756; clorexolona, la cual se puede preparar como se describe en la Patente de EUA No. 3,183,243; disulfamida, la cual se puede preparar como se describe en la Patente de Inglaterra No. 851,287; etoxolamida, la cual se puede preparar como se describe en la Patente de Inglaterra No. 795,174; furosemida, la cual se puede preparar como se describe en la Patente de EUA No. 3,058,882; mefrusida, la cual se puede preparar como se describe en la Patente de EUA No. 3,356,692; metazolamida, la cual se puede preparar como se describe en la Patente de EUA No. 2,783,241; piretanida, la cual se puede preparar como se describe en la Patente de EUA No. 4,010,273; torasemida,

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el cual se puede preparar como se describe en la Patente de EUA No. 4,018,929; tripamida, la cual se puede preparar como se describe en la Patente Japonesa No. 73 05,585; y xipamida, la cual se puede preparar como se describe en la Patente de EUA No. 3,567,777.

La osteoporosis es una enfermedad ósea sistémica, caracterizada por masa ósea baja y deterioro de tejido óseo, con un aumento consecuente en fragilidad de hueso y susceptibilidad a fractura, en los Estados Unidos, la condición afecta a más de 25 millones de personas y provoca más de 1.3 millones de fracturas cada año, que incluyen 500,000 de columna, 250,000 de cadera y 240,000 fracturas de muñeca anualmente. Las fracturas de cadera son las de consecuencias más serias de osteoporosis, con 5-20% de pacientes que mueren al año, y más de 50% de los sobrevivientes que son incapacitados. La gente mayor son los de más riesgo de osteoporosis, y el problema por lo tanto se predice que aumente significativamente a medida que envejezca la población. La incidencia de fractura a nivel mundial se proyecta que aumente tres veces durante los próximos 60 años, y un estudio ha estimado que habrá 4.5 millones de fracturas de cadera en el mundo en 2050. Las mujeres están en mayor riesgo de osteoporosis que los hombres. Las mujeres experimentan una aceleración aguda de pérdida de hueso durante los cinco años después de la menopausia. Otros

factores que aumentan el riesgo incluyen el fumar, abuso de alcohol, una vida sedentaria y consumo de calcio bajo.

Aquellos expertos en la técnica reconocerán que los agentes anti-re-absorbentes (por ejemplo, progestágenos, polifosfonatos, bisfosfonato(s), agonistas/antagonistas de estrógeno, estrógeno, combinaciones de estrógeno/ progestágenos, Premarin®, estrona, estriol o 17α- o 17β-etinil estradiol) se puede usar en conjunto con los compuestos de la presente invención.

Los progestágenos ejemplares están disponibles de fuentes comerciales e incluyen: acetofenida de algestona, altrenogest, acetato de amadinona, acetato de anagestona, acetato de clormadinona, cingestol, acetato de clogestona, acetato de clomegestona, acetato de delmadinona, desogestrel, dimetisterona, dihidrogesterona, etinerona, diacetato de etinodiol, etonogestrel, acetato de flurogestona, gestaclona, gestodeno, caproato de gestonorona, gestrinona, haloprogesterona, caproato de hidroxiprogesterona, levonorgestrel, lynestrenol, medrogestona, acetato de medroxiprogesterona, acetato de melengestrol, diacetato de metinodiol, noretindrona, acetato de noretindrona, noretinodrel, norgestimato, norgestomet, norgestrel, fenproprionato de oxogestona, progesterona, acetato de quingestanol, quingestrona, y tigestol. Los progestágenos preferidos son medroxiprogestrona, noretindrona y

noretinedrel.

Ejemplarmente la resorción de hueso que inhibe los polifosfonatos incluye fosfonatos del tipo descrito en la Patente de EUA No. 3,683,080. Los polifosfonatos preferidos son difosfonatos geminales (también referidos como bis-fosfonatos). El tiludronato de disodio es un polifosfonato especialmente preferido. El ácido ibandrónico es un polifosfonato especialmente preferido. El alendronato y resindronato son polifosfonatos especialmente preferidos. El ácido Zoledrónico es un polifosfonato especialmente preferido. Otros polifosfonatos preferidos son ácido 6-amino-1-hidroxi-hexilidene-bisfosphónico y ácido 1-hidroxi-3(metilpentilamino)-propiliden-bisfosfónico. Los polifosfonatos se pueden administrar en la forma del ácido, o de una sal de metal de álcali soluble o sal de metal de tierra alcalina. Los ésteres hidrolizables de los polifosfonatos están incluidos de esta manera. Ejemplos específicos incluyen ácido etano-1-hidroxi 1,1-difosfónico, ácido metano difosfónico, ácido pentano-1-hidroxi-1,1-difosfónico, ácido metano dicloro difosfónico, ácido metano hidroxi difosfónico, ácido etano-1-amino-1,1-difosfónico, ácido etano-2-amino-1,1-difosfónico, ácido propano-3-amino-1-hidroxi-1,1-difosfónico, ácido propano-N,N-dimetil-3-amino-1-hidroxi-1,1-difosfónico, ácido propano-3,3-dimetil-3-amino-1-hidroxi-1,1-difosfónico, ácido fenil amino metano

difosfónico, ácido N,N-dimetilamino metano difosfónico, ácido N-(2-hidroxietil) amino metano difosfónico, ácido butano-4-amino-1-hidroxi-1,1-difosfónico, ácido pentano-5-amino-1-hidroxi-1,1-difosfónico, ácido hexano-6-amino-1-hidroxi-1,1-difosfónico y ésteres y sales farmacéuticamente aceptables de estos.

En particular, los compuestos de esta invención se pueden combinar con un agonista/antagonista de estrógeno de mamífero. Cualquier agonista/antagonista de estrógeno se puede usar en el aspecto de combinación de esta invención. El término agonista/antagonista de estrógeno se refiere a compuestos los cuales se enlazan con el receptor de estrógeno, inhiben la rotación ósea y/o previene la pérdida de hueso. En particular, los agonistas de estrógeno se definen en la presente como compuestos químicos capaces de enlazarse a los sitios de receptor de estrógeno en tejido mamífero, y que imitan las acciones del estrógeno en uno o más tejidos. Los antagonistas de estrógeno se definen en la presente como compuestos químicos capaces de enlazarse a los sitios de receptor de estrógeno en tejido mamífero, y que bloquean las acciones del estrógeno en uno o más tejidos. Las actividades se determinan fácilmente por aquellos expertos en la técnica de ensayos estándar que incluyen ensayos de enlace de receptor de estrógeno, métodos histomorfométricos óseos estándar y de desitómetro (Eriksen E.F. y colaboradores, Bone

Histomorphometry, Raven Press, New York, pp. 1-74 (1994); Grier, S.J. y colaboradores, "The Use of Dual-Energy X-Ray Absorptiometry In Animals", Inv. Radiol., 31(1):50-62 (1996); Wahner H.W. y colaboradores, The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London, pp. 1-296 (1994)). Una variedad de estos compuestos se describen y se hace referencia posteriormente. Otro agonista/antagonista de estrógeno preferido es el ácido 3-(4-(1,2-difenil-but-1-enil)-fenil)-acrílico, el cual se describe en Willson y colaboradores, Endocrinology, 138:3901-3911 (1997). Otro agonista/antagonista de estrógeno preferido es el tamoxifeno: (etanamina,2-(-4-(1,2-difenil-1-butenil)fenoxi)-N,N-dimetil, (Z)-2-, 2-hidroxi-1,2,3-propanetricarboxilato(1:1)) y compuestos relacionados los cuales se describen en la Patente de EUA No. 4,536,516. Otro compuesto relacionado es el 4-hidroxi tamoxifeno, el cual se describe en la Patente de EUA No. 4,623,660. Un agonista/antagonista de estrógeno preferido es el raloxifeno: (metanona, (6-hidroxi-2-(4-hidroxifenil)benzo[b]tien-3-il)(4-(2-(1-piperidinil)etoxi)fenil)clorohidrato) el cual se describe en la Patente de EUA No. 4,418,068. Otro agonista/antagonista de estrógeno preferido es el toremifeno: (etanamina, 2-(4-(4-cloro-1,2-difenil-1-butenil)fenoxi)-N,N-dimetil-, (Z)-, 2-hydroxi-1,2,3-propanetricarboxilato (1:1) el cual se describe

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en la Patente de EUA No. 4,996,225. Otro agonista/antagonista de estrógeno preferido es el centcroman: 1-(2-((4-(-metoxi-2,2, dimetil-3-fenil-croman-4-il)-fenoxi)-etil)-pirrolidina, el cual se describe en la Patente de EUA No. 3,822,287. También se prefiere el levormeloxifeno.

Otro agonista/antagonista de estrógeno preferido es el idoxifeno: (E)-1-(2-(4-(1-(4-iodo-fenil)-2-fenil-but-1-enil)-fenoxi)-etil)-pirrolidinona, el cual se describe en la Patente de EUA No. 4,839,155. Otro agonista/antagonista de estrógeno preferido es el 2-(4-metoxi-fenil)-3-[4-(2-piperidin-1-il-etoxi)-fenoxi]- benzo[b]tiofen-6-ol, el cual se describe en la Patente de EUA No. 5,488,058. Otro agonista/antagonista de estrógeno preferido es el 6-(4-hidroxi-fenil)-5-(4-(2-piperidin-1-il-etoxi)-bencil)-naftalen-2-ol, el cual se describe en la Patente de EUA No. 5,484,795. Otro agonista/antagonista de estrógeno preferido es el (4-(2-(2-aza-biciclo[2.2.1]hept-2-il)-etoxi)-fenil)-(6-hidroxi-2-(4-hidroxifenil)-benzo[b]tiopen-3-il)-metanona el cual se describe, junto con métodos de preparación, en la Publicación PCT No. WO 95/10513. Otro agonista/antagonista de estrógeno preferido incluye los compuestos, TSE-424 (Wyeth-Ayerst Laboratories) y arazoxifeno.

Otros agonistas/antagonistas de estrógeno preferidos incluyen compuestos como se describen en la Patente de EUA No. 5,552,412. Los compuestos especialmente

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preferidos descritos en ella son: *cis*-6-(`4-fluoro-fenil)-5-(4-(2-piperidin-1-il-etoxi)-fenil)-5,6,7,8-tetrahidronaftaleno-2-ol; (-)-*cis*-6-fenil-5-(4-(2-pirrolidin-1-il-etoxi)-fenil)-5,6,7,8-tetrahidronaftaleno-2-ol (también conocido como lasofoxifeno); *cis*-6-fenil-5-(4-(2-pirrolidin-1-il-etoxi)-fenil)-5,6,7,8-tetrahidronaftaleno-2-ol; *cis*-1-(6'-pirrolodinoetoxi-3'-piridil)-2-fenil-6-hidroxi-1,2,3,4-tetrahidronaftaleno; 1-(4'-pirrolidinoetoxifenil)-2-(4"-fluorfenil)-6-hidroxi-1,2,3,44etrahidroisoquinoline; *cis*-6-(4-hidroxifenil)-5-(4-(2-piperidin-1-il-etoxi)-fenil)-5,6,7,8-tetrahidronaftaleno-2-ol; y 1-(4'-pirrolidinoletoxifenil)-2-fenil-6-hidroxi-1,2,3,4-tetrahidroisoquinolina.

Otros agonistas/antagonistas de estrógeno se describen en la Patente de EUA No. 4,133,814, la cual describe derivados de 2-fenil-3-aroil-benzotiofeno y 2-fenil-3-aroilbenzotiofeno-1-oxido.

Otros agentes anti-osteoporosis, los cuales se pueden usar como el segundo agente en combinación con un compuesto de la presente invención, incluye, por ejemplo, la siguiente: hormona paratifoidea (PTH) (un agente anabólico óseo); hormona paratifoidea (PTH) secretagogos (ver, por ejemplo, la Patente de EUA No. 6,132,774), particularmente antagonistas de receptor de calcio; calcitonina; vitamina D y análogos de vitamina D.

Cualquier modulador de receptor de andrógeno selectivo (SARM) se puede usar en combinación con un compuesto de la presente invención. Un modulador de receptor de andrógeno selectivo (SARM) es un compuesto que posee actividad androgénica y el cual ejerce efectos selectivos de tejido. Los compuestos SARM pueden funcionar como agonistas de receptor de andrógeno, agonistas parciales, antagonistas parciales o antagonistas. Ejemplos de SARM apropiados incluyen compuestos tales como acetato de ciproterona, clormadinona, flutamida, hidroxiflutamida, bicalutamida, nilutamida, espironolactona, derivados de 4-(trifluorometil)-2(1H)-pirrolidino[3,2-g] quinolina, derivados de 1,2-dihidropiridino [5,6-g]quinolina y derivados de piperidino[3,2-g]quinolinona.

La cipterona, también conocida como (1*b*,2*b*)-6-cloro-1,2-dihidro-17-hidroxi-3'H-ciclopropa[1,2]pregna-1,4,6-trien-3,20-diona se describe en la Patente de EUA No. 3,234,093. La clormadinona, también conocida como 17-(acetiloxi)-6-cloropregna-4-,6-diene-3,20-diona, en su forma de acetato, actúa como un anti-andrógeno y se describe en la Patente de EUA No. 3,485,852. La nilutamida, también conocida como 5,5-dimetil-3-[4-nito-3-(trifluorometil)fenil]-2,4-imidazolidinediona y por el nombre comercial Nilandron® se describe en la Patente de EUA No. 4,097,578. La flutamida, también conocida como 2-metil-N-[4-nitro-3-

(trifluorometil)fenil]propanamida y el nombre comercial Eulexin® se describe en la Patente de EUA No. 3,847,988. La bicalutamida, también conocida como 4'-ciano-a',a',a'-trifluoro-3-(4-fluorofenilsulfonil)-2-hidroxi-2-metilpropiono-*m*-toluidida y el nombre comercial Casodex® se describe en EP-100172. Los enantiómeros de bicultamida se describen por Tucker y colaboradores, J. Med. Chem., 31:885-887 (1988). La hidroxiflutamida, un antagonista de receptor de andrógeno conocido en la mayoría de tejidos, se ha sugerido que funcione como un SARM para efectos en la producción de IL-6 por osteoblastos y se describe en Hofbauer y colaboradores, J. Bona Miner. Res., 14:1330-1337 (1999). Los SARM adicionales se han descrito en la Patente de EUA No. 6,017,924; WO 01/16108, WO 01/16133, WO 01/16139, WO 02/00617, WO 02/16310, Publicación de Solicitud de Patente de EUA No. US 2002/0099096, Publicación de Solicitud de Patente de EUA No. US 2003/0022868, WO 03/011302 y WO 03/011824.

Cualquier compuesto que tiene actividad como un modulador de LXR puede servir como el segundo compuesto en el aspecto de terapia de combinación de la presente invención. El término modulador LXR se refiere a compuestos que modulan el receptor X de hígado (LXR), el cual se ha identificado como un regulador de metabolismo de colesterol celular y de todo el cuerpo. La actividad de modulación LXR se determina fácilmente por aquellos expertos en la técnica de acuerdo con

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ensayos estándar (por ejemplo, la Patente de EUA No. 6,140,343). Una variedad de moduladores LXR serán conocidos para aquellos expertos en la técnica, por ejemplo, aquellos descritos en las Publicaciones de Solicitud de Patente de EUA Nos. 2003/01814206, 2005/0080111, y 2005/0245515.

Todas las patentes referidas arriba y solicitudes de patente se incorporan para referencia en la presente.

Las combinaciones pueden co-formularse en la forma de kits para proporcionar las dosis apropiadas para co-administración.

Los otros agentes terapéuticos de arriba, cuando se emplean en combinación con los compuestos de la presente invención, pueden usarse, por ejemplo, en aquellas cantidades indicadas en el Physicians' Desk Reference (PDR) o como se determina de otra manera por un experto en la técnica.

Los siguientes ejemplos ilustran además la presente invención, pero por supuesto, no se construirán de ninguna manera como limitante de su alcance.

Se usan las siguientes abreviaturas en la presente:

ee = exceso enantiomérico

DMF = dimetilformamida

EtOAc = acetato de etilo

LDA = diisopropilamida de litio

Base Hünig = DIEA = $iPr_2Net$ = N,N-diisopropiletilamina

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Me = metilo

Et = etilo

n-Bu = n-butilo

Bn = bencilo

iPr = isopropilo

Alilo = 1-propenilo

TR = tiempo de retención

TFA = ácido trifluoroacético

THF = tetrahidrofurano

CCD = cromatografía de capa delgada

TMS = trimetilsililo

t-Bu = ter-butilo

MeI = yoduro de metilo

$(BOC)_2O$ = bicarbonato de di-ter-butilo

Ac2O = anhídrido acético

TEA = $NEt_3$ = $Et_3N$ = trietilamina

n-BuLi = n-butil-litio

ta = temperatura ambiente

CL = cromatografía líquida

Ph = fenilo

EtOH = etanol

BuOH = butan-1-ol

DCE = dicloroetano

DMSO = dimetilsulfóxido

EM = tamiz molecular

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EM(ES) = espectrometría de masa de electro aspersión

Sat = saturado

AcOH = ácido acético

MeOH = metanol

$Et_2O$ = éter dietílico

Ac = acetilo

h = horas

EDCI = clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida, dicarbonil diimida soluble en agua

HOBT = 1-hidroxi-benzotriazol

TBAF = fluoruro de tetrabutilamonio

$TBAF \cdot 3H_2O$ = fluoruro de tetrabutilamonio trihidratado

DMA = dimetilacetamida

DME = 1,2-dimetoxietano

EMAR = espectrometría de masa de alta resolución

TBME = MTBE = éter ter-butílico de metilo(esto es, 2-metoxi-2-metil-propano)

PyBroP = hexafluorofosfato de bromo-tris-pirrolidino-fosfonio

PyBOP = hexafluorofosfato de benzotriazol-1-il-oxitripirrolidinfosfonio

DEA = dietilamina

IPA = isopropilamina

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TMSCl = cloruro de trimetilsililo

EM = espectro de masa

RMN = resonancia magnética nuclear

TMSI = yoduro de trimetilsililo

TMS = trimetilsililo

PPA = ácido polifosfórico

LDA = diisopropilamina de litio

UV = ultravioleta

DCM = diclorometano

DMAC = N,N-dimetilacetamida

DAST = trifluoruro de dietilaminosulfuro

CLAR = cromatografía líquida de alta resolución

SFC = cromatografía de fluido super crítico

ACN = acetonitrilo

IIDQ = resina de poliestireno

TosMIC = isocianuro de tosilmetilo

BINAP = 2,2'-bis(difenilfosfino)-1,1'-binaftilo

$Pd_2(dba)_3$ = tris-(dibencilidenacetona)dipaladio (O)

$Pd(PPh_3)_4$ = tetraquis(trifenilfosfina)paladio (O)

$[Ir(COD)Cl]_2$ = dímero de cloro-1,5-ciclooctadieno iridio (I)

Ar = argón

TBAB = bromuro de tetrabutilamonio

9-BBN = 9-borabiciclo[3.3.1]nonano

DEAD = azodicarboxilato de dietilo

DPPA = difenil fosforil azida

NBS = N-bromosuccinimida

DMAP = 4-di(metilamino)piridina

LAH = hidruro de aluminio de litio

NMP = 1-metil-2-pirrolidona

NMM = 1-metil-2-morfolina

Super-hidruro = trietilborohidruro de litio

DIBAL-H = hidruro de diisobutilaluminio

Periodinano Dess-Martin = 1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona

Reactivo Lawesson = 2,4-disulfuro de 2,4-bis(4-metoxifenil)-1,2,3,4-ditiadifosfetano

Reactivo Jones[O] = $CrO_3/H_2SO_4/H_2O$/acetona

$PCy_3$ = triciclohexilfosfina

$Tf_2O$ = anhídrido tríflico = anhídrido trifluorometansulfónico

$Bu_4NBr$ = bromuro de tetrabutilamonio

TBDMSCl = ter-butilclorodimetilsilano

TFFH = hexafluorofosfato de fluoro-N,N,N',N'-tetrametilformamidinio

R,R-MnCl (Salen) = cloruro de (1R,2R)-(-)-[1,2-ciclohexandiamino-N,N'-bis(3,5-di-t-butilsaliciliden)]manganeso (III)

LiOTf = trifluorometansulfonato de litio

Tf = trifluorometansulfonato

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$EtAlCl_2$ = cloruro de etil aluminio

$ZnEt_2$ = zinc de dietilo

TsOH = ácido 4-metilbencensulfónico

Ts = 4-metilbencensulfonato

$n\text{-}Bu_2SnO_2$ = óxido de dibutilestaño (IV)

Boc = t-Boc = t-butoxicarbonilo

$Pd(OH)_2/C$ = hidróxido de paladio (II) en carbono

Pd/C = paladio en carbono

Fmoc = 3,9-fluorenilmetoxicarbonilo

Cbz = carbobenzoxi

alilMgBr = bromuro de 1-propenil magnesio

diglima = éter dimetílico de dietilenglicol = 1-metoxi-2-(2-metoxietoxi)etano

TBME = éter metílico de ter-butilo

L-prolina = ácido (S)-pirrolidin-2-carboxílico

$P(t\text{-}Bu)_3$ = tri-t-butil fosfina

Trifosgeno = carbonato de bis(triclorometilo)

Los compuestos ejemplificados específicamente de la fórmula Ia y Ib se enlistan a lo largo, con la estructura, nombre, tiempo de retención CLAR, masa molecular y el procedimiento empleado para hacer tales ejemplos, en el texto del procedimiento y en las tablas establecidas a continuación. La configuración absoluta de los ejemplos quirales se asigna por la comparación RMN de las amidas de sulfinilo diastereoméricas intermediarias, pero no se

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confirma por cristalografía. Las aminas intermediarias enantioméricamente puras se obtienen por la separación de las mezclas racémicas usando SFC o por la síntesis quiral descrita en los procedimientos 4, 5 y 6.

Las técnicas de cromatografía usadas para determinar los tiempos de retención del compuesto en las tablas son como sigue:

(1) CLEM = columna Phenomenex Luna C18, 4.6 x 50 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, se monitoreó a 220 nm;

(2) CLEM = columna Phenomenex Luna C18, 4.6 x 30 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, se monitoreó a 220 nm;

(3) CLEM = columna Phenomenex Luna C18, 4.6 x 50 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de $NH_4OAc$; 4 ml/min, se monitoreó a 220 nm;

(4) CLEM = columna Waters Sunfire C18, 4.6 x 50 mm x 5 µm eluyendo con 10-90% de MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, se monitoreó a 220 nm;

(5) CLEM = columna YMC ODS, 4.6 x 50 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, se monitoreó a 220 nm;

(6) CL = columna Chromolith SpeedROD, 4.6 x 50 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 4 minutos que contiene 0.2% de ácido fósforico; 4 ml/min, se monitoreó a

220 nm;

(7) CL = columna Phenomenex Synergi 4u POLAR-RP, 21.2 x 100 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 12 minutos que contiene 0.1% de TFA; 4 ml/min, se monitoreó a 220 nm;

(8) CLEM = columna Phenomenex Luna C18, 4.6 x 50 mm eluyendo con 10-90% de ACN/$H_2O$ durante 4 minutos que contiene 0.1% de $NH_4OAc$; 4 ml/min, se monitoreó a 220 nm;

(9) CL = columna Chromolith SpeedROD, 4.6 x 50 mm eluyendo con 10-90% de ACN/$H_2O$ durante 2 minutos que contiene 0.1% de ácido fosfórico; 5 ml/min, se monitoreó a 220 nm;

(10) CLEM = columna Waters Sunfire C18, 4.6 x 50 mm eluyendo con 10-90% de ACN/$H_2O$ durante 4 minutos que contiene 10 mM $NH_4OAc$; 4 ml/min, se monitoreó a 220 nm;

(11) CL = columna Phenomenex Luna C18, 4.6 x 50 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de ácido fosfórico; 4 ml/min, se monitoreó a 220 nm;

(12) CLEM = columna Chromolith Performance RP-18e, 4.6 x 100 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de ácido trifluoroacético; 5 ml/min, se monitoreó a 220 nm;

(13) CL = columna Chromolith Performance RP-

18e, 4.6 x 100 mm eluyendo con 10-90% de acetonitrilo/$H_2O$ durante 2 minutos que contiene 0.1% de ácido trifluoroacético; 4 ml/min, se monitoreó a 220 nm;

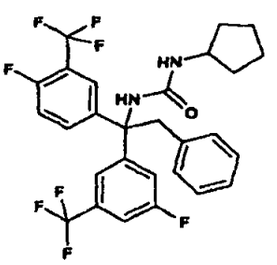
(14) CLEM = columna Phenomenex Luna C18, 4.6 x 30 mm eluyendo con 10-90% de ACN/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, se monitoreó a 220 nm;

(15) CLEM = columna Phenomenex Luna C18, 4.6 x 50 mm eluyendo con 10-90% de ACN/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, se monitoreó a 220 nm;

(16) CLEM = columna Waters sunfire C18, 4.6 x 50 mm eluyendo con 10-90% de MeOH/$H_2O$ durante 8 minutos que contiene 0.1% de TFA; 4 ml/min, se monitoreó a 220 nm;

La masa molecular de los compuestos enlistados en las tablas de abajo se determina por EM (ES) por la fórmula m/z.

**EJEMPLO 1**

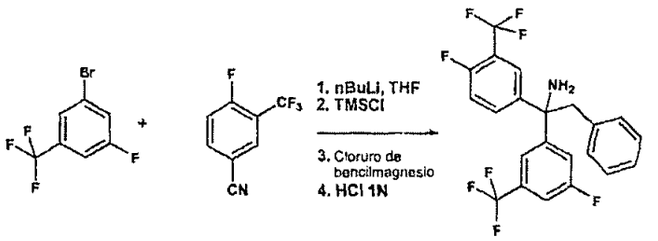



**1-ciclopentil-3-fl-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea**

1125

**Procedimiento 1**

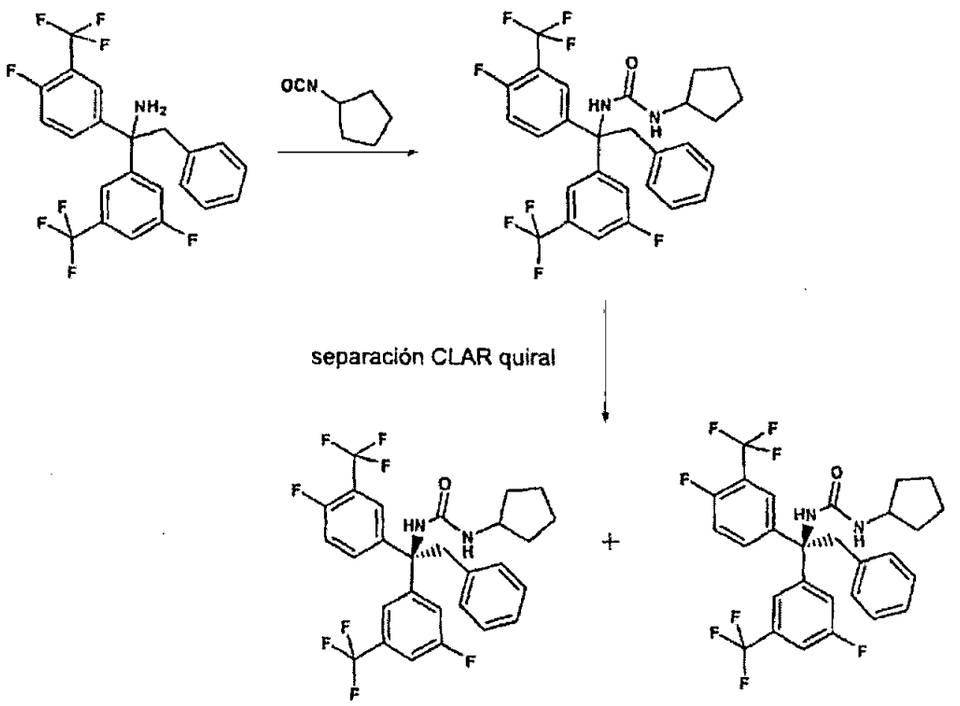
**1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletanamina**




Una solución de éter (40 ml) de 1-bromo-3-fluoro-5-(trifluorometil)benceno (2.0 g, 8.23 mmoles) se agitó en un matraz de fondo redondo secado al horno a -78°C bajo Ar. Se agregó gota a gota n-BuLi (2.5 M en hexanos, 3.6 ml, 9.05 mmoles, 1.1 eq). La solución resultante se agitó a -78°C durante 30 min. Una solución de 4-fluoro-3-(trifluorometil)benzonitrilo (1.55 g, 8.23 mmoles, 1.0 eq) en $Et_2O$ (5 ml) se agregó gota a gota. La mezcla rojiza resultante se agitó a -78°C durante 2h. TMSCl (pretratado con $Et_3N$ (TMSCl:$Et_3N$ = 10:1, v:v), 1.14 ml, 1.2 eq) se agregó gota a gota. El baño de hielo seco se removió, y la mezcla espesa resultante se agitó a temperatura ambiente durante 2 h. Esto se volvió a enfriar hasta -78°C, una solución de cloruro de bencil magnesio en THF (2.0 M, 8.4 ml, 2 eq) se agregó gota a gota. La mezcla resultante se entibió lentamente hasta temperatura ambiente y se agitó a temperatura ambiente durante la noche. Se agregó HCl 1N (100 ml). La mezcla se agitó a temperatura ambiente durante 30 min. Esto se extrajo

con $Et_2O$ (2x), se lavó con NaOH 1N, $H_2O$, salmuera, se secó ($Na_2SO_4$), se filtró y se concentró hasta secarse. El residuo se purificó por cromatografía de columna de vaporización instantánea (gel de sílice, hexanos: acetato de etilo) para dar 1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletanamina (1.6 g, rendimiento: 44%). CL-EM ESI 3.42 min 429.2 ($M-NH_3+H$); $^1H$ RMN (400 MHz, CLOROFORMO-D) $\delta$ ppm 7.66 (dd, J=6.7, 2.3 Hz, 1 H), 7.49-7.59 (m, 1 H), 7.45 (s, 1 H), 7.18-7.30 (m, 6 H), 6.74 (d, J=6.9 Hz, 2 H), 3.57 (m, 2 H).

**Procedimiento 2**



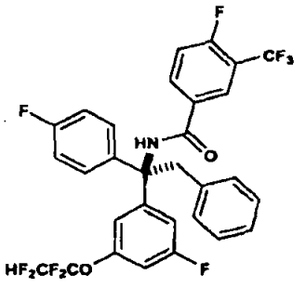

La 1-(4-Fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletanamina (300 mg, 0.67 mmoles) y isocianato de ciclopentilo (0.4 ml, 5.3 eq) se

agitaron en 1,4-dioxano (2 ml) a temperatura ambiente durante la noche. La mezcla de reacción se concentró, y se purificó por cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar la mezcla racémica de 1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea (250 mg, rendimiento: 67%). Los racematos (250 mg) se disolvieron en 10% de isopropanol en heptano, y se resolvió por CLAR preparativa quiral al usar columna AD (10% de isopropanol/heptano/0.1% de DEA, isocrático) para dar el enantiómero de rápida elución 1 (110 mg) que corresponde a (S)-1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea: CLAR quiral analítica (AD, 10% de isopropanol/heptano/0.1% de DEA, isocrático), tiempo de retención = 4.85 min; y el enantiómero de lenta elución 2 (105 mg) que corresponde a (R)-1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea: CLAR quiral analítica (AD, 10% de isopropanol/heptano/0.1% de DEA, isocrático), tiempo de retención = 14.11 min. CLEM (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min), tiempo de retención = 4.33 min, 557.32 (M+H); $^1$H RMN (400 MHz, $CDCl_3$) $\delta$ ppm 7.36-7.44 (m, 2 H), 7.23-7.29 (m, 3 H), 7.13-7.21 (m, 4 H), 6.68-6.74 (m, 2 H), 4.84 (s, 1 H), 4.40 (s, br, 1 H), 3.84-3.95 (m, 3 H), 1.88-1.98 (m, 2 H), 1.56-1.68 (m, 4 H),

1178

1.34 (d, J=6.36 Hz, 2 H).

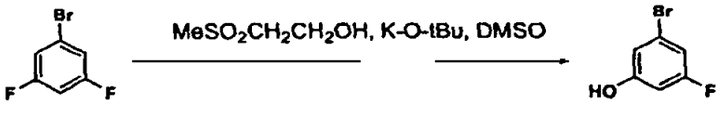
**EJEMPLO 2**




**(R)-4-Fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)benzamida**

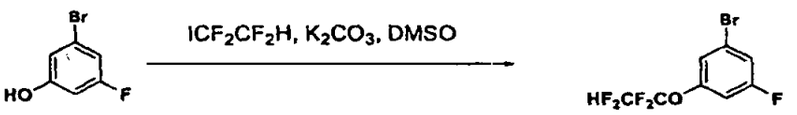
**Procedimiento 3**

**Preparación de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno**




A una solución de 1-bromo-3,5-difluorobenceno (30.6 ml, 0.266 mol) y 2-(metilsulfonil)etanol (66 g, 0.531 moles) en DMSO (240 ml) se agregó ter-butóxido de potasio (76.6 g, 0.682 mol) a 0°C. La mezcla resultante se agitó a temperatura ambiente durante 3h y se extinguió con HCl 4N lentamente hasta pH $\leq$ 1. El producto deseado se extrajo con $Et_2O$ (12 L) hasta que no hay presencia del producto en la capa acuosa. El $Et_2O$ se evaporó bajo presión reducida hasta una tercera cantidad del solvente y se lavó con NaOH 1N (12 L). Luego, la

solución NaOH se ajustó hasta pH = 3 y se extrajo con $Et_2O$ hasta que el producto no se desea en la capa acuosa. El $Et_2O$ se evaporó bajo presión reducida y se pasó a través de una columna $Al_2O_3$ eluida con $Et_2O$ para proporcionar 3-bromo-5-fluorofenol como un aceite incoloro (48 g, 94% rendimiento). CL-EM 190.33 (M+H); CLAR analítica = 2.26 minutos (0-100% $CH_3CN$ en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CD_3OD$) $\delta$ ppm 6.88-6.64 (m, 2H), 6.58-6.30 (m, 1 H), 4.99 (s, 1 H).



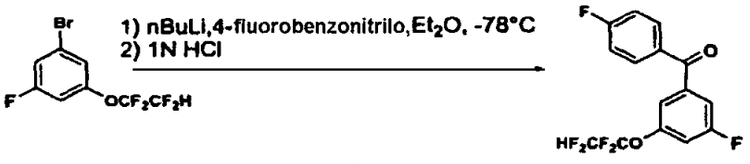

A una solución de 3-bromo-5-fluorofenol (47 g, 0.249 mol) y 2,2,3,3-tetrafluoroetilyodo (68 g, 0.298 mol) en DMSO (260 ml) se agregó carbonato de potasio (137 g, 0.992 mol). La mezcla resultante se agitó a 70°C durante 16 h. La sal orgánica se removió por filtración y se lavó la torta filtro con $Et_2O$ (500 ml). El filtrado se diluyó con 500 ml de $H_2O$ y se extrajo con exceso de $Et_2O$ (1.5 L). La capa $Et_2O$ se lavó con NaOH 0.5 N (250 ml), $H_2O$, salmuera, y se secó sobre $Na_2SO_4$. El solvente se evaporó bajo presión reducida y el producto crudo se pasó a través de una columna $Al_2O_3$ usando $Et_2O$ como solvente de elución para proporcionar 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (63 g, rendimiento: 87%) como un aceite amarillento. CL-EM (ESI):

1180

290.21 (M+H), tiempo de retención = 3.66 minutos (0-100% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CD_3OD$) $\delta$ ppm 7.45-7.22 (m, 2 H), 7.10 (d, J = 9.23 Hz, 1 H), 6.59-5.94 (m, 1 H).

**Procedimiento 4**

**(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metanona**

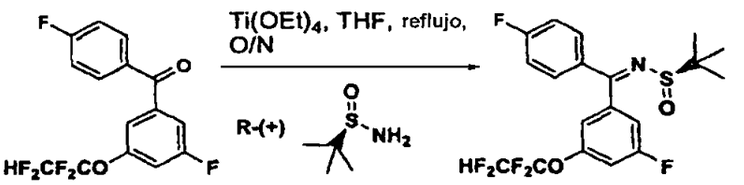



A un matraz de fondo redondo secado al horno enfriado a -78°C, se cargó con 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (7.20 g, 24.82 mmoles) en éter anhidro (300 ml) bajo argón, y se agitó a -78°C durante 10 min. n-BuLi (2.5 M en hexanos, 11.5 ml, 28.75 mmoles, 1.16 eq) se agregó gota a gota a -78°C. La mezcla de reacción se agitó a -78°C durante 45 min. Una solución $Et_2O$ (20 ml) de 4-fluorobenzonitrilo (3.06 g, 25.29 mmoles, 1.02 eq) se agregó gota a gota. La solución rojiza resultante se agitó a -78°C durante 2 h. La mezcla de reacción se extinguió al agregar HCL 1N (200 ml), y el baño de acetona-hielo seco se removió. La mezcla espesa resultante se agitó a temperatura ambiente durante 1 h. Se agregó $Et_2O$ (100 ml). La capa orgánica se separó, y luego se lavó con $NaHCO_3$ saturado, $H_2O$, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró hasta secarse. El

residuo se purificó por cromatografía de vaporización instantánea (EtOAc/hexanos = 0 hasta 30%) para dar (3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metanona como un aceite ligeramente marrón (7.20 g, rendimiento: 86.9%). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.85-7.80 (m, 2H), 7.40-7.37 (m, 2H), 7.20-7.14 (m, 3H), 5.92 (tt, J = 52, 2.8Hz, 1H); CL-EM (ESI) 335.31 (M+H), tiempo de retención = 3.81 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min).

**Procedimiento 5**

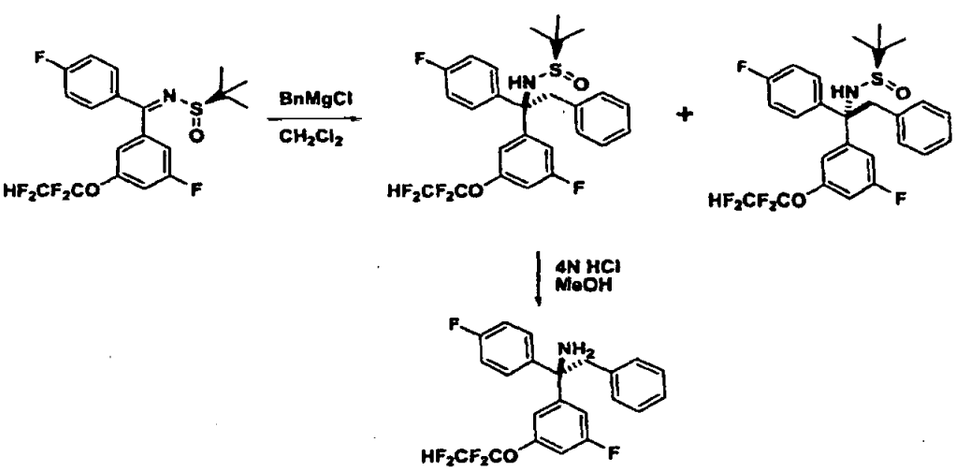
**(R,E/Z)-N-((3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metilen)-2-metilpropan-2-sulfinamida**




(3-Fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metanona (3.3 g, 9.88 mmoles) se agitó en THF anhidro (20 ml) a temperatura ambiente bajo $N_2$. (R)-(+)-2-Metilpropan-2-sulfinamida (1.21 g, 10 mmoles, 1.01 eq) se agregó como una porción sencilla, seguido por la adición de $Ti(OEt)_4$ (3.09 ml, 14.91 mmoles, 1.51 eq). La solución resultante se calentó a reflujo durante 48 horas. La mezcla enfriada se evaporó. Se agregó $H_2O$ (100 ml), seguido por la adición de EtOAc (100 ml). Esto se filtró a través de Celite, y se lavó con EtOAc (200 ml). El filtrado se lavó con $H_2O$, salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró hasta

secarse. El residuo se purificó por cromatografía de vaporización instantánea y se eluyó con hexanos y EtOAc (0-30% EtOAc en hexanos) para dar (R,E/Z)-N-((3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metileno)-2-metilpropan-2-sulfinamida como un aceite amarillo viscoso el cual se solidifica después de secarse bajo vacío como sólidos amarillo ligero (3.50 g, rendimiento: 81.0%). CL-EM ESI 437.88 (M+H), tiempo de retención = 3.83 min (10-90% MEOH en $H_2O$ con 0.1% de TFA en un gradiente de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.82-6.99 (br, m, 7H), 5.90 (tt, J = 52, 4 Hz, 1H), 1.31 (s, 9H).

**Procedimiento 6**




La (R)-N-((3-Fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metilen)-2-metilpropan-2-sulfinamida (150 mg, 0.34 mmoles) se agitó en $CH_2Cl_2$ anhidro (7 ml) a -78°C durante 5 min bajo argón. $BF_3$ $Et_2O$ (0.10 ml, 2.0 eq) se agregó gota a gota. La mezcla se agitó a -78°C

durante 10 min. Cloruro de bencilmagnesio (1.0 M en $Et_2O$, 1.4 ml, 3.0 eq) se agregó lentamente a -78°C, y la mezcla resultante se agitó a -78°C durante 1.5 h. Esto se extinguió con $NH_4Cl$ saturado. Esto se extrajo con $Et_2O$ (2x). Los orgánicos se lavaron con $H_2O$, salmuera, se secaron ($Na_2SO_4$), se filtraron y se concentraron hasta secarse. El residuo se purificó por cromatografía de vaporización instantánea (gel de sílice, EtOAc/hexanos = 0-30%) para dar la fracción de elución rápida que corresponde a (R)-N-((S)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropan-2-sulfinamida (29 mg): $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 1.23 (s, 9 H) 3.63 (d, J=12.4 Hz, 1H), 3.94 (d, J=12.4 Hz, 1H), 4.21 (s, 1H), 6.90 (m, 1H), 5.90 (m, 1H), 6.94-7.09 (m, 4H), 7.16-7.20 (m, 4H), 7.31-7.39 (m, 2H); CL-EM (ESI) 530.36 (M+H), tiempo de retención = 4.11 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min); y la fracción de elución lenta que corresponde a (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropan-2-sulfinamida (146 mg, rendimiento total: 96.4%): $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.35-7.43 (m, 2 H), 7.13-7.20 (m, 3 H), 7.07 (t, J=8.72 Hz, 2 H), 6.93 (dd, J=7.58, 1.77 Hz, 2 H), 6.84 (d, J=8.59 Hz, 1 H), 6.70 (m, 2 H), 5.85 (tt, J= 52, 4 Hz, 1H), 4.25 (s, 1 H), 4.02 (d, J=12.63 Hz, 1 H), 3.58 (d, J=12.63 Hz, 1 H), 1.20 (s, 9 H); $^{13}C$ RMN ($CDCl_3$) δ ppm 23.02, 46.99, 56.53, 65.70, 104.55,

104.96, 105.37, 107.06, 107.47, 107.92, 108.17, 109.56, 109.97, 112.32, 112.55, 115.37, 115.58, 116.13, 116.41, 116.69, 119.12, 127.21, 128.14, 130.91, 130.99, 132.07, 134.34, 137.48, 137.51, 149.09, 149.21, 150.52, 150.45, 161.20, 163.67; CL-EM (ESI) 530.36 (M+H), tiempo de retención = 4.11 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min).

**(R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina**

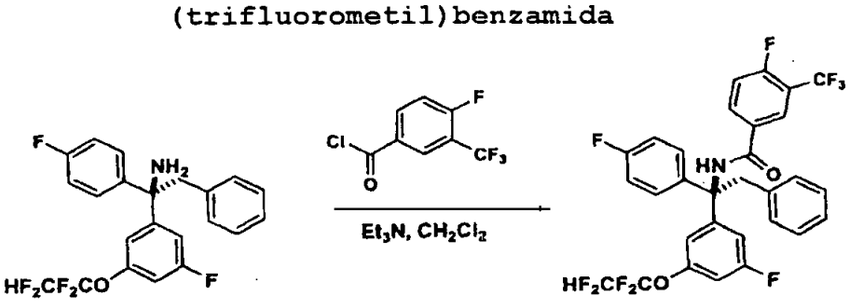



La (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropan-2-sulfinamida (234 mg, 0.442 mmoles) se agitó en HCl 4N en dioxano (1.5 ml) y MeOH (1.5 ml) a temperatura ambiente bajo Ar durante 10 min. Esto se concentró, y entonces se purificó por cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (169 mg, 90%). CL-EM (ESI) 409.16 ($M-NH_3+H$), tiempo de retención = 3.26 minutos (0-100% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4 min); CLAR analítica: 2.52 minutos (0-100% $CH_3CN$ en $H_2O$ con TFA 0.1% en una corrida de 4

minutos); $^1$H RMN (400 MHz, $CD_3OD$) δ ppm 7.29-7.50 (m, 2H), 6.87-7.22 (m, 8H), 6.77 (d, J=6.15 Hz, 2H), 6.04-6.48 (m, 1 H), 3.57 (s, 2 H).

**Procedimiento 7**

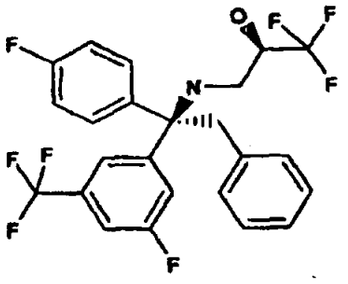
**(R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)benzamida**




A una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (30 mg, 0.079 mmoles) en $CH_2Cl_2$ (0.2 ml) se agregó cloruro de 4-fluoro-3-(trifluorometil)benzoilo (0.048 ml, 0.158 mmoles), seguido por $Et_3N$ (0.04 ml, 0.158 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 5h. El producto crudo se purificó en una CLAR preparativa usando 30 hasta 100% $CH_3CN$ en $H_2O$ con TFA 0.1% durante 10 minutos como una fase móvil. El solvente se removió bajo presión reducida y se bombeó hasta secarse para proporcionar (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)benzamida (35 mg, 80% rendimiento) como polvo blanco. CL-EM (ESI) 568.30 (M+H), tiempo de retención = 4.27 min (0-100% MeOH en $H_2O$ con TFA

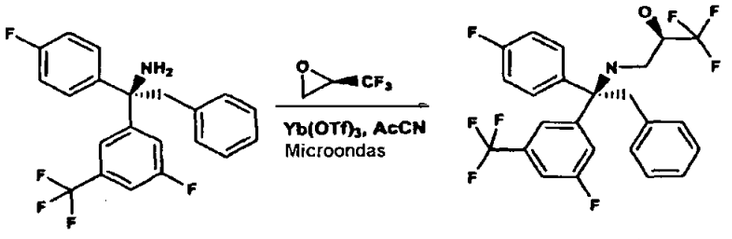
0.1% en una corrida de 4-min); CLAR analítica: 3.95 min (0-100% $CH_3CN$ en $H_2O$ con TFA 0.1% en una corrida de 4-min, pureza 100%); $^1H$ RMN (400MHz, $CD_3OD$) $\delta$ ppm 3.88-4.01 (m, 1 H), 4.10 (d, J=13.18 Hz, 1 H), 6.69 (d, J=7.47 Hz, 2 H), 6.97-7.51 (m, 11 H), 7.99 (d, J=5.71 Hz, 2 H), 8.90 (s, 1 H).

**EJEMPLO 3**



**(R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil-2-feniletilamino)propan-2-ol**

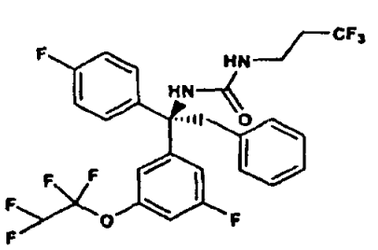
**Procedimiento 8**




La (R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletanamina se preparó como se describió en los procedimientos 4, 5 y 6. (R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletanamina (50 mg, 0.133 mmoles) se disolvió en acetonitrilo anhidro (0.26 ml). (R)-2-(trifluorometil)oxirano (relación aproximada 85:15

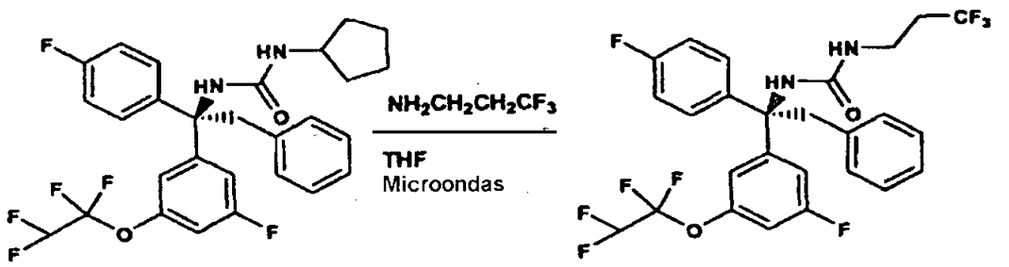
de R a S) (0.07 ml, 0.625 mmoles) se agregó a la solución en un frasco de microondas seguido por $Yb(OSO_2CF_3)_3$ (0.005 g, 0.008 mmoles). El frasco sellado se calentó a 160°C durante 30 minutos bajo radiación de microondas. El producto crudo se purificó por CLAR preparativa usando 30-100% acetonitrilo en $H_2O$ con TFA 0.1% como una fase móvil para dar (R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletilamino)propan-2-ol como un aceite incoloro (30 mg, 46% rendimiento). CL-EM (ESI): 361.15 (M+H), tiempo de retención = 4.10 min (0-100% MeOH en $H_2O$ con TFA 0.1%); CLAR analítica: 3.49 min ($CH_3CN$ en $H_2O$ con TFA 0.1% en una corrida de 4 minutos, pureza 100%); $^1H$ RMN (400 MHz, $CD_3OD$) δ ppm 2.59-2.73 (m, 1 H), 2.72-2.84 (m, 1 H), 3.69 (m, 2 H), 4.09 (m, 1 H), 6.61-6.82 (m, 2 H), 7.00-7.19 (m, 5 H), 7.20-7.48 (m, 5H).

**EJEMPLO 4**



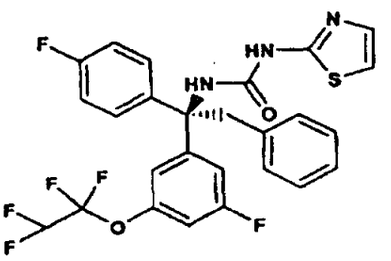

**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3,3,3-trifluoropropil)urea**

**Procedimiento 9**



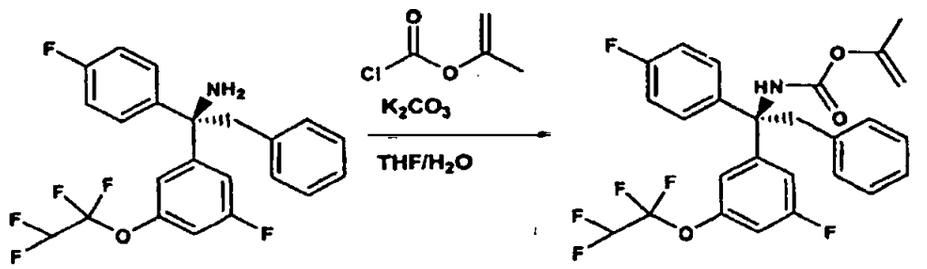

La (R)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea se preparó como se describió en el procedimiento 2. A un frasco de microondas de (R)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (20 mg, 0.037 mmoles) se agregó una solución pre-mezclada de 3,3,3-triflurometilpropilamina (25 mg, 0.224 mmoles) y $Et_3N$ (0.03 ml, 0.224 mmoles) en THF (0.025 ml). El frasco sellado se procesó bajo radiación de microondas a 150°C durante 1500 segundos y se diluyó con MeOH. El producto crudo se aisló por CLAR preparativa usando 30-100% acetonitrilo en $H_2O$ con TFA 0.1% como una fase móvil para proporcionar (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3,3,3-trifluoropropil)urea (76%) como polvo blanco. CLEM (ESI): 565.36 (M+H), tiempo de retención = 3.96 min (0-100% MeOH en $H_2O$ en una corrida de 4-min); $^1H$ RMN (400 MHz, $CD_3OD$) $\delta$ ppm 2.18-2.41 (m, 2H), 3.34 (m, 2H), 3.75-3.87 (m, 1 H), 3.88-4.00 (m, 1 H). 6.07-6.45 (m, 1H), 6.71 (d, J=7.03 Hz, 2H), 6.85-7.05 (m, 5 H), 7.05-7.22 (m, 5 H).

**EJEMPLO 5**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(tiazol-2-il)urea**

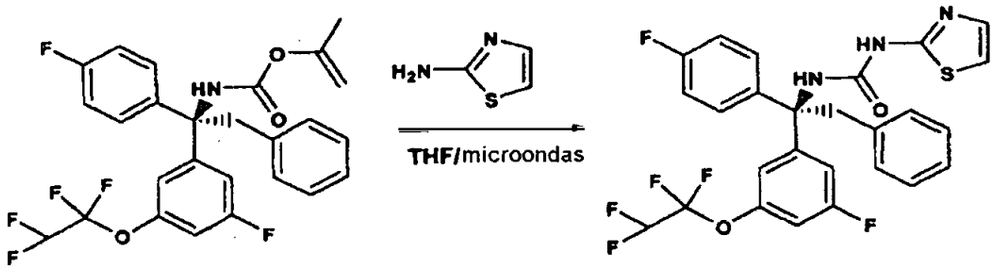
**Procedimiento 10**



La (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (48 mg, 0.11 mmoles) se agitó en THF (0.5 ml) y $H_2O$ (0.05 ml) a temperatura ambiente. El $K_2CO_3$ (100 mg, 0.72 mmoles, 6.6 eq) se agregó seguido por la adición de cloroformiato de isopropenilo (0.030 ml, 0.275 mmoles, 2.5 eq). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Esto se filtró, y se concentró hasta secarse para dar 1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilcarbamato de (R)-prop-1-en-2-il crudo como película incolora (60 mg, rendimiento: cuantitativo) después

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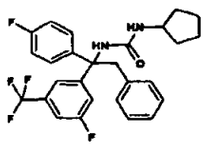
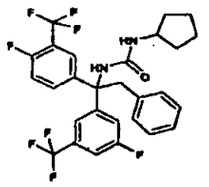
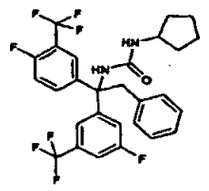
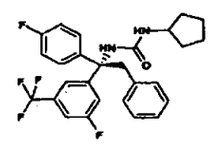
de secarse bajo vacío. CLEM: 4.18 min 409.27 (M-COOisopropenil-$NH_3$+H) (gradiente 4 min, MeOH/$H_2O$ TFA 0.1%).

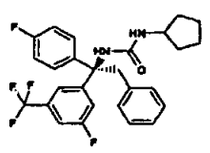
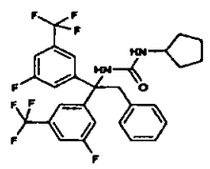
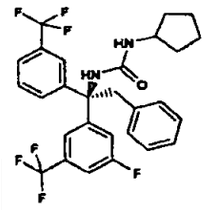
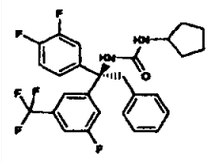
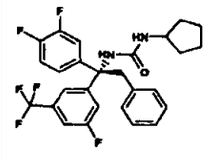



El 1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilcarbamato de (R)-prop-1-en-2-il (15 mg, 0.029 mmoles) y 2-aminotiazol (8.2 mg, 0.082 mmoles, 2.8 eq), y N-metilpirrolidina (0.9 µl, 0.3 eq) se agitaron en THF (0.3 ml) en un frasco de microondas. La mezcla de reacción se calentó a 150°C durante 20 min bajo radiación de microondas. Después del enfriamiento, el solvente se evaporó. El residuo se purificó por CLAR de fase inversa (20-90% $CH_3CN$ en $H_2O$ con TFA 0.1%) para dar (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(tiazol-2-il)urea puro como sólidos blancos (6.5 mg, rendimiento: 40.6%). $^1H$ RMN (400 MHz, $CDCl_3$-D) δ ppm 7.29 (m, 1H), 7.23-7.18 (m, 3H), 7.16 (t, J = 8.0 Hz, 2H), 7.02 (t, J= 8.5 Hz, 2H), 6.94-6.89 (m, 4H), 6.71 (d, J =6.82 Hz, 2H), 5.86 (tt, J = 47.1, 2.9 Hz, 1H), 3.84-3.75 (m, 2H); CL-EM (ESI) 552.28 (M+H), tiempo de retención = 4.12 (10-90% de MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min).

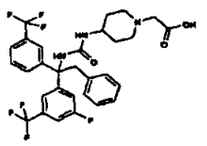
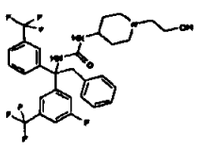
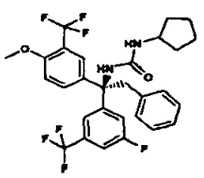
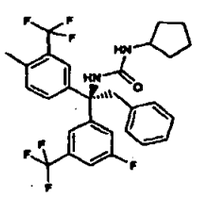
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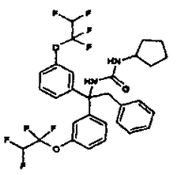
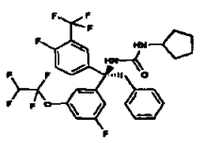
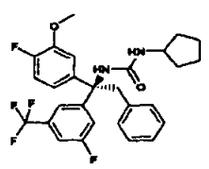
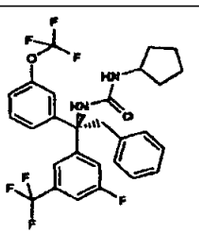
**TABLA 1**

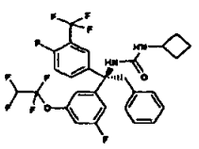
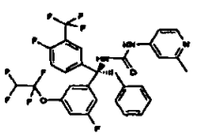
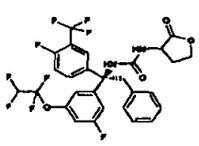
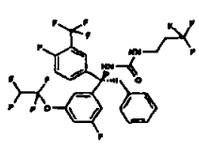
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 6 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.61 CL 489.34 [M+H]+ | Procedimiento 1 y 2 |
| 7 |  | 1-ciclopentil-3-(1-(4-fluoro-3-(trifluoro metil)fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) urea | 4.30 CL 557.3 [M+H]+ | Procedimiento 1 y 2 |
| 8 |  | 1-ciclopentil-3-(1-(4-fluoro-3-(trifluoro metil)fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.30 CL 557.3 [M+H]+ | Procedimiento 1 y 2 |
| 9 |  | (S)-1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.60 CL 489.33 [M+H]+ | Procedimiento 4, 5, 6 y 2 |

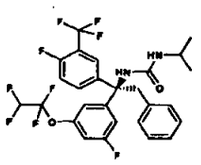
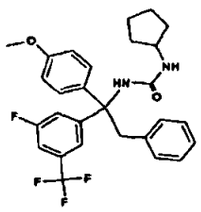
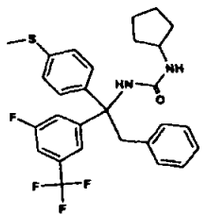
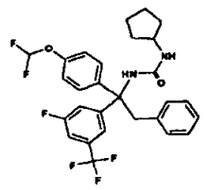
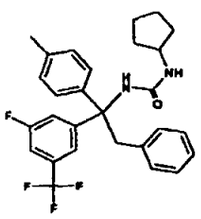
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 10 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.61 CL 489.33 [M+H]+ | Procedimiento 4, 5, 6 y 2. |
| 11 |  | 1-(1,1-bis(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentil urea | 3.87 CL 557.34 [M+H]+ | Procedimiento 14 y 2 |
| 12 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) fenil)etil)urea | 4.30 CL 539.38 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 13 |  | (R)-1-ciclopentil-3-(1,(3,4-difluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil-2-feniletil)urea | 3.64 CL 507.34 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 14 |  | (S)-1-ciclopentil-3-(1-(3,4-difluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 3.64 CL 507.14 [M+H]+ | Procedimiento 4, 5, 6 y 2 |

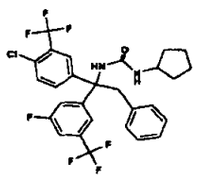
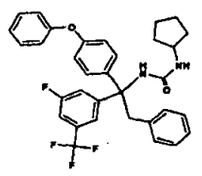
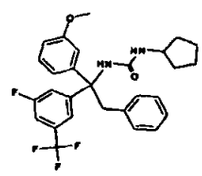
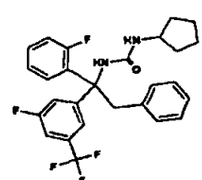
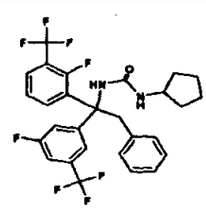
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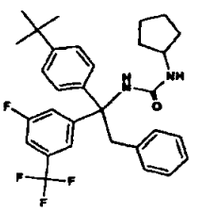
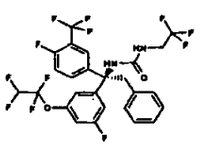
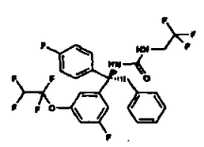
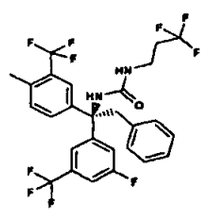
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 15 |  | Ácido 2-(4-(3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) fenil)etil) ureido)piperidin-1-il)acético | 3.75 CL 612.4 [M+H]+ | Procedimiento 1 y 2 |
| 16 |  | 1-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) fenil)etil)-3-(1-(2-hidroxietil) piperidin-4-il)urea | 3.72 CL 598.45 [M+H]+ | Procedimiento 1 y 2 |
| 17 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metoxi-3-(trifluorometil) fenil)-2-feniletil)urea | 4.22 CL 569.39 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 18 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metil-3-(trifluorometil) fenil)-2-feniletil)urea | 4.42 CL 553.38 [M+H]+ | Procedimiento 4, 5, 6 y 2 |

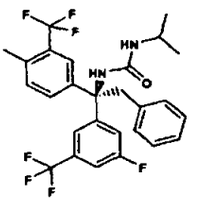
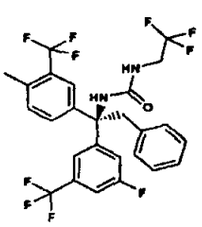
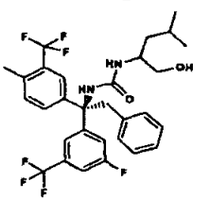
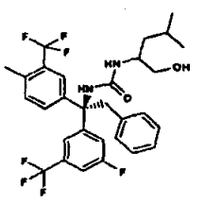
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 19 |  | 1-ciclopentil-3-(2-fenil-1,1-bis(3-(1,1,2,2-tetrafluoroetoxi) fenil) etil)urea | 4.13 CL 617.4 [M+H]+ | Procedimiento 1 y 2 |
| 20 |  | (R)-1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.74 CL 605.37 [M+H+]+ | Procedimiento 1, 3 y 2 |
| 21 |  | (R)-1-ciclopentil-3-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.17 CL 519.37 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 22 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) fenil) etil)urea | 4.30 CL 555.40 [M+H]+ | Procedimiento 4, 5, 6 y 2 |

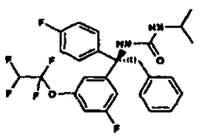
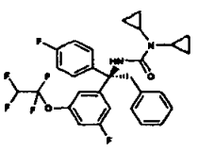
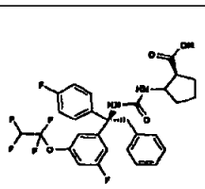
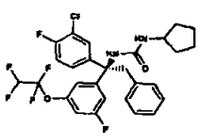
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 23 |  | (R)-1-ciclobutil-3-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.64 CL 591.39 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 24 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2-metilpiridin-4-il)urea | 2.64 CL 648.49 [M+Na]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 25 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluroroetoxi) fenil)-2-feniletil)-3-(2-oxo-tetrahidrofuran-3-il)urea | 3.30 CL 621.39 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 26 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(3,3,3-trifluoropropil) urea | 3.59 CL 633.32 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |

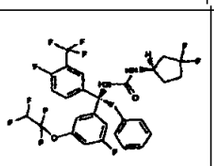
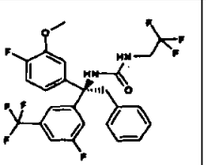
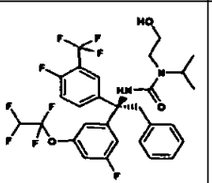
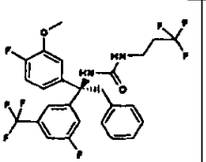
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 27 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-isopropilurea | 3.62 CL 579.34 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 28 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metoxifenil)-2-feniletil)urea | 4.13 CL 501.3 [M+H]+ | Procedimiento 1 y 2 |
| 29 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-(metiltio)fenil)-2-feniletil)urea | 4.24 CL 517.26 [M+H]+ | Procedimiento 1 y 2 |
| 30 |  | 1-ciclopentil-3-(1-(4-(difluorometoxi) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.12 CL 537.27 [M+H+] | Procedimiento 1 y 2 |
| 31 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-p-toliletil)urea | 4.24 CL 485.32 [M+H]+ | Procedimiento 1 y 2 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 32 |  | 1-(1-(4-cloro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.30 CL 573.23 [M+H]+ | Procedimiento 1 y 2 |
| 33 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fenoxifenil)-2-feniletil)urea | 4.38 CL 563.32 [M+H]+ | Procedimiento 1 y 2 |
| 34 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil fenil)-1-(3-metoxifenil)-2-feniletil)urea | 4.14 CL 501.32 [M+H]+ | Procedimiento 1 y 2 |
| 35 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(2-fluorofenil)-2-feniletil)urea | 4.12 CL 489.26 [M+H]+ | Procedimiento 1 y 2 |
| 36 |  | 1-ciclopentil-3-(1-(2-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.17 CL 557.26 [M+H]+ | Procedimiento 1 y 2 |

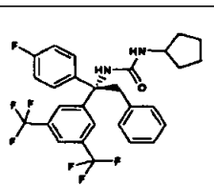
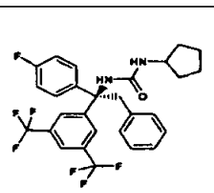
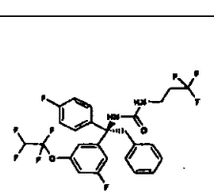
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 37 |  | 1-(1-(4-ter-butilfenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentil urea | 4.47 CL 527.33 [M+H]+ | Procedimiento 1 y 2 |
| 38 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil) urea | 3.32 CL 619.31 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 39 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(2,2,2-trifluoroetil) urea | 3.14 CL 551.21 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 40 |  | (R)-1-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metil-3-(trifluorometil) fenil)-2-feniletil)-3-(3,3,3-trifluoropropil) urea | 4.37 CL 580.98 [M+H]+ | Procedimiento 4, 5, 6 y 9 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 41 |  | (R)-1-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metil-3-(trifluorometil) fenil)-2-fenileti)-3-isopropilurea | 4.36 CL 527.08 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 42 |  | (R)-1-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metil-3-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil) urea | 4.32 CL 567.04 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 43 |  | 1-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metil-3-(trifluorometil) fenil)-2-feniletil)-3-(1-hidroxi-4-metilpentan-2-il)urea | 4.40 CL 585.13 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 44 |  | 1-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metil-3-(trifluorometil) fenil)-2-feniletil)-3-(1-hidroxi-4-metilpentan-2-il)urea | 4.41 CL 585.1 [M+H]+ | Procedimiento 4, 5, 6 y 2 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 45 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoro etoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-isopropilurea | 3.95 CL 511.39 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 46 |  | (R)-1,1-diciclopropil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1(4-fluorofenil)-2-feniletil)urea | 4.12 CL 549.32 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 47 |  | Ácido (1S)-2-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) ureido) ciclopentan carboxílico | 3.93 CL 581.04 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 48 |  | (S)-1-(1-(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 3.72 CL 571.36 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |

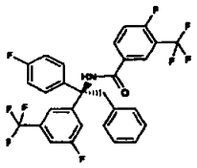
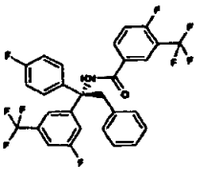
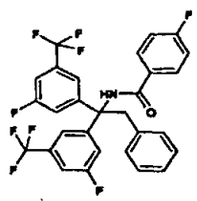
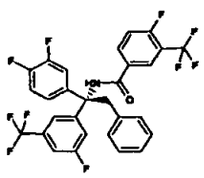
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 49 |  | 1-((R)-3,3-difluorociclopentil)-3-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 4.17 CL 641.3 [M+H]+ | Procedimiento 3, 4, 5, 6 y 9 |
| 50 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil) urea | 3.94 CL 532.98 [M+H]+ | Procedimiento 4, 5, 6 y 9 |
| 51 |  | (R)-3-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-1-(2-hidroxietil)-1-isopropilurea | 4.09 CL 623.02 [M+H]+ | Procedimiento 4, 5, 6 y 9 |
| 52 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(3,3,3-trifluoropropil)urea | 3.49 CL 547.00 [M+H]+ | Procedimiento 4, 5, 6 y 9 |

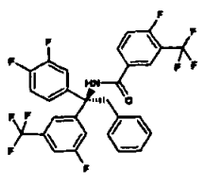
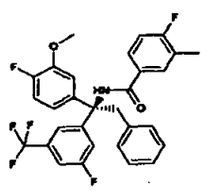
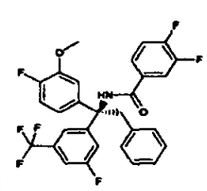
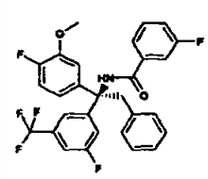
1202

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 53 |  | (S)-1-(1-(3,5-bis(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-ciclopentilurea | 3.82 CL 539.03 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 54 |  | (R)-1-(1-(3,5-bis(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-ciclopentilurea | 3.80 CL 539.03 [M+H]+ | Procedimiento 4, 5, 6 y 2 |
| 55 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3,3,3-trifluoropropil) urea | 3.96 CL 565.36 [M+H]+ | Procedimiento 3, 4, 5, 6 y9 |

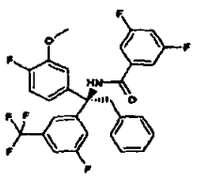
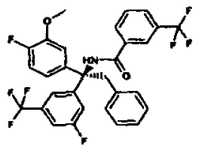
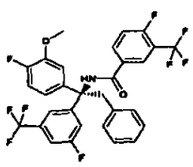
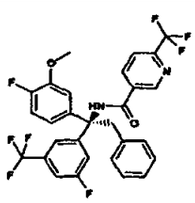
1203

**TABLA 2**

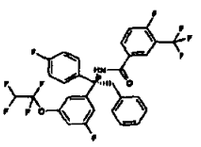
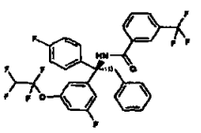
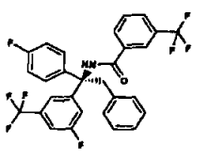
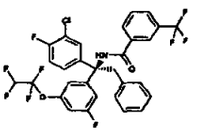
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 56 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.95 CL 568.30 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 57 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1(4-fluorofenil)-2-feniletil)-3-(trifluoro metil) benzamida | 3.95 CL 568.24 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 58 |  | N-(1,1-bis(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro benzamida | 3.83 CL 568.3 [M+H]+ | Procedimiento 1 y 7 |
| 59 |  | (S)-N-(1-(3,4-difluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) fenil) benzamida | 3.95 CL 586.26 [M+H]+ | Proce4dimiento 4, 5, 6 y 7 |

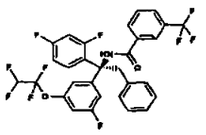
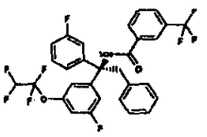
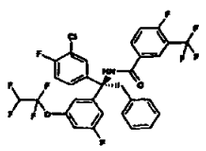
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 60 |  | (R)-N-(1-(3,4-difluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluoro metil) benzamida | 3.93 Cl 497.3 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 61 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluometil) fenil)-2-feniletil)-3-metilbenzamida | 3.79 CL 544.35 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 62 |  | (R)-3,4-difluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) benzamida | 3.73 CL 570.32 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 63 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) benzamida | 3.67 CL 530.33 [M+H]+ | Procedimiento 4, 5, 6 y 7 |

1205

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 64 |  | (R)-3,5-difluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) benzamida | 3.75 CL 548.33 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 65 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.86 CL 580.36 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 66 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluoro metil) benzamida | 3.90 CL 598.36 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 67 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-6-(trifluorometil) nicotinamida | 3.70 CL 581.34 [M+H]+ | Procedimiento 4, 5, 6 y 7 |

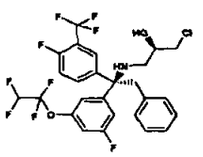
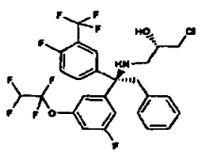
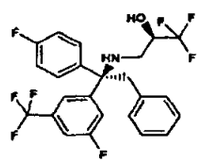
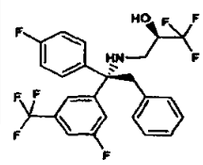
1206

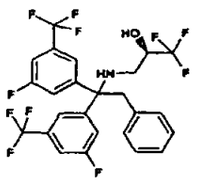
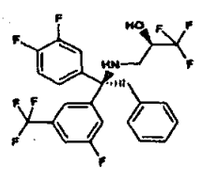
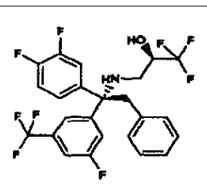
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 68 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.95 CL 616.17 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 69 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.83 CL 598.37 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 70 |  | (R)-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.89 CL 550.36 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 71 |  | (S)-N-(1-(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.95 CL 632.32 [M+H]+ | Procedimiento 4, 5, 6 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 72 |  | (S)-N-(1-(2,4-difluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.86 CL 616.34 [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 73 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(3-fluorofenil)-2-feniletil)-3-(trifluoro metil) benzamida | 3.81 CL N. observado [M+H]+ | Procedimiento 4, 5, 6 y 7 |
| 74 |  | (S)-N-(1,(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluoro metil) benzamida | 4:03 CL 650.05 [M+H]+ | Procedimiento 4, 5, 6 y 7 |

120 05

**TABLA 3**

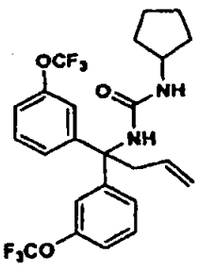
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 75 |  | (R)-1-cloro-3-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil-2-feniletilamino) propan-2-ol | 3.24 CL 586.43 [M+H]+ | Procedimiento 3, 4, 5, 6 y 8 |
| 76 |  | (S)-1-cloro-3-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino) propan-2-ol | 3.24 CL 586.43 [M+H]+ | Procedimiento 3, 4, 5, 6 y 8 |
| 77 |  | (R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletilamino) propan-2-ol | 3.83 CL No obs [M+H]+ | Procedimiento 4, 5, 6 y 8 |
| 78 |  | (R)-1,1,1-trifluoro-3-((S)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletilamino) propan-2-ol | 3.48 CL No obs [M+H]+ | Procedimiento 4, 5, 6 y 8 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 79 |  | (R)-3-(1,1-bis(3-fluoro-5-(trifluorometil) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 3.88 CL No obs. [M+H]+ | Procedimiento 4, 5, 6 y 8 |
| 80 |  | (R)-3-((R)-1-(3,4-difluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 3.63 CL No obs. [M+H]+ | Procedimiento 4, 5, 6 y 8 |
| 81 |  | (R)-3-((S)-1-(3,4-difluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 3.64 CL No obs. [M+H]+ | Procedimiento 4, 5, 6 y 8 |

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos descritos arriba y a los procedimientos adicionales descritos más adelante.

1210

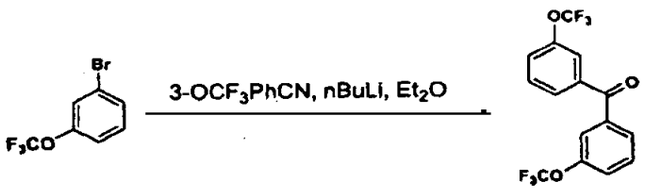
**EJEMPLO 82**




**1-(1,1-bis(3-(trifluorometoxi)fenil)but-3-enil)-3-ciclopentilurea**

**Procedimiento 11**

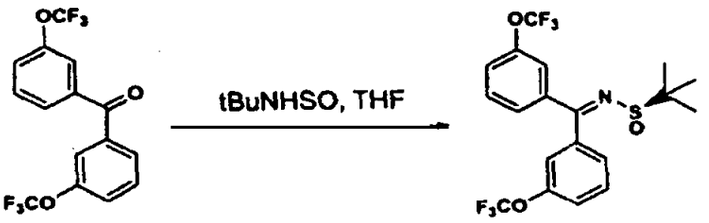
**Bis(3-(trifluorometoxi)fenil)metanona**




Usando el mismo procedimiento como se describió en el Ejemplo 2, Procedimiento 4, bis(3-(trifluorometoxi)fenil)metanona se obtuvo. $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.39 - 7.45 (m, 1H),) 7.36 (m, 1H), 7.25 (d, J=15.92 Hz, 1H), 7.15 - 7.20 (m, 1H); $^{13}$C RMN ($CDCl_3$) δ ppm 193.27, 149.29, 138.66, 130.10, 128.27, 125.23, 124.26, 122.26, 121.69, 119.13, 116.56; CL-EM (ESI) 351.2 (M+H), tiempo de retención = 4.0 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min).

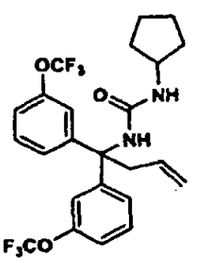
(211

**(R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida**




Usando el mismo procedimiento como el del Procedimiento 5, (R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida se obtuvo. $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.62-7.28 (br, m, 8H),) 1.34 (s, 9H); CL-EM (ESI) 454.28 (M+H), tiempo de retención = 4.12 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min).

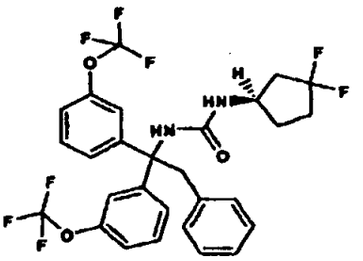
**1-(1,1-bis(3-(trifluorometoxi)fenil)but-3-enil)-3-ciclopentilurea**




Usando procedimientos similares como el Procedimiento 6, y 2, 1-(1,1-bis(3-(trifluorometoxi)fenil)but-3-enil)-3-ciclopentilurea se obtuvo. $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.41 (t, J=7.96 Hz, 2 H), 7.37 - 7.31 (m, 2 H) 7.27 (m, 2 H), 7.18 (d, J=8.08 Hz, 2 H), 5.48 - 5.36 (m, 1 H), 5.25 - 5.15 (m, 3 H), 4.10 (s, br,

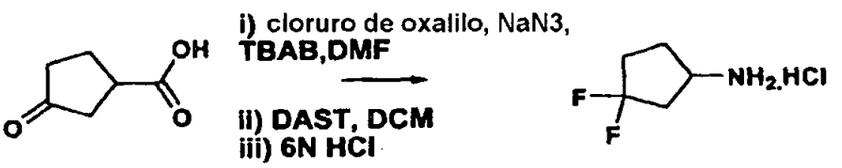
1 H), 3.86-3.96 (m, 1 H), 3.17 (d, 7=6.82 Hz, 2 H), 1.86 - 1.76 (m, 2 H), 1.53 - 1.42, (m, 4 H) 1.18 - 1.07 (m, 2 H); CL-EM (ESI) 503.33 (M+H), tiempo de retención = 4.26 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min).

**EJEMPLO 83**



**(R)-1-(3,3-difluorociclopentil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)urea**

**Procedimiento 12**




A la solución de ácido 3-oxociclopentancarboxílico (2.85 g, 22.2 mmoles) en $CH_2Cl_2$ seco (4 ml) se le agregó cloruro de oxalilo (2.0M en diclorometano, 13 ml) a 0°C sobre 15 min seguido por DMF (50 ml) Después de que la adición se completó, la mezcla de reacción se agitó durante 2 h (0°C hasta temperatura ambiente). El bromuro de tetrabutilamonio (35 mg) se agregó entonces seguido por una solución de azida de sodio (2.17 g, 26.7 mmoles, en la cantidad mínima de $H_2O$, 9 ml) a 0°C, y la mezcla de reacción café ligera resultante se agitó durante 1 h a temperatura ambiente. La reacción se

observó y durante la terminación, la fase orgánica se separó. La fase acuosa se extrajo con $CH_2Cl_2$ (3 x 8 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron con sulfato de sodio, y se filtraron a través de un tapón 2 cm de sílice. El tapón de gel de sílice se lavó con $CH_2Cl_2$ dos veces seguido con EtOAc 10% en $CH_2Cl_2$. El filtrado amarillo pálido resultante se concentró parcialmente. El alcohol de bencilo (25 ml) se agregó y el resto de $CH_2Cl_2$ se removió bajo vacío. La solución café ligero se calentó a 100°C durante 3h. Después de que esto se enfrió a temperatura ambiente, la solución café se destiló al vacío. El alcohol de bencilo se colectó y el residuo de aceite café viscoso se purificó por cromatografía de vaporización instantánea (120 g $SiO_2$, 0-40% EtOAc/hexano) para proporcionar 3-oxociclopentilcarbamato de bencilo como un aceite amarillo pálido e incoloro (2.39 g, 46% rendimiento). $^1H$ RMN ($CDCl_3$, 400 MHz): 7.35 (m, 5H), 5.09 (s, 2H), 4.87 (br, 1H), 4.28 (m, 1H), 2.63 (m, 1H), 2.39-2.15 (m, 4H), 1.86 (m, 1H). $^{13}C$ RMN ($CDCl_3$, 400 MHz): 215.7, 155.8, 136.2, 128.6, 128.3, 128.2, 66.9, 49.3, 45.2, 37.0, 29.9. CL/EM: [M+H] = 234.1

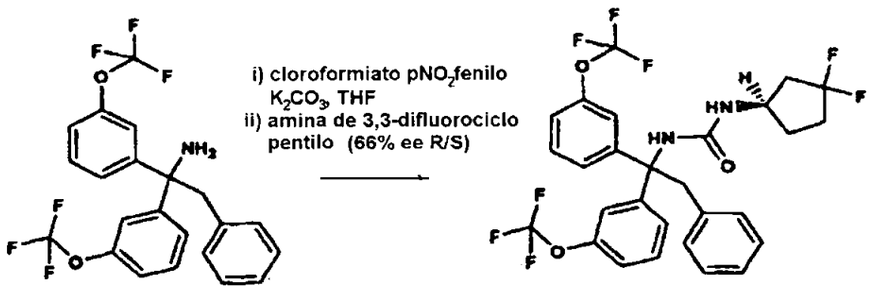
A una solución de 3-oxociclopentilcarbamato de bencilo (2.32 g, 9.96 mmoles) en $CH_2Cl_2$ (10 ml) se agregó DAST (4.3 ml, 28.9 mmoles) a temperatura ambiente. La mezcla de reacción se volvió café mientras se agitaba a temperatura ambiente durante la noche. Cuando la transformación se

completó por CLAR, se agregó salmuera a 0°C lentamente hasta apagar la reacción [Precaución: reaccionó violentamente]. El $CH_2Cl_2$ se agregó y la solución se extrajo con $CH_2Cl_2$ (3x10 ml). Las fases orgánicas combinadas se secaron sobre $Na_2SO_4$, y se concentró. El residuo se purificó por cromatografía de vaporización instantánea (40 g $SiO_2$, 0-40% EtOAc/hexano) para suministrar 3,3-difluorociclopentilcarbamato de bencilo como un sólido blanco apagado (1.5 g, 59%). $^1H$ RMN ($CDCl_3$, 400 MHz): 7.35 (m, 5H), 5.09 (s, 2H), 4.90 (br, 1H), 4.23 (m, 1H), 2.50 (m, 1H), 2.25-1.98 (m, 4H), 1.70 (m, 1H). $^{13}C$ RMN ($CDCl_3$, 400 MHz): 155.6, 136.2, 128.6, 128.3, 128.2, 66.9, 50.86, 49.3, 42.6 (t), 34.2 (t), 30.6. $^{19}F$ RMN ($CDCl_3$, con $CFCl_3$ como estándar, 400 MHz): -88.2 (m, 1F), -91.4 (m, 1F).

El 3,3-difluorociclopentilcarbamato de bencilo (1.5 g, 5.88 mmoles) en HCl 6N (6 ml) se calentó a 100°C durante 20 h. Después de que la mezcla de reacción se enfrió a temperatura ambiente, la solución café se extrajo con $Et_2O$ (2 x 2 ml) para remover material de partida sin reaccionar y tolueno. La fase acuosa se secó en un speed vac (centrifugación + vacío) con calentamiento para dar clorohidrato de 3,3-difluorociclopentanamina como un sólido café ligero (0.79 g, 85% rendimiento). $^1H$ RMN (MeOD-$d_4$, 400 MHz): 4.79 (m, 1H), 2.62 (m, 1H), 2.32 (m, 2H), 2.18 (m, 2H), 1.87 (m, 1H). $^{13}C$ RMN (MeOD-$d_4$, 400 MHz): 131.4 (t), 41.0 (t), 34.8 (t), 28.9. $^{19}F$ RMN (MeOD-$d_4$, con $CFCl_3$ como estándar, 400

1215

MHz): -93.0 (m, 2F). CL/EM: [M+H]= 121.9.



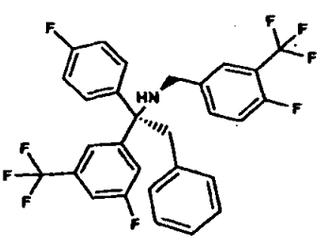

La 2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etanamina se preparó de conformidad como se describió por el Procedimiento 6. A una solución de 2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etanamina (77 mg, 0.17 mmoles) en $CH_2Cl_2$ (1 ml), se le agregó $K_2CO_3$ (241 mg, 1.7 mmoles) seguido por cloroformiato de 4-nitrofenilo (70 mg, 0.35 mmoles). La mezcla de reacción se agitó a temperatura ambiente hasta que el material de partida se consumió. La solución se diluyó con $CH_2Cl_2$ y se lavó con $NaHCO_3$. La capa orgánica se separó y la capa acuosa se extrajo con $CH_2Cl_2$ (3x). Los orgánicos combinados se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se tomó en $CH_2Cl_2$ anhidro (1.6 ml) y esta mezcla se usó como una solución de reserva del carbamato intermediario (0.11 M en $CH_2Cl_2$).

El 2-Fenil-1,1-bis(3-(trifluorometoxi)fenil)etilcarbamato de 4-nitrofenilo (400 µL de la solución de reserva anterior, 0.044 mmoles) se agregó a un frasco seguido por clorohidrato 3,3-

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difluorociclopentanamina (14 mg, 0.087 mmoles, 66.4% ee R) y base Hunig (15 µl, 0.087 mmoles). La reacción se observó para la desaparición del carbamato. Durante la terminación, la mezcla de reacción se diluyó con $CH_2Cl_2$, se lavó sucesivamente con $NaHCO_3$ y NaOH 1N, y se extrajo con $CH_2Cl_2$ (3x). Los orgánicos combinados se secaron sobre $Na_2SO_4$, se filtraron, concentraron bajo presión reducida. La purificación del residuo se terminó por CLAR preparativa (YMC Combiprep ODS-A 30x50 mm; fase móvil: 10% MeOH / 90% $H_2O$ / 0.1% de TFA) para proporcionar la urea deseada (9.1 mg) como una película. $^1H$ RMN (500 MHz, $CDCl_3$), mezcla diaestereomérica, aprox. 83:17) δ 7.36 (t, J= 7.5 Hz, 2H), 7.22-7.10 (m, 7H), 7.06 (s, 2H), 6.65 (d, J= 5.0 Hz, 2H), 4.89 (s, 1H), 4.33-4.24 (m, 1H), 4.23-4.14 (m, 1H), 3.76 (s, 2H), 2.42-2.30 (m, 1H), 2.13-1.93 (m, 3H), 1.77-1.67 (m, 1H), 1.48-1.41 (m, 1H); CL/EM (MeOH/$H_2O$/$NH_4OAc$ fase móvil) tr = 4.26 min; [M+H] = 589.3.

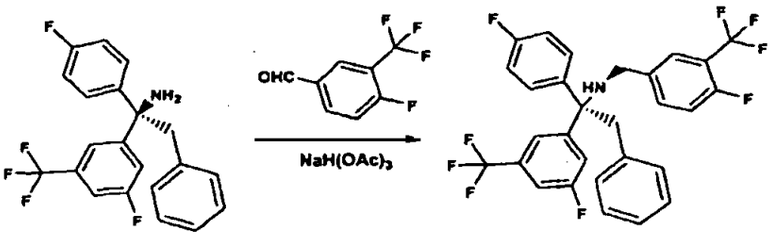
**EJEMPLO 84**




**(R)-N-(4-fluoro-3-(trifluorometil)bencil)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletanamina**

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**Procedimiento 13**




La (R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletanamina (21.5 mg, 0.057 mmoles) en dicloroetano (0.5 ml) en un frasco de dos cilindros se agregó 4-fluoro-3-(trifluorometil)benzaldehído (21.9 mg, 0.114 mmoles) seguido por una gota de ácido acético. La mezcla de reacción se agitó durante 20 minutos a temperatura ambiente antes $NaBH(OAc)_3$ (36.3 mg, 0.171 mmoles) se agregó. La reacción se agitó a temperatura ambiente durante la noche. Los solventes se removieron y el residuo se purificó por CLAR preparativa (columna phenominex C18, 21x100 mm, 5 µ) usando MeOH/H2O (con TFA 0.1%) para dar (R)-N-(4-fluoro-3-(trifluorometil)bencil)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletanamina como un aceite incoloro (17.5 mg, 46% rendimiento). CLEM: 4.32 min (gradiente 4 min, $MeOH/H_2O$ TFA 0.1%); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 3.78-3.91 (m, 4 H), 6.60 (d, J=7.47 Hz, 2 H), 7.14-7.27 (m, 7 H), 7.35-7.48 (m, 6 H).

1218

**TABLA 4**

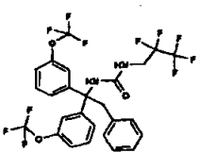
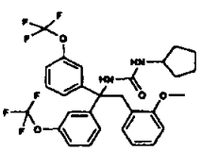
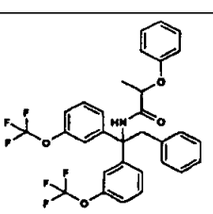
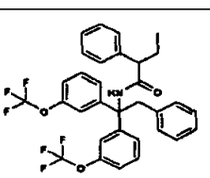
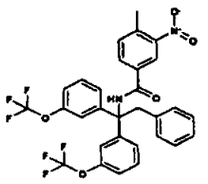
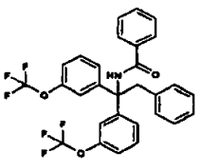
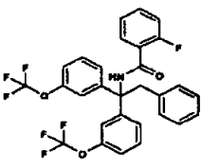
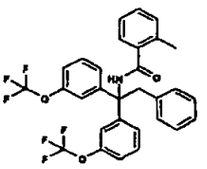
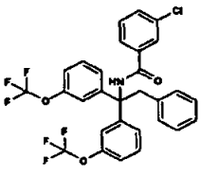
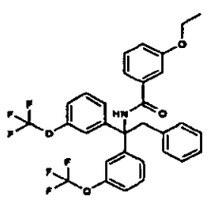
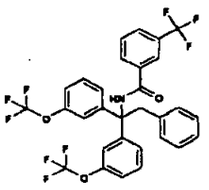
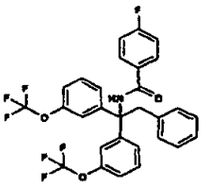
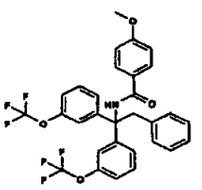
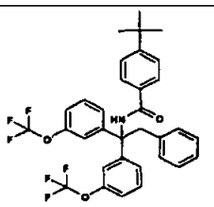
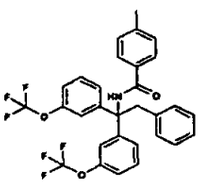
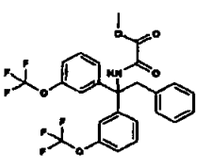
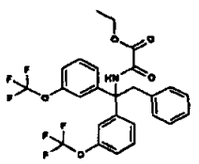
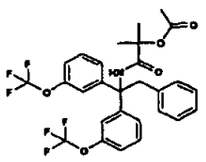
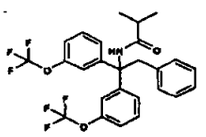
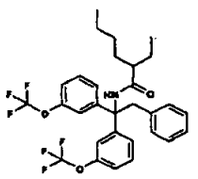
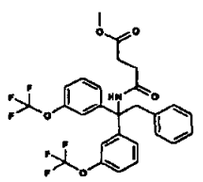
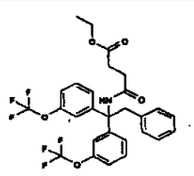
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|---|---|---|---|---|
| 85 |  | 1-(2,2,3,3,3-pentafluoropropil)-3-(2-fenil-a,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.30 CL 617.3 [M+H]+ | Procedimiento 11 y 12 |
| 86 |  | 1-ciclopentil-3-(2-(2-metoxifenil)-1,1-bis(3-trifluorometoxi) fenil) etil)urea | 3.92 CL 583.03 [M+H]+ | Procedimiento 11 y 12 |

**Tabla 5**

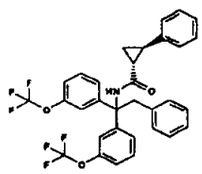
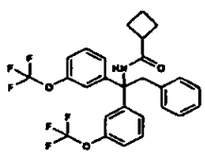
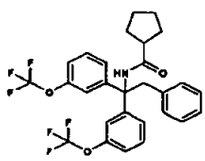
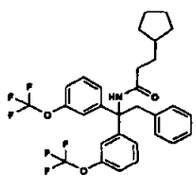
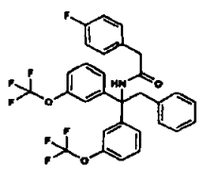
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| 87 |  | 2-fenoxi-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil) propanamida | 4.37 CL 590.16 [M+H]+ | Procedimiento 11 y 7 |
| 88 |  | 2-fenil-N-(2-fenil-1,1-bis(3-trifluorometoxi) fenil) etil) butanamida | 4.39 CL 588.22 [M+H]+ | Procedimiento 11 y 7 |

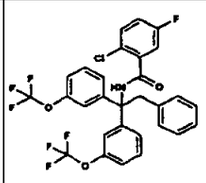
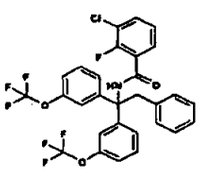
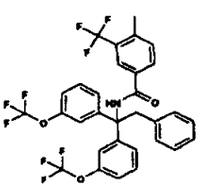
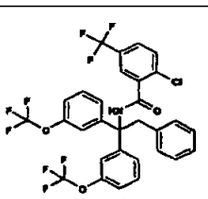
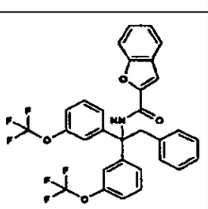
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 89 |  | 4-metil-3-nitro-N-(2-fenil-1,1-bis(3-trifluorometoxi) fenil) etil)benzamida | 4.31 CL 605.15 [M+H]+ | Procedimiento 11 y 7 |
| 90 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.24 CL 546.14 [M+H]+ | Procedimiento 11 y 7 |
| 91 |  | 2-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.27 CL 564.09 [M+H]+ | Procedimiento 11 y 7 |
| 92 |  | 2-metil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.26 CL 560.14 [M+H]+ | Procedimiento 11 y 7 |
| 93 |  | 3-cloro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.36 CL 580.09 [M+H]+ | Procedimiento 11 y 7 |
| 94 |  | 3-etoxi-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.32 CL 590.16 [M+H]+ | Procedimiento 11 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 95 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluoro metil) benzamida | 4.36 CL 614.1 [M+H]+ | Procedimiento 11 y 7 |
| 96 |  | 4-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.28 CL 564.12 [M+H]+ | Procedimiento 11 y 7 |
| 97 |  | 4-metoxi-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.26 CL 576.15 [M+H]+ | Procedimiento 11 y 7 |
| 98 |  | 4-ter-butil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.51 CL 602.16 [M+H]+ | Procedimiento 11 y 7 |
| 99 |  | 4-metil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.30 CL 560.14 [M+H]+ | Procedimiento 11 y 7 |
| 100 |  | acetato de metil 2-oxo-2-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilamino) | 4.13 CL 528.08 [M+H]+ | Procedimiento 11 y 7 |

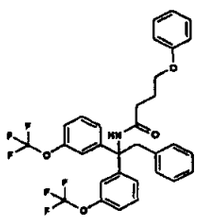
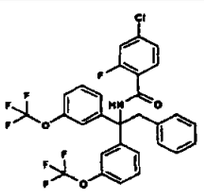
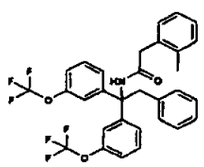
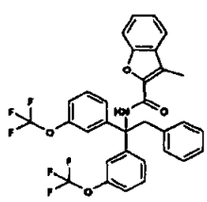
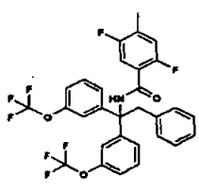
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 101 |  | acetato de etil 2-oxo-2-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilamino) | 4.18 CL 542.14 [M+H]+ | Procedimiento 11 y 7 |
| 102 |  | acetato de 2-metil-1-oxo-1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilamino) propan-2-ilo | 4.19 CL 570.15 [M+H]+ | Procedimiento 11 y 7 |
| 103 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil) isobutiramida | 4.22 CL 512.14 [M+H]+ | Procedimiento 11 y 7 |
| 104 |  | 2-etil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)hexanamida | 4.45 CL 568.21 [M+H]+ | Procedimiento 11 y 7 |
| 105 |  | 4-oxo-4-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilamino) butanoato de metilo | 4.17 CL 556.13 [M+H]+ | Procedimiento 11 y 7 |
| 106 |  | 4-oxo-4-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilamino) butanoato de etilo | 4.21 CL 570.15 [M+H]+ | Procedimiento 11 y 7 |

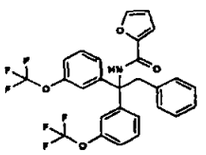
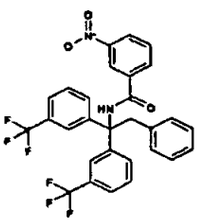
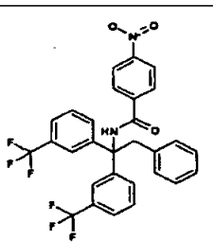
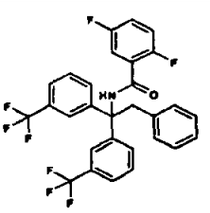
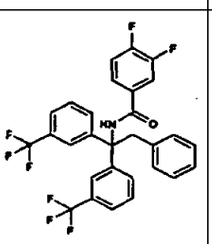
1222

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 107 |  | (1R,2R)-2-fenil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ciclopropano carboxamida | 4.37 CL 586.15 [M+H]+ | Procedimiento 11 y 7 |
| 108 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ciclobutan carboxamida | 4.27 CL 524.13 [M+H]+ | Procedimiento 11 y 7 |
| 109 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil) ciclopentan carboxamida | 4.32 CL 538.14 [M+H]+ | Procedimiento 11 y 7 |
| 110 |  | 3-ciclopentil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil) propanamida | 4.48 CL 566.17 [M+H]+ | Procedimiento 11 y 7 |
| 111 |  | 2-(4-fluorofenil)-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)acetamida | 4.29 CL 578.1 [M+H]+ | Procedimiento 11 y 7 |

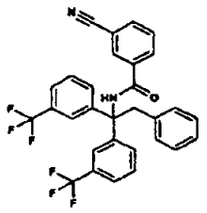
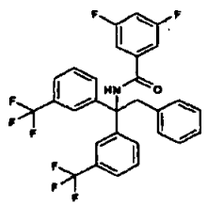
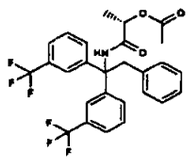
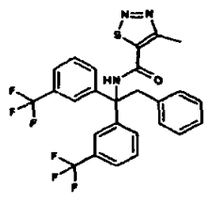
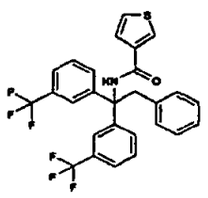
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 112 |  | 2-cloro-5-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil) benzamida | 4.27 CL 598.06 [M+H]+ | Procedimiento 11 y 7 |
| 113 |  | 3-cloro-2-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil) benzamida | 4.35 CL 598.04 [M+H]+ | Procedimiento 11 y 7 |
| 114 |  | 4-metil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.43 CL 628.11 [M+H]+ | Procedimiento 11 y 7 |
| 115 |  | 2-cloro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-5-(trifluorometil) benzamida | 4.36 CL 648.05 [M+H]+ | Procedimiento 11 y 7 |
| 116 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil) benzofuran-2-carboxamida | 4.39 CL 586.12 [M+H]+ | Procedimiento 11 y 7 |

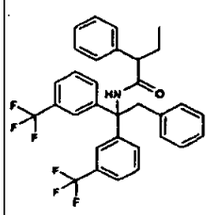
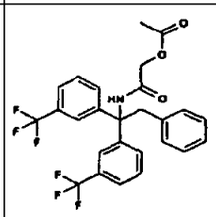
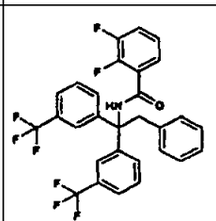
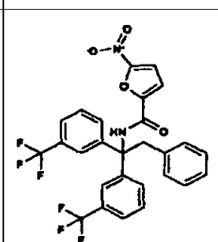
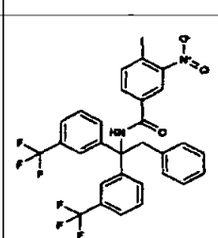
1224

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 117 |  | 4-fenoxi-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil) butanamida | 4.39 CL 604.16 [M+H]+ | Procedimiento 11 y 7 |
| 118 |  | 4-cloro-2-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.39 CL 598.1 [M+H]+ | Procedimiento 11 y 7 |
| 119 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-2-o-tolilacetamida | 4.35 CL 574.15 [M+H]+ | Procedimiento 11 y 7 |
| 120 |  | 3-metil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzofura-2-carboxamida | 4.57 CL 600.14 [M+H]+ | Procedimiento 11 y 7 |
| 121 |  | 2,5-difluoro-4-metil-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)benzamida | 4.40 CL 596.1 [M+H]+ | Procedimiento 11 y 7 |

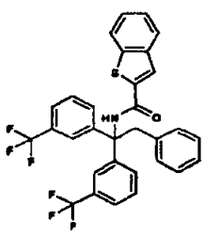
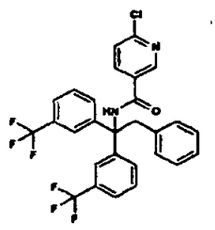
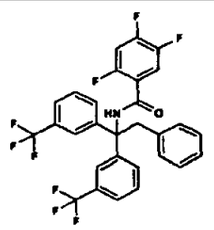
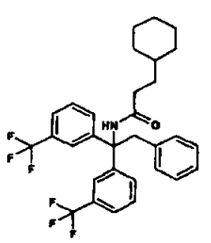
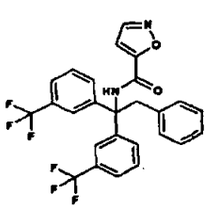
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 122 |  | N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)furan-2-carboxamida | 4.19 CL 536.13 [M+H]+ | Procedimiento 11 y 7 |
| 127 |  | 3-nitro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.19 CL 559.22 [M+H]+ | Procedimiento 11 y 7 |
| 128 |  | 4-nitro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.19 CL 559.21 [M+H]+ | Procedimiento 11 y 7 |
| 129 |  | 2,5-difluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.19 CL 550.21 [M+H]+ | Procedimiento 11 y 7 |
| 130 |  | 3,4-difluoro--N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.22 CL 550.2 [M+H]+ | Procedimiento 11 y 7 |

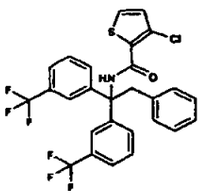
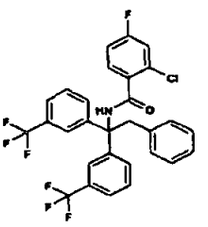
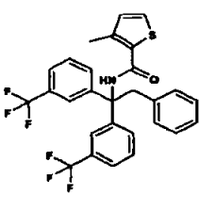
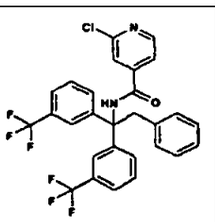
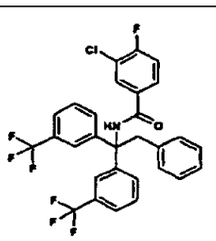
1226

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 131 |  | 3-ciano-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.10 CL 539.2 [M+H]+ | Procedimiento 11 y 7 |
| 132 |  | 3,5-difluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.24 CL 550.21 [M+H]+ | Procedimiento 11 y 7 |
| 133 |  | acetato de (S)-1-oxo-1-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etilamino) propan-2-il | 4.04 CL 524.23 [M+H]+ | Procedimiento 11 y 7 |
| 134 |  | 4-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-1,2,3-tiadiazol-5-carboxamida | 4.14 CL 520.17 [M+H]+ | Procedimiento 11 y 7 |
| 135 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)tiofen-3-carboxamida | 4.10 CL 520.17 [M+H]+ | Procedimiento 11 y 7 |

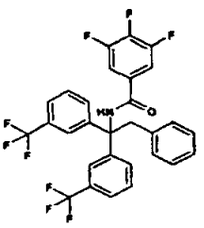
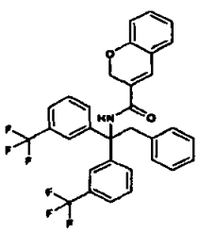
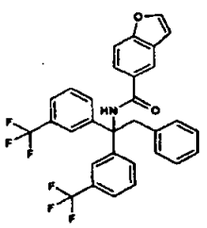
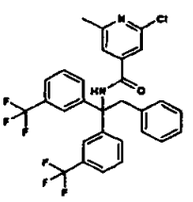
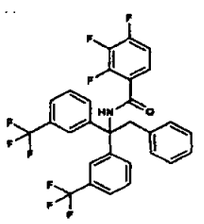
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 136 |  | 2-fenil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil) butanamida | 4.29 CL 556.26 [M+H]+ | Procedimiento 11 y 7 |
| 137 |  | acetato de 2-oxo-2-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etilamina)etilo | 4.00 CL 510.2 [M+H]+ | Procedimiento 11 y 7 |
| 138 |  | 2,3-difluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.16 CL 550.14 [M+H]+ | Procedimiento 11 y 7 |
| 139 |  | 5-nitro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)furan-2-carboxamida | 4.11 CL 549.16 [M+H]+ | Procedimiento 11 y 7 |
| 140 |  | 4-metil-3-nitro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.23 CL 573.21 [M+H]+ | Procedimiento 11 y 7 |

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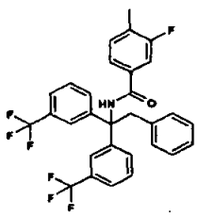
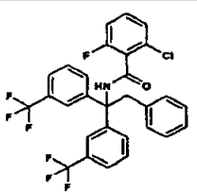
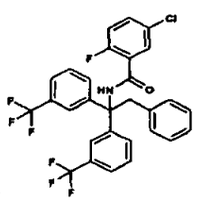
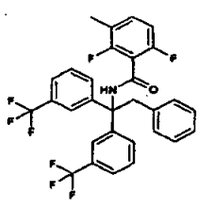
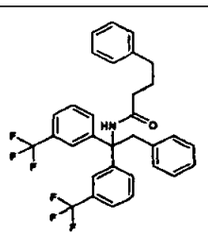
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 141 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzo[b] tiofen-2-carboxamida | 4.29 CL 570.17 [M+H]+ | Procedimiento 11 y 7 |
| 142 |  | 6-cloro-N-(2-fenil-1,1-bis(3-(trifluorometil )fenil)etil) nicotinamida | 4.15 CL 549.17 [M+H]+ | Procedimiento 11 y 7 |
| 143 |  | 2,4,5-trifluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.24 CL 568.2 [M+H]+ | Procedimiento 11 y 7 |
| 144 |  | 3-ciclohexil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil) propanamida | 4.44 CL 548.27 [M+H]+ | Procedimiento 11 y 7 |
| 145 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)isoxazol-5-carboxamida | 4.00 CL 505.18 [M+H]+ | Procedimiento 11 y 7 |

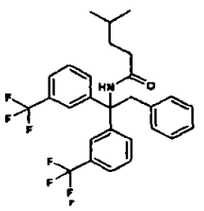
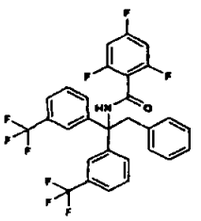
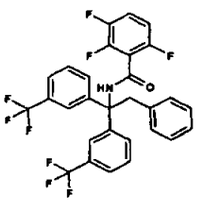
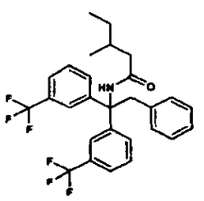
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 146 |  | 3-cloro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)tiofen-2-carboxamida | 4.22 CL 554.12 [M+H]+ | Procedimiento 11 y 7 |
| 147 |  | 2-cloro-4-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.18 CL 566.15 [M+H]+ | Procedimiento 11 y 7 |
| 148 |  | 3-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)tiofen-2-carboxamida | 4.15 CL 534.19 [M+H]+ | Procedimiento 11 y 7 |
| 149 |  | 2-cloro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) isonicotinamida | 4.17 CL 534.19 [M+H]+ | Procedimiento 11 y 7 |
| 150 |  | 3-cloro-4-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.30 CL 566.15 [M+H]+ | Procedimiento 11 y 7 |

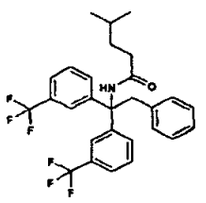
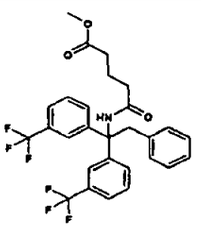
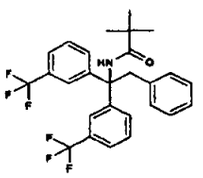
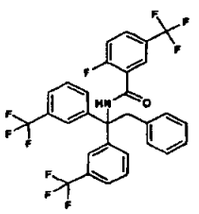
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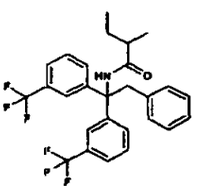
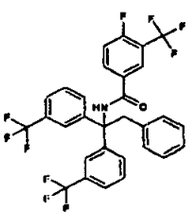
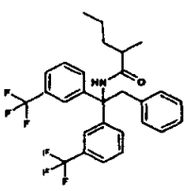
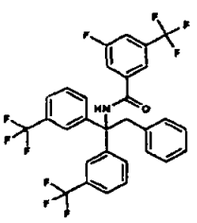
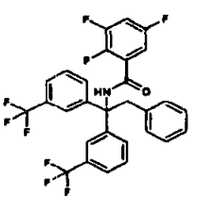
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 151 |  | 3,4,5-trifluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.33 CL 568.15 [M+H]+ | Procedimiento 11 y 7 |
| 152 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)-2H-cromen-3-carboxamida | 4.31 CL 568.17 [M+H]+ | Procedimiento 11 y 7 |
| 153 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzo furan-5-carboxamida | 4.17 CL 554.16 [M+H]+ | Procedimiento 11 y 7 |
| 154 |  | 2-cloro-6-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil) isonicotinamida | 4.23 CL 563.15 [M+H]+ | Procedimiento 11 y 7 |
| 155 |  | 2,3,4-trifluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.23 CL 563.15 [M+H]+ | Procedimiento 11 y 7 |

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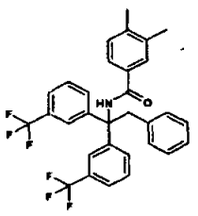
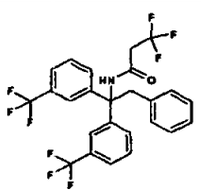
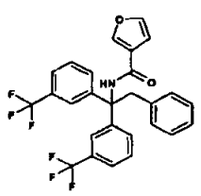
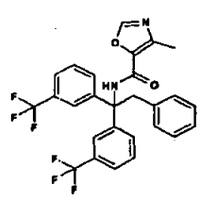
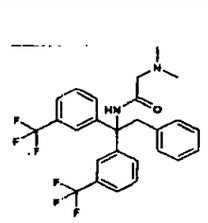
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 156 |  | 3-fluoro-4-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.24 CL 546.15 [M+H]+ | Procedimiento 11 y 7 |
| 157 |  | 2-cloro-6-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.11 CL 566.13 [M+H]+ | Procedimiento 11 y 7 |
| 158 |  | 5-cloro-6-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.27 CL 566.09 [M+H]+ | Procedimiento 11 y 7 |
| 159 |  | 2,6-difluoro-3-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.13 CL 564.15 [M+H]+ | Procedimiento 11 y 7 |
| 160 |  | 4-fenil- -N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)butanamida | 4.30 CL 556.21 [M+H]+ | Procedimiento 11 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 161 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzo[b] tiofen-3-carboxamida | 4.28 CL 570.12 [M+H]+ | Procedimiento 11 y 7 |
| 162 |  | 2,4,6-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)benzamida | 4.12 CL 568.11 [M+H]+ | Procedimiento 11 y 7 |
| 163 |  | 2,3,6-trifluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) **fenil)** etil)benzamida | 4.11 CL 568.15 [M+H]+ | Procedimiento 11 y 7 |
| 164 |  | 3-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) pentanamida | 4.24 CL 508.26 [M+H]+ | Procedimiento 11 y 7 |

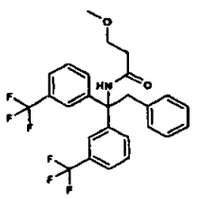
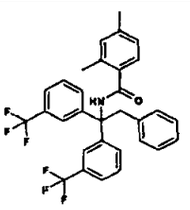
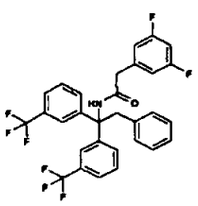
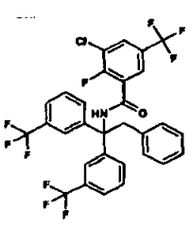
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 165 |  | 4-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)pentanamida | 4.25 CL 508.19 [M+H]+ | Procedimiento 11 y 7 |
| 166 |  | metil-5-oxo-5-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etilamina) pentanoato | 4.06 CL 538.2 [M+H]+ | Procedimiento 11 y 7 |
| 167 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) pivalamida | 4.18 CL 494.19 [M+H]+ | Procedimiento 11 y 7 |
| 168 |  | 2-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil)-5-trifluorometil) benzamida | 4.26 CL 600.1 [M+H]+ | Procedimiento 11 y 7 |

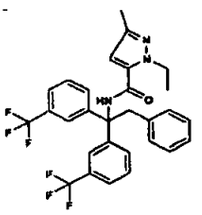
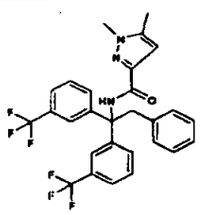
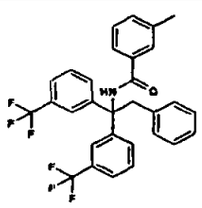
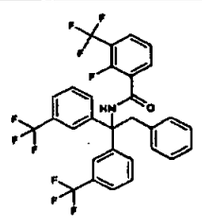
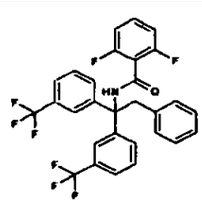
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 169 |  | 2-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) butanamida | 4.16 CL 494.19 [M+H]+ | Procedimiento 11 y 7 |
| 170 |  | 4-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-3-(trifluorometil) benzamida | 4.30 CL 600.12 [M+H]+ | Procedimiento 11 y 7 |
| 171 |  | 2-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) pentanamida | 4.22 CL 508.26 [M+H]+ | Procedimiento 11 y 7 |
| 172 |  | 3-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-5-trifluorometil) benzamida | 4.35 CL 600.2 [M+H]+ | Procedimiento 11 y 7 |
| 173 |  | 2,3,5-trifluoro - N-(2- fenil-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.22 CL 568.11 [M+H]+ | Procedimiento 11 y 7 |

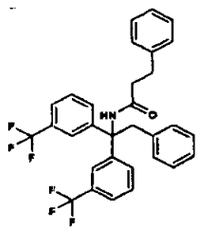
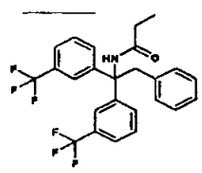
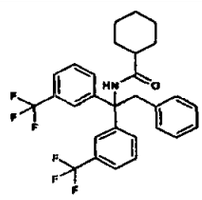
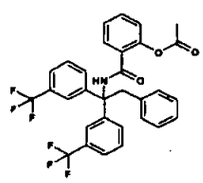
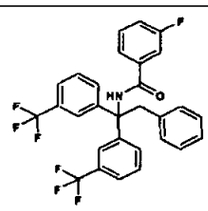
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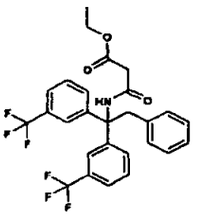
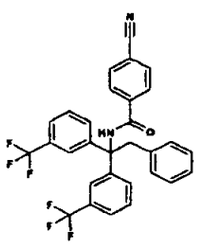
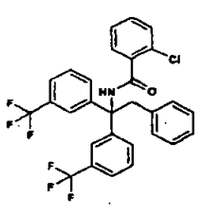
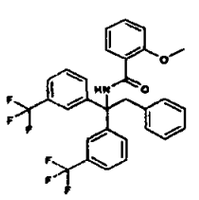
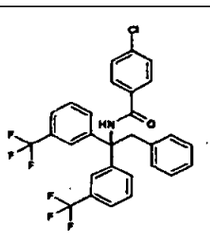
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 174 |  | 3,4-dimetil- N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.26 CL 542.2 [M+H]+ | Procedimiento 11 y 7 |
| 175 |  | 3,3,3-trifluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) propanamida | 4.07 CL 520.14 [M+H]+ | Procedimiento 11 y 7 |
| 176 |  | -N-(2-fenil-1,1-bis(3-(trifluoro metil)fenil) etil)furan-3-carboxamida | 4.06 CL 504.15 [M+H]+ | Procedimiento 11 y 7 |
| 177 |  | 4-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)oxazol-5-carbozamida | 4.06 CL 504.15 [M+H]+ | Procedimiento 11 y 7 |
| 178 |  | 2-(dimetilamino)-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) acetamida | 3.50 CL 495.22 [M+H]+ | Procedimiento 11 y 7 |

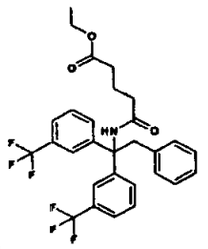
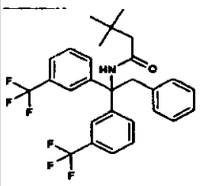
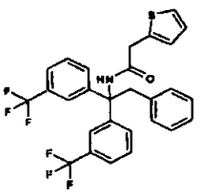
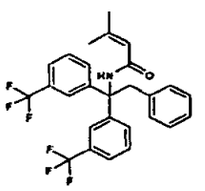
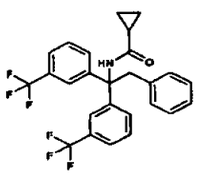
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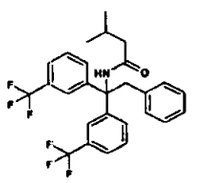
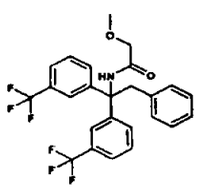
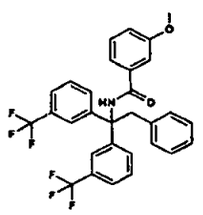
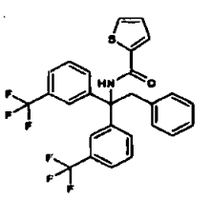
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 179 |  | 3-metoxi-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) propanamida | 4.06 CL 496.19 [M+H]+ | Procedimiento 11 y 7 |
| 180 |  | 2,4-diemtil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.23 CL 542.19 [M+H]+ | Procedimiento 11 y 7 |
| 181 |  | 2-3,5-difluorofenil)-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil) etil) acetamida | 4.21 CL 564.15 [M+H]+ | Procedimiento 11 y 7 |
| 182 |  | 3-cloro-2-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-5-trifluorometil) benzamida | 4.38 CL 634.17 [M+H]+ | Procedimiento 11 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 183 |  | 1-etil-3-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-1-H-pirazolo-5-carboxamida | 4.17 CL 546.27 [M+H]+ | Procedimiento 11 y 7 |
| 184 |  | 1,5-dimetil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-1-H-pirazolo-3-carboxamida | 4.09 CL 532.27 [M+H]+ | Procedimiento 11 y 7 |
| 185 |  | 3-metil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.20 CL 528.26 [M+H]+ | Procedimiento 11 y 7 |
| 186 |  | 2-fluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil)-3-(trifluorometil) benzamida | 4.23 CL 600.17 [M+H]+ | Procedimiento 11 y 7 |
| 187 |  | 2,6-difluoro-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.07 CL 550.17 [M+H]+ | Procedimiento 11 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 188 |  | 3-fenil-N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) propanamida | 4.25 CL 542.26 [M+H]+ | Procedimiento 11 y 7 |
| 189 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) propionamida | 4.06 CL 466.25 [M+H]+ | Procedimiento 11 y 7 |
| 190 |  | N-(2-fenil-1,1-bis(3-(trifluorometil) fenil)etil) ciclohexan carboxamida | 4.26 CL 520.26 [M+H]+ | Procedimiento 11 y 7 |
| 191 |  | acetato de 2-((2-fenil-1,1- bis(3-(trifluorometil) fenil)etil) carbamoil)fenil | 4.07 CL 572.22 [M+H]+ | Procedimiento 11 y 7 |
| 192 |  | 3-fluoro-N-(2-fenil-1,1- bis(3-(trifluorometil) fenil)etil) benzamida | 4.17 CL 532.21 [M+H]+ | Procedimiento 11 y 7 |

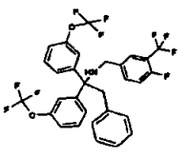
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 193 |  | etil-3-oxo-3-(2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etilamino) propanoato | 4.10 CL 539.2 [M+H]+ | Procedimiento 11 y 7 |
| 194 |  | 4-ciano-N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.10 CL 539.2 [M+H]+ | Procedimiento 11 y 7 |
| 195 |  | 2-cloro-N-(2-fenil-3-1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.13 CL 548.17 [M+H]+ | Procedimiento 11 y 7 |
| 196 |  | 2-metoxi--N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.21 CL 544.2 [M+H]+ | Procedimiento 11 y 7 |
| 197 |  | 4-cloro-N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.25 CL 548.16 [M+H]+ | Procedimiento 11 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 198 |  | etil 5-oxo-5- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etilamina) pentanoato | 4.11 CL 552.26 [M+H]+ | Procedimiento 11 y 7 |
| 199 |  | 3,3-dimetil -N-(2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) butanamida | 4.23 CL 508.26 [M+H]+ | Procedimiento 11 y 7 |
| 200 |  | N- (2-fenil-3-1,1- bis(3-(trifluorometil) fenil)etil)-2-tiofen-2-il)acetamida | 4.14 CL 534.18 [M+H]+ | Procedimiento 11 y 7 |
| 201 |  | 3-metil-N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil)but-2-enamida | 4.14 CL 492.26 [M+H]+ | Procedimiento 11 y 7 |
| 202 |  | N- (2-fenil-3-1,1- bis(3-(trifluorometil) fenil)etil)ciclo propancarboxamida | 4.07 CL 478.23 [M+H]+ | Procedimiento 11 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 203 |  | 3-metil-N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) butanamida | 4.17 CL 494.26 [M+H]+ | Procedimiento 11 y 7 |
| 204 |  | 2-metoxi-N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) acetamida | 4.03 CL 482.25 [M+H]+ | Procedimiento 11 y 7 |
| 205 |  | 3-metoxi-N- (2-fenil-3- 1,1-bis(3-(trifluorometil) fenil)etil) benzamida | 4.15 CL 544.27 [M+H]+ | Procedimiento 11 y 7 |
| 206 |  | N- (2-fenil-3- 1,1- bis(3-(trifluorometil) fenil)etil)tiofen-2-carboxamida | 4.09. CL 520.2 [M+H]+ | Procedimiento 11 y 7 |

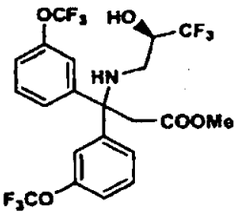
1242

**TABLA 6**

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 207 |  | N-(4-fluoro-3-(trifluorometil) bencil)-2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etanamina | 4.51 CL No obs. [M+H]+ | Procedimiento 11 y 13 |

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos descritos arriba y a los procedimientos adicionales descritos abajo.

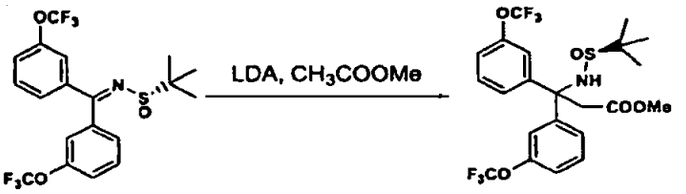
**EJEMPLO 208**




**3-(3,3,3-trifluoro-2-hidroxipropilamino)-3,3-bis(3-(trifluorometoxi)fenil)propanoato de (R)-metilo**

**Procedimiento 14**

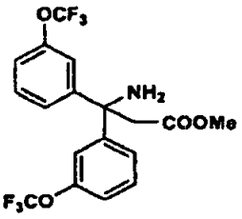
**3-(2-metilpropan-2-ilsulfmamido)-3,3-bis(3-(trifluorometoxi)fenil)propanoato de (R)-metilo**




La (R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-

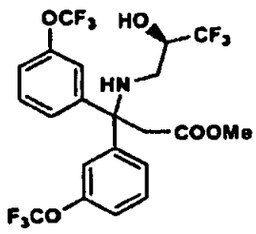
metilpropan-2-sulfinamida se preparó como se describió por el Procedimiento 11. Bajo una atmósfera de argón, $CH_3COOMe$ (0.70 ml, 8.83 mmoles, 2.0 eq) se agitó en $Et_2O$ anhidro (50 ml) en un matraz de fondo redondo secado al horno a -78°C. LDA (2.0 M, 4.4 ml, 8.8 mmoles, 2.0 eq) se agregó gota a gota. La mezcla resultante se agitó a -78°C durante 30 min. (R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida (2.0 g, 4.42 mmoles) en $Et_2O$ (10 ml) se agregó gota a gota a la solución agitada antes. La mezcla de reacción se agitó a -78°C durante 1.5 h. El $NH_4Cl$ saturado se agregó, seguido por la adición de EtOAc. La capa orgánica se lavó con $H_2O$, salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró hasta secarse. El residuo se purificó por cromatografía (gel de sílice, EtOAc/Hexanos = 0 hasta 100%) para dar N-(2-ciano-1,1-bis(3-(trifluorometoxi)fenil)-etil)-2-metilpropan-2-sulfinamida como un aceite color marrón ligero (1.96 g, rendimiento: 84.1%). CL-EM (ESI) 528.34 (M+H), tiempo de retención = 4.00 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) $\delta$ ppm 7.36 (d, J=8.0 Hz, 2H), 7.31 (t, J=8.0 Hz, 1H), 7.25-7.18 (m, 2H), 7.14-7.05 (m, 3H), 6.14 (s, 1H), 3.93 (d, J=16.1 Hz, 1H), 3.54 (d, J=15.9 Hz, 1H), 3.86 (m, 2 H), 3.49 (s, 3H), 1.26 (s, 9H). $^{13}C$ RMN (400 MHz, $CDCl_3$) $\delta$ ppm 22.71, 43.84, 1.68, 56.41, 63.69, 118.63, 119.52, 120.49, 121.35, 124.27, 125.73, 129.81, 129.92, 143.83, 147.52, 149.33, 171.93.

**3-amino-3,3-bis(3-(trifluorometoxi)fenil)propanoato de metilo**




Usando el mismo procedimiento como el del Procedimiento 6,3-amino-3,3-bis(3-(trifluorometoxi)fenil)propanoato de metilo se obtuvo. CL-EM (ESI) 407.16 ($M-NH_3+H$), tiempo de retención = 3.18 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.18 - 7.27 (m, 6 H), 7.02 (d, J=8.07 Hz, 2 H), 3.47 (s, 3H), 3.17 (s, 2H).

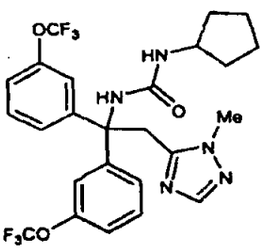
**3-(3,3,3-trifluoro-2-hidroxipropilamino)-3,3-bis(3-(trifluorometoxi)fenil)propanoato de (R)-metilo**




Usando procedimiento similar como el del Procedimiento 8, 3-(3,3,3-trifluoro-2-hidroxipropilamino)-3,3-bis(3-(trifluorometoxi)fenil)propanoato de (R)-metilo se obtuvo. CL-EM (ESI) 536.29 (M+H), tiempo de retención = 3.93 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.38-7.35 (m, 2H), 7.24-7.19 (m, 2H), 7.13 (m, 4H), 3.44 (s, 3H), 3.22-3.35 (m, 2H),

2.57-2.74 (m, 2H).

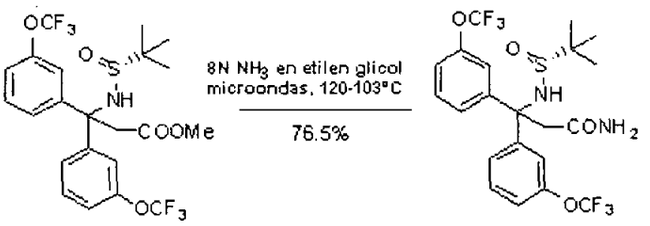
**EJEMPLO 209**




**1-ciclopentil-3-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea**

**Procedimiento 15**

**(R)-3-(2-metilpropan-2-ilsulfinamido)-3,3-bis(3-(trifluorometoxi)fenil)propanamida**



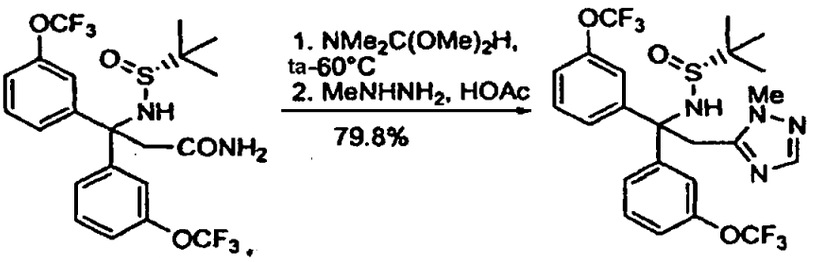

El (R)-metil-3-(2-metilpropan-2-ilsulfinamido)-3,3-bis(3-(trifluorometoxi)fenil)propanoato (se preparó como se describió por el Procedimiento 11, 0.70 g, 1.33 mmoles) se disolvió en etilenglicol saturado con $NH_3$(g) (6 ml) a temperatura ambiente en un frasco de microondas. La mezcla de reacción se calentó a 120°C durante 1200 segundos, y luego a 130°C durante 1200 seg bajo radiación de microondas. Después del enfriamiento, la tapa se removió, y $H_2O$ se agregó. La mezcla se extrajo con EtOAc (3x), se lavó con $H_2O$, salmuera, se secó ($Na_2SO_4$), se filtró y se concentró. El residuo se

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purificó por cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc, luego 10% MeOH en EtOAc) para dar 3-(2-metilpropan-2-ilsulfinamido)-3,3-bis(3-(trifluorometoxi)fenil)-propanamida como sólidos blancos (0.52 g, rendimiento: 76.4%) CLEM: 3.88 min [M+1] 513.28 (gradiente 4 min, MeOH/$H_2O$ TFA 0.1%); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.40-7.29 (m, 3 H), 7.22-7.12 (m, 3 H), 7.11-7.02 (m, 2 H), 6.29 (m, 2 H), 5.40 (s, br, 1H), 3.78 (d, J=14.50 Hz, 1 H), 3.71 (s, 2 H), 3.35 (d, J=14.50 Hz, 1 H), 1.21-1.28 (m, 9 H).

**Procedimiento 16**

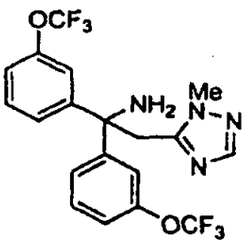
**(R)-2-metil-N-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)propan-2-sulfinamida**




La (R)-3-(2-metilpropan-2-ilsulfinamido)-3,3-bis(3-(trifluorometoxi)fenil)propanamida (Procedimiento 15, 0.21 g, 0.41 mmoles) se agitó en N,N-dimetilformamida dimetilacetal (6 ml) a temperatura ambiente durante 1.5 h, luego 60°C durante 20 min. El solvente se evaporó para dar N-(5-(dimetilamino)-3-oxo-1,1-bis(3-(trifluorometoxi)fenil)pent-4-enil)-2-metilpropan-2-sulfinamida cruda. CL-EM (ESI) 568.4

(M+H), tiempo de retención = 3.60 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min). Este residuo de tono café se disolvió en HOAc (2 ml), e hidracina de metilo (0.4 ml) se agregó. La mezcla de reacción resultante se calentó a 60°C durante 1.5 h. CL-EM mostró la terminación de la reacción. Después del enfriamiento, $H_2O$ se agregó. Esto se extrajo con EtOAc (2x), se lavó con $NaHCO_3$ saturado, $H_2O$, salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró hasta secarse. Esto se purificó por cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar 2-metil-N-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)propano-2-sulfinamida (0.18 g, rendimiento: 79.8%). CL-EM (ESI) 551.35 (M+H), tiempo de retención = 3.99 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min);

**2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)-etanamina**

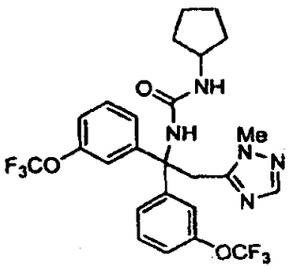



Usando el mismo procedimiento como el descrito en los procedimientos 6, 2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etanamina se obtuvo. CL-EM (ESI) 447.24 (M+H), tiempo de retención = 2.90 min (10-90% MeOH en

1248

$H_2O$ con TFA 0.1% en una corrida de 4-min);

**1-ciclopentil-3-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea**




Usando el mismo procedimiento como se describió por el Procedimiento 2, 1-ciclopentil-3-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea se obtuvo. CL-EM (ESI) 558.43 (M+H), tiempo de retención = 3.81 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.44 (s, 1H), 7.32 (t, J=8.0 Hz, 2H), 7.26 (m, 2H), 7.18 (m, 2H), 7.11 (d, J= 8.0Hz, 2H), 6.96 (br, s, 1H), 4.56 (m, 1H), 3.87 (m, 1H), 3.73 (s, 2H), 3.35 (s, 3H), 1.92-1.85 (m, 2H), 1.61-1.49 (m, 4H), 1.29-1.22 (m, 2H).

**EJEMPLO 210**

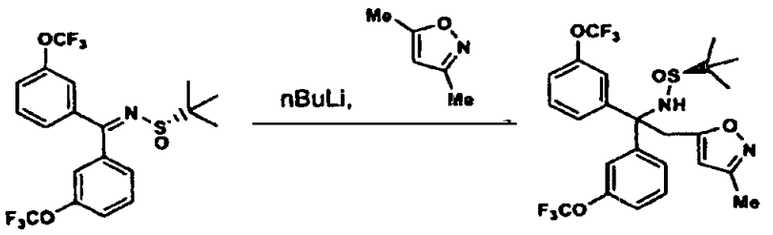



**1-ciclopentil-3-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea**

1249

**Procedimiento 17**

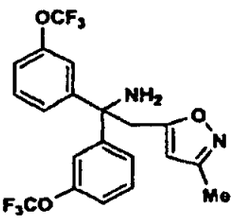
**(R)-2-metil-N-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)propan-2-sulfinamida**




La (R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida se preparó como se describió por el Procedimiento 11. Bajo una atmósfera de argón, 3,5-dimetilisoxazol (0.20 ml) se agitó en THF anhidro en un matraz de fondo redondo secado al horno a -78°C. Se agregó nBuLi (2.5 M en hexanos, 0.84 ml, 2.1 mmoles) gota a gota. La solución amarillenta resultante se agitó a -78°C durante 2h. N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida (0.81 g, 1.8 mmoles) en THF (2 ml) se agregó gota a gota a la solución agitada antes. La mezcla de reacción se agitó a -78°C durante 5 h, luego se entibió lentamente a temperatura ambiente durante la noche. El $NH_4Cl$ saturado se agregó, seguido por la adición de EtOAc. La capa orgánica se lavó con $H_2O$, salmuera, se secó sobre $Na_2SO_4$, se filtró, y se concentró hasta secarse. El residuo se purificó por cromatografía de vaporización instantánea (gel de sílice, EtOAc/Hexanos = 0 hasta 100%, regresando a 100% EtOAc) para dar 2-metil-N-(2-(3-metilisoxazol-5-il)-1,1-bis(3-

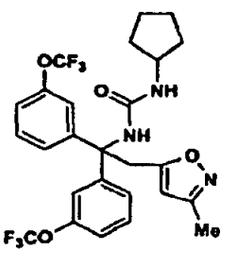
(trifluorometoxi)fenil)etil)propano-2-sulfinamida como aceite viscoso color marrón ligero (0.14 g, rendimiento: 13.5% con 0.55 g recuperación del material de partida). CL-EM (ESI) 551.38 (M+H), tiempo de retención = 3.98 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.49-7.40 (m, 2H), 7.37-7.28 (m, 1H), 7.19 (d, J=6.57 Hz, 1 H), 7.05-7.14 (m, 4 H), 5.70 (s, 1H), 4.61 (s, 1H), 4.14 (d, J=14.40 Hz, 1H), 3.88 (d, J=14.40 Hz, 1H), 2.26 (s, 2 H), 2.13 (s, 3H), 1.26 (s, 9H).

**2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etanamina**




Usando el mismo procedimiento como el descrito por el Procedimiento 6, el compuesto del título se obtuvo. CL-EM (ESI) 447.35 (M+H), tiempo de retención = 3.16 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min).

**1-ciclopentil-3-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi)-fenil)etil)urea**

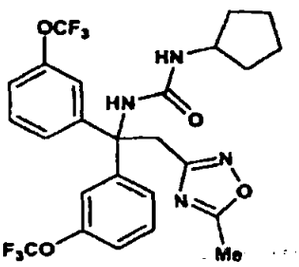



Usando el mismo procedimiento como el descrito por

1251

el Procedimiento 2, el compuesto del título se obtuvo. CL-EM (ESI) 558.41 (M+H), tiempo de retención = 3.98 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.39-7.35 (m, 2H), 7.28-7.26 (m, 2H), 7.15-7.13 (m, 4H), 5.57 (s, 1H), 5.29 (m, 1H), 4.04 (s, 2H), 3.93 (m, 1H), 2.19 (s, 3H), 1.92-1.89 (m, 2H), 1.64-1.59 (m, 4H), 1.35-1.26 (m, 2H).

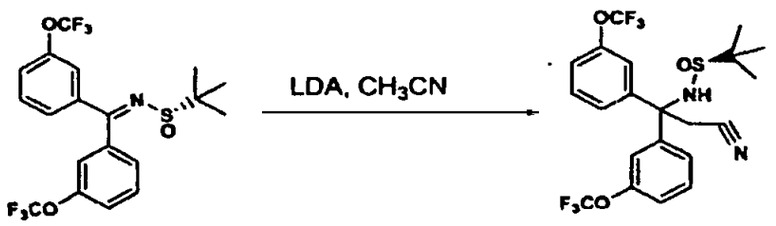
**EJEMPLO 211**




**1-ciclopentil-3-(2-(5-metil-1,2,4-oxadiazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea**

**Procedimiento 18**

**(R)-N-(2-ciano-1,1-bis(3-(trifluorometoxi)fenil)etil)-2-metilpropan-2-sulfinamida**

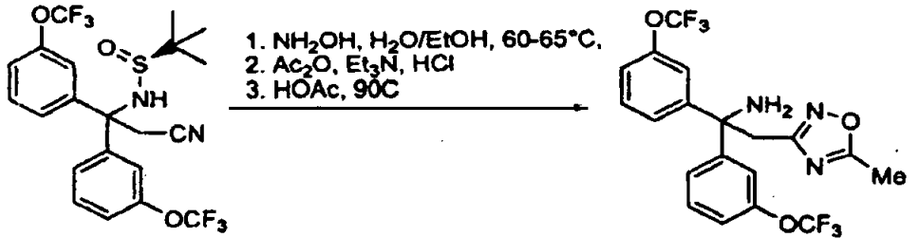



La (R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida se preparó como se describió por el

Procedimiento 11. Bajo una atmósfera de argón, acetonitrilo (0.46 ml, 8.84 mmoles, 2.0 eq) se agitó en $Et_2O$ anhidro (40 ml) en un matraz de fondo redondo secado al horno a -78°C. LDA (2.0 M, 4.42 ml, 8.84 mmoles, 2.0 eq) se agregó gota a gota. La mezcla resultante se agitó a -78°C durante 30 min. (R)-N-(bis(3-(trifluorometoxi)fenil)metilen)-2-metilpropan-2-sulfinamida (2.0 g, 4.42 mmoles) en $Et_2O$ (10 ml) se agregó gota a gota a la solución agitada antes. La mezcla de reacción se agitó a -78°C durante 4 h. El $NH_4Cl$ saturado se agregó, seguido por la adición de EtOAc. La capa orgánica se lavó con $H_2O$, salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró hasta secarse. El residuo se purificó por cromatografía (gel de sílice, EtOAc/Hexanos = 0 hasta 100%) para dar (R)-N-(2-ciano-1,1-bis(3-(trifluorometoxi)fenil)etil)-2-metilpropan-2-sulfinamida como un aceite color marrón ligero (1.15g, rendimiento: 52.7% con 0.85 g recuperación del material de partida). CL-EM (ESI) 495.26 (M+H), tiempo de retención = 3.84 min (10-90% MeOH en $H_2O$ con TFA 0.1% en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) $\delta$ ppm 7.40-7.35 (m, 2H), 7.29 (d, J = 8Hz, 1H), 7.21-7.16 (m, 4H), 7.08 (m, 1H), 4.53 (s, 1H), 3.75 (d, J=16 Hz, 1H) 3.56 (d, J=16Hz, 1H), 1.21 (s,9H)

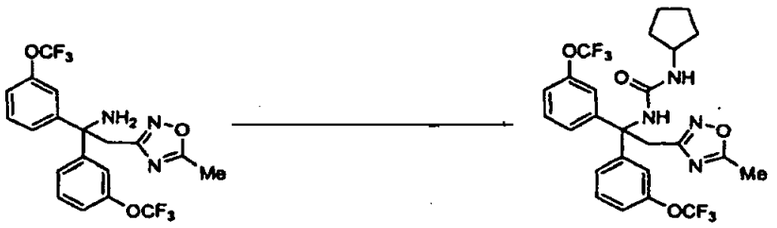
**Procedimiento 19**

**2-Metil-N-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)propano-2-sulfinamida**




La (R)-N-(2-Ciano-1,1-bis(3-(trifluorometoxi)fenil)etil)-2-metilpropan-2-sulfinamida (140 mg, 0.28 mmoles) se agitó en EtOH (3 ml) y $NH_2OH$ en $H_2O$ (3 ml) en un tubo de microondas tapado. La mezcla se calentó en un baño de aceite a 60-65°C durante 2 h. CL-EM mostró la terminación de la reacción. CL-EM (ESI) 528.42 (M+H), tiempo de retención = 3.46 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min). La tapa se removió, los solventes se concentraron. El residuo se disolvió en $CH_2Cl_2$, se lavó con $H_2O$, se secó sobre $MgSO_4$, se filtró y se concentró para dar N-hidroxi-3-(2-metilpropan-2-ilsulfinamido)-3,3-bis(3-(trifluorometoxi)fenil)propanamidina cruda. Después de secarse bajo vacío durante 2 h, el residuo se disolvió en $CH_2Cl_2$ (5 ml). El $Et_3N$ (0.25 ml, mmoles, eq) se agregó seguido por la adición de $Ac_2O$ (0.1 ml). La mezcla resultante se agitó a temperatura ambiente durante 24 h. CL-EM mostró la terminación de la reacción. CL-EM (ESI) 570.49 (M+H), 592.49 (M+Na), tiempo de retención = 3.92 min (10-90% MeOH en $H_2O$

con 0.1% de TFA en una corrida de 4-min). $CH_2Cl_2$ (5 ml) se agregó. Esto se lavó con $H_2O$, se secó sobre $MgSO_4$, se filtró y se concentró hasta secarse para dar película incolora (0.255g) después de secarse bajo vacío. Este residuo se disolvió en HOAc (5 ml), y se calentó a 90°C en un baño de aceite durante 4 h. CL-EM mostró un pico mayor. Después del enfriamiento, $H_2O$ se agregó. Esto se extrajo con $CH_2Cl_2$ (2x), se lavó con $NaHCO_3$ saturado (2x), $H_2O$, salmuera, se secó sobre $MgSO_4$, se filtró y concentró. El residuo se purificó por cromatografía de vaporización instantánea (gel de sílice, EtOAc/Hexanos = 0 hasta 100%) para dar 2-metil-N-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)propano-2-sulfinamida como aceite incoloro (52 mg, rendimiento total durante 3 etapas: 41%). CL-EM (ESI) 441.29 ($M-NH_2$), tiempo de retención = 3.14 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.26 - 7.19 (m, 5H), 7.00 (m, 3H), 3.57 (s, 2H), 2.39 (s, 3H).

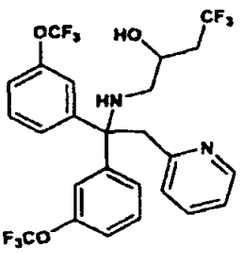



Usando el mismo procedimiento descrito por el Procedimiento 2, 1-ciclopentil-3-(2-(5-metil-1,2,4-oxadiazol-3-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea se obtuvo

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después de la purificación usando CLAR de fase inversa (30-90% MeOH en $H_2O$ con 0.1% de TFA en un gradiente de 10 minutos, regresando 17.53-18.00 min). CL-EM (ESI) 559.25 (M+H), tiempo de retención = 4.06 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.36-7.28 (m, 4H), 7.20 (m, 2H), 7.10 (m, 2H), 3.93 (m, 1H), 3.84 (s, 2H), 2.46 (s, 3H), 1.89 (m, 2H), 1.56 (m, 4H), 1.28 (m, 2H).

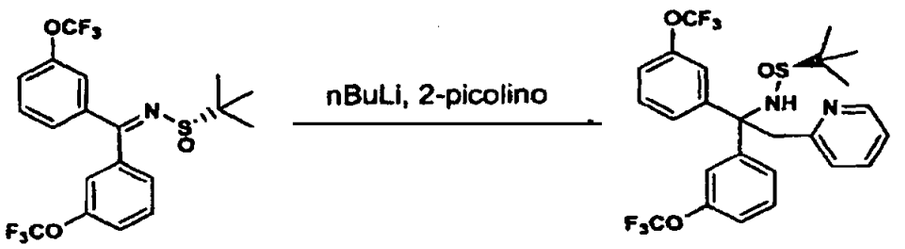
**EJEMPLO 219**




**4,4,4-trifluoro-1-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etilamino)butan-2-ol**

**Procedimiento 20**

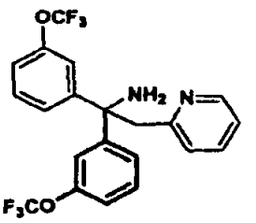
**(R)-2-metil-N-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)propano-2-sulfinamida**




El 2-Picolino (0.20 ml, 2.0 mmoles) se agitó en $Et_2O$ anhidro (20 ml) a 0°C bajo Argón. El nBuLi (2.5 M en hexanos, 0.84 ml, mmoles) se agregó gota a gota. La mezcla de

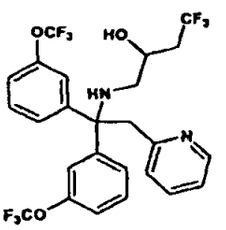
reacción se volvió café oscuro, y se agitó a 0°C durante 20 min, luego a temperatura ambiente durante 1 h. Esto se volvió a enfriar hasta 0°C, y (R)-N-(bis(3-(trifluorometoxi)fenil)-metilen)-2-metilpropan-2-sulfinamida (preparado como se describió en el Ejemplo 82, Procedimiento 11) (0.906g, 2.0 mmoles) en $Et_2O$ (4.0 ml) se agregó gota a gota. La mezcla se agitó a 0°C durante 1h., luego a temperatura ambiente durante 1 h. La reacción se extinguió por la adición de $NH_4Cl$ saturado. EtOAc se agregó; la capa orgánica se lavó con $H_2O$, salmuera, se secó ($Na_2SO_4$), se filtró y se concentró hasta secarse. El residuo se purificó por cromatografía de vaporización instantánea (gel de sílice, EtOAc/Hexanos = 0 hasta 100%) para dar 2-metil-N-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)-etil)propano-2-sulfinamida como sólidos color marrón ligero (0.19g con recuperación de 0.59 g de material de partida, rendimiento: 48% basado en recuperación del material de partida). CL-EM (ESI) 547.38 (M+H), tiempo de retención = 3.90 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4 min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 8.36 - 8.44 (m, 1H), 7.90 (m, 1H), 7.51 (d, J=8.59 Hz, 1H), 7.37 (td, J=7.83, 2.27 Hz, 2H), 7.19-7.24 (m, 2H), 7.11-7.17 (m, 3 H), 6.98-7.07 (m, 2H), 6.75 (d, J=7.83 Hz, 1H), 4.15 (d, J=13.90 Hz, 1H), 3.81 (d, J=13.90 Hz, 1H), 1.25-1.33 (m, 9H)

**2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etanamina**



Usando el mismo procedimiento descrito por el Procedimiento 6, 2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etanamina se obtuvo. CL-EM (ESI) 444.38 (M+H), tiempo de retención = 3.10 min (10-90% MeOH en H2O con 0.1% de TFA en una corrida de 4-min);

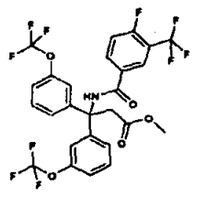
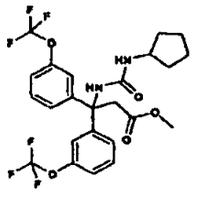
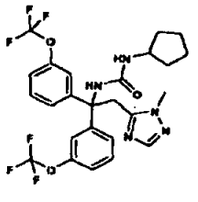
**4,4,4-trifluoro-1-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etilammo)butan-2-ol**



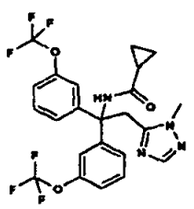
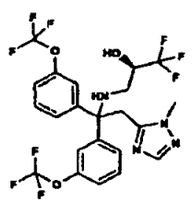
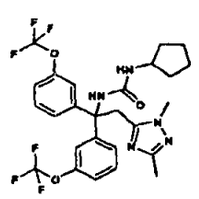
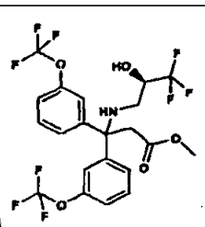
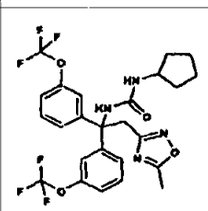
Usando el procedimiento descrito por el Procedimiento 8, (+/-)-4,4,4-trifluoro-1-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etilamino)butan-2-ol se obtuvo después de la purificación por medio de CLAR de fase inversa para dar (+/-)-4,4,4-trifluoro-1-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etilamino)butan-2-ol puro como una sal TFA. CL-EM (ESI) 569.31 (M+H), tiempo de retención = 3.21 min (10-90% MeOH en $H_2O$ con 0.1% de TFA en una corrida de 4-min); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 8.65 (d,

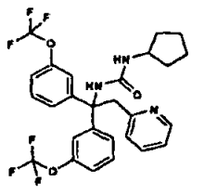
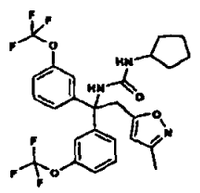
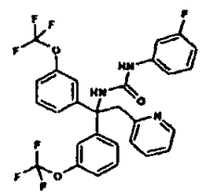
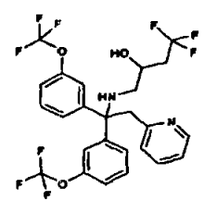
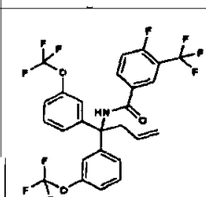
J=4.39 Hz, 1H), 7.63-7.70 (m, 1H), 7.41-7.47 (m, 1H), 7.34-7.38 (m, 2H), 7.30-7.14 (m, 5H), 6.98 (m, 1H), 6.81 (d, J=7.91 Hz, 1H), 4.47-4.53 (m, 1 H), 3.86 (m, 2 H), 2.84 (dd, J=12.08, 9.89 Hz, 1 H), 2.67 (dd, J=11.86, 2.64 Hz, 1 H), 2.46 (m, 1 H), 2.22 (m, 1H)

**TABLA 7**

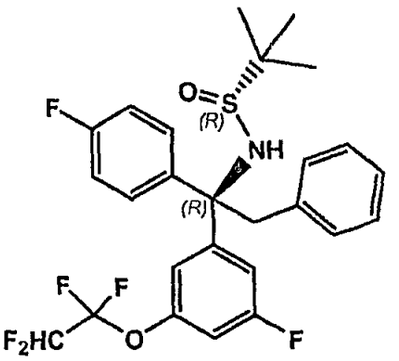
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 220 |  | 3-(4-fluoro-3-(trifluorometil) benzamido)-3,3-bis(3-(trifluorometoxi) fenil) propanoato de metilo | 4.10 CL 614.36 [M+H]+ | Procedimientos 11, 14 y 7 |
| 221 |  | 3-(3-ciclopentil ureido)-3,3-bis(3-(trifluorometoxi) fenil) propanoato de metilo | 4.02 CL 535.38 [M+H]+ | Procedimientos 11, 14 y 2 |
| 222 |  | 1-ciclopentil-3-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.81 CL 558.43 [M+H]+ | Procedimientos 15, 16 y 2 |

125a

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 223 |  | N-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)ciclopropan carboxamida | 3.61 CL 515.33 [M+H]+ | Procedimientos 15, 16 y 7 |
| 224 |  | (R)-1,1,1-trifluoro-3-(2-(2-metil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi) fenil) etilamina) propan-2-ol | 3.73 CL 559.4 [M+H]+ | Procedimientos 15, 16 y 8 |
| 225 |  | 1-ciclopentil-3-(2-(2,5-dimetil-2H-1,2,4-triazol-3-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.73 CL 572.48 [M+H]+ | Procedimientos 15, 16 y 2 |
| 226 |  | (R)-metil 3-(3,3,3-trifluoro-2-hidroxipropil amino)-3,3-bis(3-(trifluorometoxi) fenil) propanoato | 3.93 CL 536.29 [M+H]+ | Procedimientos 14 y 8 |
| 227 |  | 1-ciclopentil-3-(2-(5-metil-1,2,4-oxadiazol-3-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.06 CL 559.25 [M+H]+ | Procedimientos 18, 19 y 2 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./masa molecular | Preparado de la misma manera como se describe en: |
|---|---|---|---|---|
| 228 |  | 1-ciclopentil-3-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.43 CL 554.4 [M+H]+ | Procedimientos 20 y 2 |
| 229 |  | 1-ciclopentil-3-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.98 CL 558.41 [M+H]+ | Procedimientos 17 y 2 |
| 230 |  | 1-(3-fluorofenil)-3-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.56 CL 580.33 [M+H]+ | Procedimientos 20 y 2 |
| 231 |  | 4,4,4-trifluoro-1-(2-(piridin-2-il)-1,1-bis(3-(trifluorometoxi) fenil) etilamino)butan-2-ol | 3.21 CL 569.31 [M+H]+ | Procedimientos 20 y 8 |
| 232 |  | N-(1,1-bis(3-(trifluorometoxi) fenil) but-3-enil)-4-fluoro-3-(trifluorometil) benzamida | 581.402 | Procedimientos 11 y 7 |

**EJEMPLO 233**

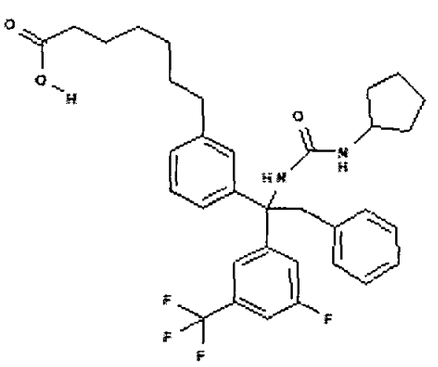


**(R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropano-2-sulfinamida**

**Procedimiento 21**

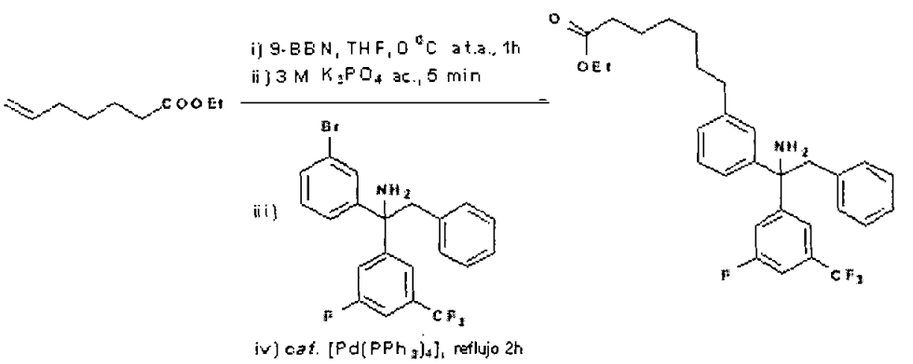
La (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropano-2-sulfinamida se preparó mediante procedimientos análogos descritos en los Procedimientos 3, 4 y 5. El material se cristalizó a partir de $CDCl_3$ y una estructura de rayos X obtenida.

**EJEMPLO 234**



**7-(3-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)heptanoico**

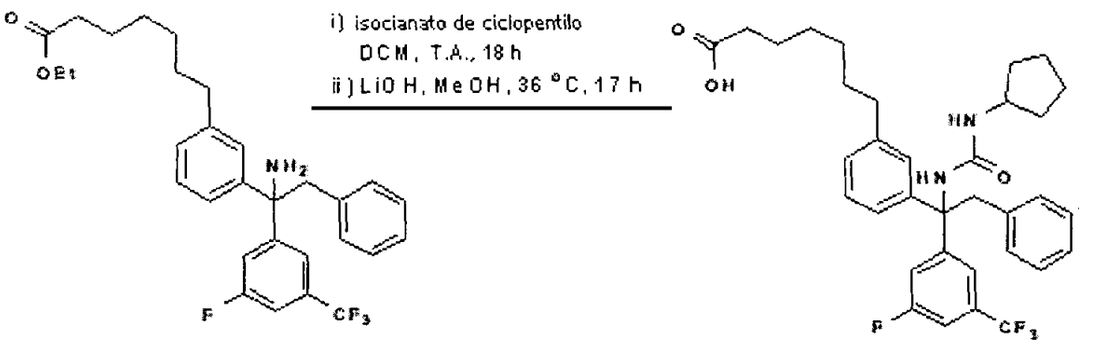
**Procedimiento 22**




A una solución de hept-6-enoato de etilo (156 mg, 1 mmoles) en THF seco (4 ml) frío en un baño de agua con hielo se agregó una solución de 9-BBN (0.5 M en THF, 2.0 ml, 1 mmoles). El baño frío se retiró y la mezcla de reacción se agitó durante 1 h a temperatura ambiente. A la mezcla de reacción se agregó una solución acuosa de fosfato de potasio (3 M, 0.66 ml, 2 mmoles) y se agitó durante 5 minutos adicionales. A la mezcla de reacción se agregó una solución de 1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletanamina, preparada como se describe en el Procedimiento 1, (0.2 M en THF, 3 ml, 0.6 mmoles), seguido por tris-(dibencilidenacetona) dipaladio(0) (45 mg, 0.04 mmoles). La solución amarilla resultante se calentó bajo reflujo durante 20 h. La mezcla de reacción se enfrió y se concentró bajo presión reducida. El residuo se extrajo entre agua (10 ml) y éter (10 ml). La capa de éter se lavó dos veces con agua, se secó sobre $Na_2SO_4$ y se concentró bajo presión reducida. El residuo se purificó por cromatografía de

vaporización instantánea de gel de sílice (2% hasta 10% EtOAc en Heptano) para producir 7-(3-(1-amino-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)heptanoato de etilo (169 mg, 54 % rendimiento). CLEM: T.R. = 3.61 min, Pureza 84% [M+H] 516.3 (columna Sunfire-S5-C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

**Procedimiento 23**



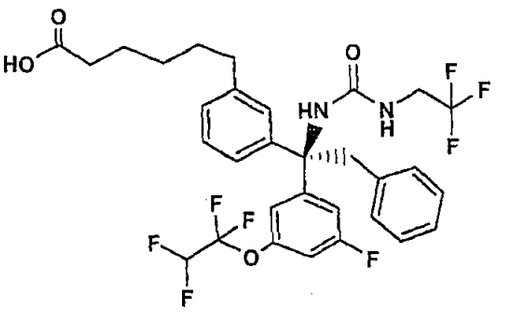

A una solución de 7-(3-(1-amino-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)heptanoato de etilo (169 mg, 0.33 mmoles) en DCM anhidro (1 ml) se agregó ciclopentil isocianato (22 mg, 0.2 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. A la mezcla de reacción se agregó THF anhidro (1 ml) y la mezcla se agitó a temperatura ambiente durante 1h adicional. Los solventes se evaporaron en un evaporador giratorio y el residuo se disolvió en metanol y se purificó por CLAR preparativa (T.A. = 11.3 min, Waters Sunfire C18 OBD, 19 X 100 mm eluyendo con 26-90% MeCN/$H_2O$ que contiene 0.1% de TFA

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durante 9 min y se mantuvo a 90% durante 7 minutos más; 40 ml/min, observando a 220 nm). El sólido resultante se disolvió en metanol (1 ml) seguido por la adición de hidróxido de litio acuoso (1 N, 0.25 ml, 0.25 mmoles). La mezcla de reacción se calentó a 36°C durante 18 h. El producto crudo se purificó por CLAR preparativa (T.A. = 10.7 min, Waters Sunfire C18 OBD, 19 X 100 mm eluyendo con 18-90% MeCN/$H_2O$ durante 10 min y se mantuvo a 90% durante 6 minutos adicionales que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para producir ácido 7-(3-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)heptanoico (Ejemplo 234, 32 mg, 53 % rendimiento durante 2 etapas). CLEM: T.R. = 4.33 min, Pureza >95%, [M+H] 599.4 (columna Sunfire-S5-C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) 7.36 ppm, 1 H, s; 7.16-7.24 ppm, 4 H, m; 7.10-7.13 ppm, 3 H, m; 6.97 ppm, 1 H, d, J = 7.7 Hz; 6.94 ppm, 1 H, s; 6.67 ppm, 2 H, d, J=7.1 Hz; 5.58 ppm, 1 H, brd, s; 3.87 ppm, 1 H, d, J=12.6 Hz; 3.83 ppm, 1 H, m; 3.65 ppm, 1 H, d, J=12.7 Hz; 2.54, 2 H, t, J=7.5 Hz; 2.29 ppm, 2 H, t, J=7.4 Hz; 1.73-1.84 ppm, 2 H, m; 1.50-1.60 ppm, 8 H, m; 1.15-1.36 ppm, 6 H, m.

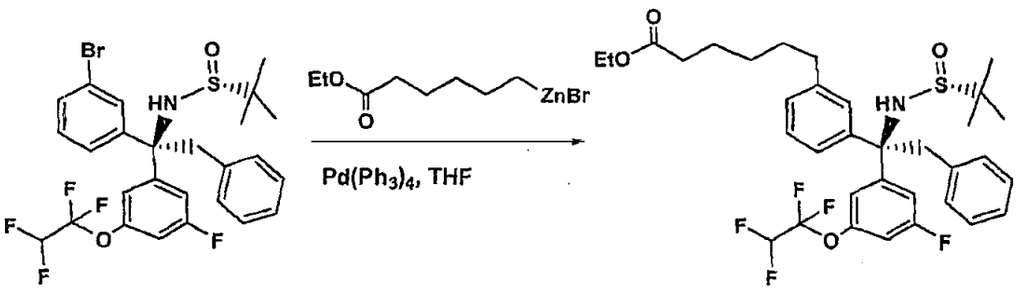
1265

**EJEMPLO 235**



**Ácido (R)-6-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil)ureido)etil)fenil)hexanoico**

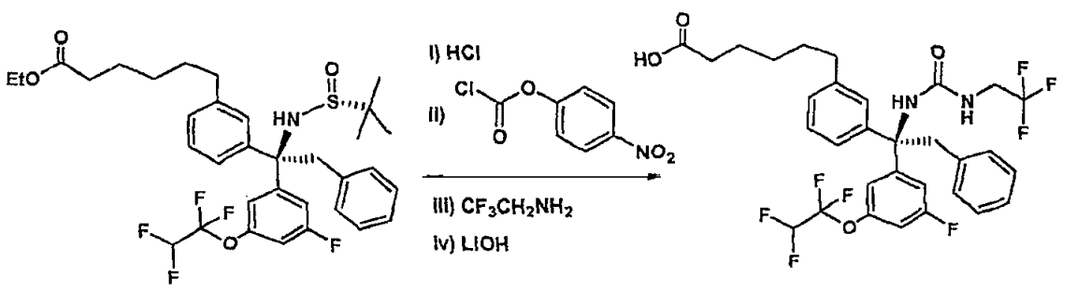
**Procedimiento 24**




A una solución de (R)-N-((S)-1-(3-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (236 mg, 0.4 mmoles), preparada como se describe en el Procedimiento 3, 4, 5 y 6 (67% rendimiento), en THF anhidro (1 ml) se agregó bromuro de (6-etoxi-6-oxohexil)zinc(II) (2.4 ml, 1.2 mmoles) seguido por tetraquis(trifenilfosfina)paladio(0) (23 mg, 0.02 mmoles). Bajo una atmósfera Ar, la mezcla de reacción se calentó a 130°C bajo radiación por microondas durante 15 min. El residuo se diluyó con EtOAc (10 ml) y se lavó con $NH_4Cl$

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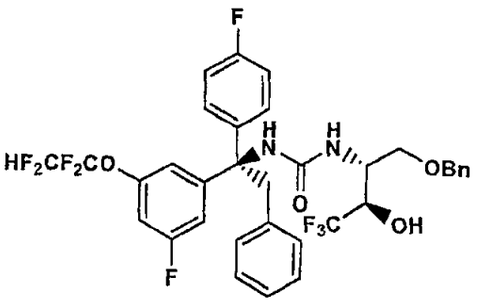
saturado (2 x 5 ml). La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se disolvió en metanol y se purificó por CLAR preparativa (columna Waters Sunfire C18 19 x 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 7 min; 20 ml/min, observando a 220 nm) para dar 6-(3-((R)-1-((R)-1,1-dimetiletilsulfinamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)fenil)hexanoato de etilo (60 mg, 23% rendimiento). CLEM: T.R. = 3.97 min [M+H] 654.52 (columna YMC-ODS 4 min, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). $^1H$ RMN (500 MHz, $CDCl_3$) $\delta$ ppm 7.24 - 7.33 (2 H, m), 7.11 - 7.19 (5 H, m), 6.89 - 6.94 (2 H, m), 6.82 (1 H, d, J=8.52 Hz), 6.67 - 6.73 (2 H, m), 5.85 (1 H, ttt, J=53.06, 2.61 Hz), 4.25 (1 H, s), 4.11 (2 H, q, J=7.15 Hz), 4.03 (1 H, d, J=12.65 Hz), 3.60 (1 H, d, J=12.65 Hz), 2.59 (2 H, dd), 2.26 (2 H, t, J=7.56 Hz), 1.61 (4 H, tt, J=15.77, 7.87 Hz), 1.28 - 1.34 (2 H, m), 1.22 - 1.27 (3 H, m), 1.20 (9 H, s).




El ácido (R)-6-(3-(1-(3-fluoro-5-(1,1,2,2-

tetrafluoroetoxi)fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil)ureido)etil)fenil)hexanoico (Ejemplo 235, 13 mg, 50% rendimiento) fue preparado como se describe en el Procedimiento 6, 12 y 23. CLEM: T.R. = 4.10 min [M+H] 647.30 (columna Sunfire-S5-C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 1.17 - 1.26 (m, 2 H), 1.53 - 1.63 (m, 4 H), 2.23 - 2.32 (m, 2 H), 2.56 (t, J=7.15 Hz, 2 H), 3.60 (ddd, J=15.05, 9.14, 5.77 Hz, 1 H), 3.66 (d, J=12.92 Hz, 1 H), 3.83 (ddd, J=15.67, 8.80, 7.15 Hz, 1 H), 3.93 (d, J=12.92 Hz, 1 H), 5.09 (t, J=5.91 Hz, 1 H), 5.64 (s, 1 H), 5.86 (ttt, J=53.06, 2.61 Hz, 1 H), 6.69 (d, J=7.15 Hz, 2 H), 6.87 (d, J=8.80 Hz, 1 H), 6.90 (s, 1 H), 6.96 (d, J=7.97 Hz, 1 H), 6.99 - 7.02 (m, 2 H), 7.06 - 7.12 (m, 3 H), 7.16 (t, J=7.29 Hz, 1 H), 7.22 (t, J=7.70 Hz, 1 H), 7.26 (s, 1 H).

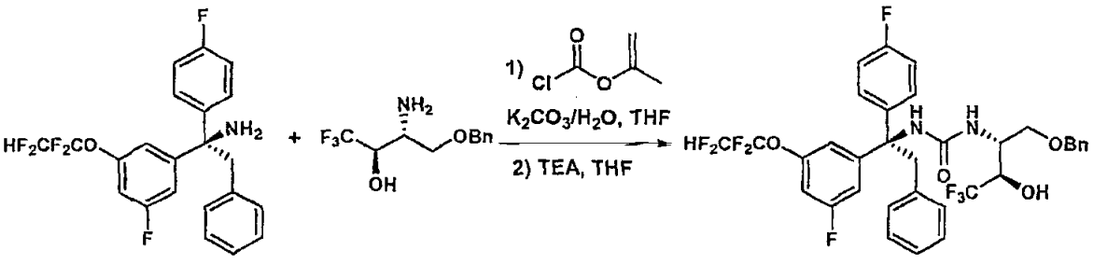
**EJEMPLO 236**




**1-((2R,3R)-1-(benciloxi)-4,4,4-trifluoro-3-hidroxibutan-2-il)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

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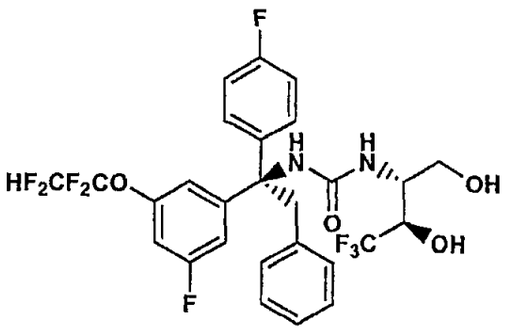
**Procedimiento 25**




A una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (20 mg, 0.047 mmoles), preparada como se describe en el Procedimiento 3, 4, 5 y 6, en THF (0.5 ml) se agregó $K_2CO_3$ en $H_2O$ (10 mg, 2 M en $H_2O$, 0.071 mmoles), seguido por la adición de clorhidrato de prop-1-en-2-ilo carbono (6 µl, 0.052 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, se diluyó con EtOAc (25 ml), se lavó con NaCl saturado (25 ml), se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. Al residuo se agregó (2R,3R)-3-amino-4-(benciloxi)-1,1,1-trifluorobutan-2-ol (23 mg, 0.094 mmoles), preparado de conformidad al Procedimiento descrito en J. Org. Chem., 68(19):7545 (2003), TEA (20 µl, 0.14 mmoles) en THF (0.5 ml). La mezcla de reacción se calentó a 70°C durante 18 h. La solución de reacción se concentró bajo presión reducida y se purificó cromatografía ISCO (columna 12 g) al usar hexano/EtOAc (0-30% durante 20 min) para dar 1-((2R,3R)-1-(benciloxi)-4,4,4-trifluoro-3-hidroxibutan-2-il)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea

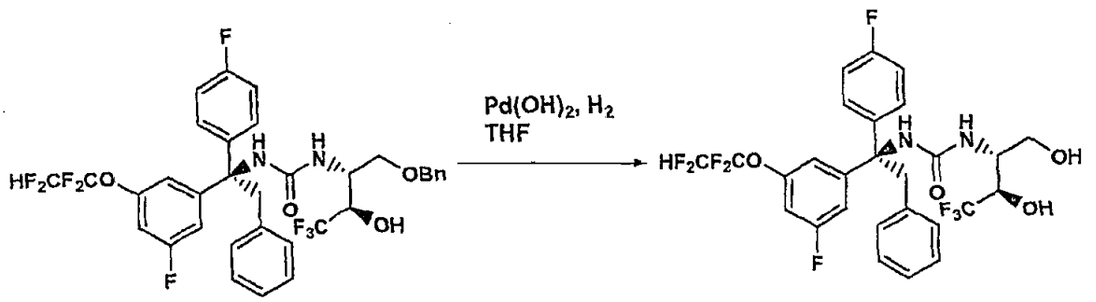
(Ejemplo 236) como un sólido blanco a un tiempo de retención de 17 min (19 mg, 59% rendimiento). CLEM: T.R. = 2.138 min [M+H] 701.29 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA, 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.335 min, Pureza 94% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.37 ppm, 3 H, m; 7.25 ppm, 3 H, m; 7.20 ppm, 1 H, t, J=7.03 Hz; 7.13 ppm, 4 H, m; 6.97 ppm, 2 H, t, J=8.35 Hz; 6.89 ppm, 3 H, m; 6.69 ppm, 2 H, d, J=7.47 Hz; 5.86 ppm, 1 H, m; 5.18 ppm, 1 H, d, J=8.35 Hz; 5.13 ppm, 1 H, s; 4.44 ppm, 2 H, m; 4.26 ppm, 1 H, d, J=9.67 Hz; 4.14 ppm, 1 H, dd, J=8.13, 3.30 Hz; 3.99 ppm, 1 H, m; 3.81 ppm, 2 H, m; 3.71 ppm, 1 H, m; 3.59 ppm, 1 H, m.

**EJEMPLO 237**




**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((2R,3R)-4,4,4-trifluoro-1,3-dihidroxibutan-2-il)urea**

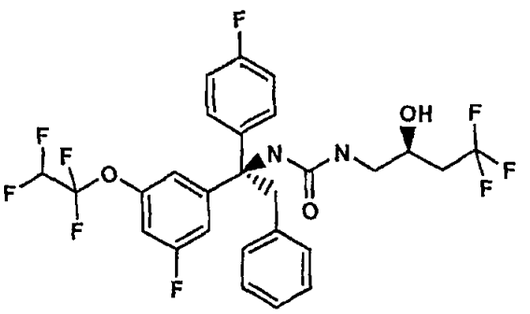
**Procedimiento 26**




A una solución de 1-((2R,3R)-1-(benciloxi)-4,4,4-trifluoro-3-hidroxibutan-2-il)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 236, 17 mg, 0.024 mmoles) en THF (1 ml) se agregó 20% $Pd(OH)_2/C$ (8 mg) y la solución espesa se sometió a hidrogenación en globo durante 18 h. La mezcla de reacción se filtró y el producto filtrado se concentró y se purificó por CLAR preparativa (columna Shimadzu-YMC-ODS-A 5µ, 30 × 100 mm eluyendo con 30-100% MeOH (90% en $H_2O$, 0.1%TFA) gradiente durante 12 min con relación de flujo 40 ml/min y detección UV a 220 nm) para producir 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((2R,3R)-4,4,4-trifluoro-1,3-dihidroxibutan-2-il)urea (Ejemplo 237) eluyendo un tiempo de retención de 11.54 min como un aceite transparente (11 mg, rendimiento 78%). CLEM: T.R. = 1.983 min [M+H] 611.26 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA, 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.081 min, Pureza 100% (columna Phenomenex Luna

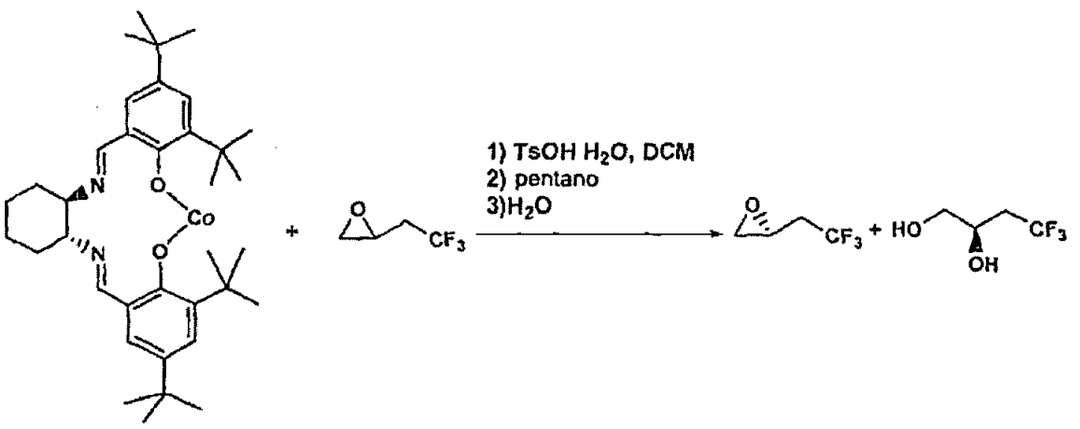
C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.20 ppm, 1 H, s; 7.16 ppm, 5 H, m; 6.99 ppm, 2 H, m; 6.91 ppm, 3 H, m; 6.70 ppm, 2 H, d, J=7.47 Hz; 5.87 ppm, 1 H, m; 5.38 ppm, 1 H, d, J=7.47 Hz; 5.35 ppm, 1 H, s; 4.28 ppm, 1 H, d, J=5.71 Hz; 4.11 ppm, 2 H, m; 3.94 ppm, 2 H, d, J=7.91 Hz; 3.82 ppm, 1 H, m; 3.73 ppm, 1 H, m; 3.67 ppm, 1 H, d, J=8.35 Hz.

**EJEMPLO 238**



**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((S)-4,4,4-trifluoro-2-hidroxibutil)urea**

**Procedimiento 27**

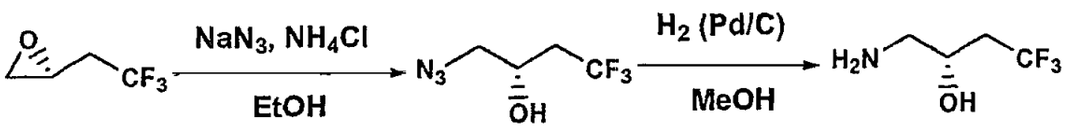


A una solución de (R,R)-(-)-N'N'-bis(3,5-di-ter-butilsalicilideno)-1,2-ciclo-hexanodiamina (0.92 g, 1.53 mmoles) en DCM (35 ml) se agregó TsOH $H_2O$ (308 mg, 1.62 mmoles) y la mezcla de reacción se agitó a temperatura ambiente mientras se abrió al aire durante 1 h. La mezcla de reacción se concentró bajo presión reducida y pentano se agregó al residuo. El sólido resultante se filtró, se enjuagó con pentano una vez, se diluyó con DCM y se transfirió al matraz de reacción. El DCM luego se removió bajo presión reducida y 2-(2,2,2-trifluoroetil)oxirano (37 g, 294 mmoles) se agregó al sólido resultante. La mezcla se enfrió a 0°C y $H_2O$ (3.7 ml, 206 mmoles) se agregó gota a gota. Después de que la adición finalizó, la mezcla de reacción se agitó a temperatura ambiente durante 72 h. El (S)-2-(2,2,2-trifluoroetil)oxirano se aisló como un aceite transparente (10 g, 28%) por destilación al vacío a partir de la mezcla de reacción en un matraz de recepción enfriado (-78 °C). RMN: 400MHz $^1H$ ($CDCl_3$) 3.16 ppm, 1 H, m; 2.87 ppm, 1 H, t, J=4.39 Hz; 2.59 ppm, 1 H, dd, J=4.61, 2.42 Hz; 2.39 ppm, 1 H, m; 2.29 ppm, 1 H, m, J=10.44, 10.44, 5.05, 4.83 Hz.

El epóxido recuperado se determinó que es >99% ee de conformidad al Procedimiento usado por Jacobsen (J. Am. Chem. Soc., 124(7):1307-1315 (2004)). (Análisis CLAR quiral del derivado de 2-naftilsulfuro (obtenido por la abertura del anillo con 2-naftalentiol en MeOH al usar 1 equivalente TEA y

análisis directo del producto obtenido, Chiralcel® AD, 95:5 hexanos: i-PrOH, 1 ml / min, 254 nm, T.R. (menor) = 16.52 min, T.R. (mayor) = 19.28 min).

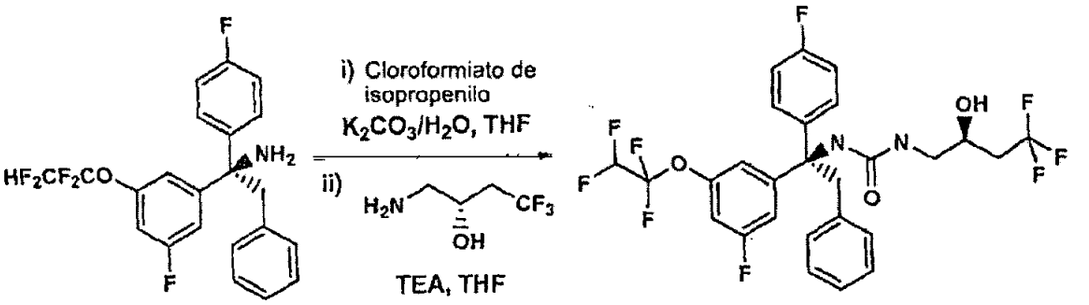
**Procedimiento 28**




A una solución de (S)-2-(2,2,2-trifluoroetil)oxirano (2.00 g, 16.0 mmoles) en una mezcla de EtOH (16 ml) y $H_2O$ (4 ml) donde se agregó $NaN_3$ (2.06 g, 32.0 mmoles) y $NH_4Cl$ (1.70 g, 32.0 mmoles). Después de agitar a temperatura ambiente durante 18 h, la mezcla de reacción se diluyó con $H_2O$ (50 ml), se extrajo con $Et_2O$ (2 × 75 ml). La capa orgánica combinada se secó sobre $MgSO_4$, se filtró y se concentró para dar (S)-1-azido-4,4,4-trifluorobutan-2-ol como un aceite (2.26 g, 83% rendimiento). RMN: 400MHz $^1H$ ($CDCl_3$) 4.17 ppm, 1 H, ddd, J=6.81, 3.74, 3.52 Hz; 3.48 ppm, 1 H, m; 3.37 ppm, 1 H, m; 2.35 ppm, 2 H, m.

El (S)-1-azido-4,4,4-trifluorobutan-2-ol crudo (2.26 g, 13.0 mmoles) se sometió a hidrogenación en globo durante 18 h. Después de la filtración, el producto filtrado se concentró para dar (S)-1-amino-4,4,4-trifluorobutan-2-ol (1.02 g, 45% rendimiento). RMN: 400MHz $^1H$ ($CDCl_3$) 3.88 ppm, 1 H, m, J=7.85, 7.85, 3.84, 3.74 Hz; 2.93 ppm, 1 H, dd,

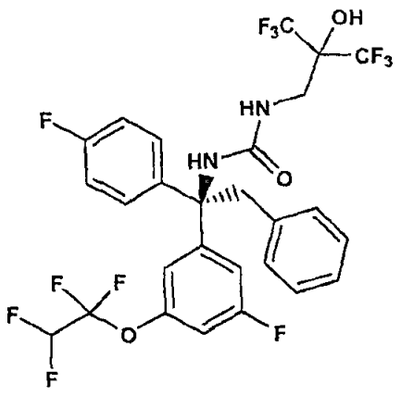
J=12.74, 3.52 Hz; 2.61 ppm, 1 H, dd, J=12.52, 8.13 Hz; 2.34 ppm, 1 H, m; 2.21 ppm, 1 H, m; 1.91 ppm, 3 H, s.




La 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((S)-4,4,4-trifluoro-2-hidroxibutil)urea (Ejemplo 238) fue preparada como se describe en el Procedimiento 25 (27 mg, 65% rendimiento). CLEM: T.R. = 2.02 min [M+H] 595.28 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA, 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.165 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.16 ppm, 5 H, m; 6.94 ppm, 5 H, m; 6.69 ppm, 2 H, d, J=7.03 Hz; 5.73 ppm, 1 H, m; 4.10 ppm, 2 H, m; 3.93 ppm, 1 H, s; 3.84 ppm, 1 H, m; 3.73 ppm, 1 H, m; 3.52 ppm, 1 H, s; 3.29 ppm, 1 H, m; 3.04 ppm, 1 H, m; 2.17 ppm, 2 H, m.

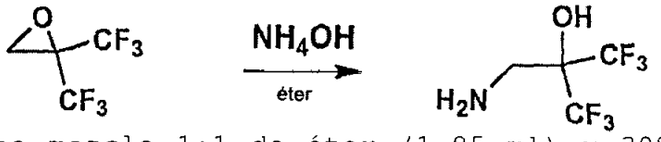
1245

**EJEMPLO 239**



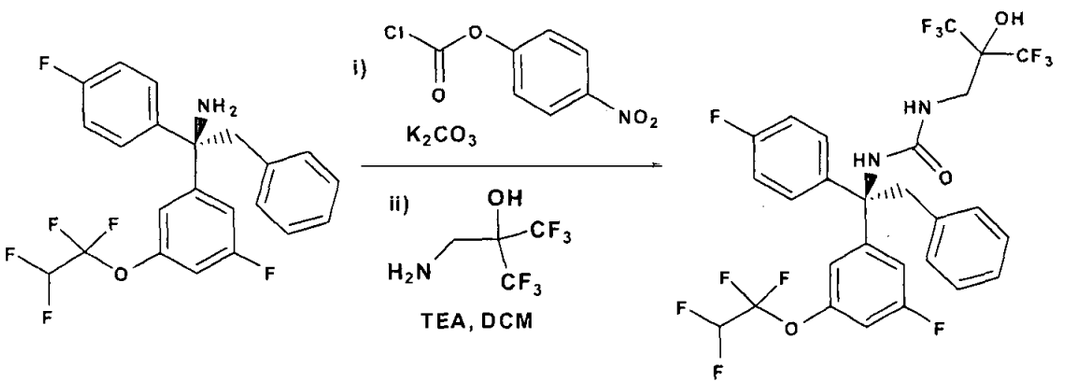
**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3,3,3-trifluoro-2-hidroxi-2-(trifluorometil)propil)urea**

**Procedimiento 29**



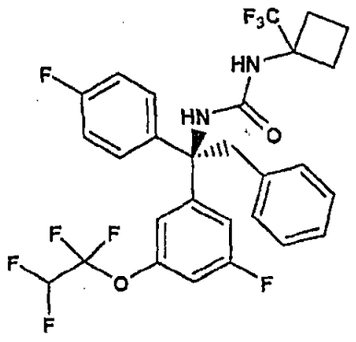

A una mezcla 1:1 de éter (1.85 ml) y 30% hidróxido de amonio (1.85 ml) se agregó gota a gota 2,2-bis(trifluorometil)oxirano (1.00 g, 5.5 mmoles). La mezcla de reacción se agitó durante 2 h a temperatura ambiente, luego se diluyó con éter y $H_2O$. La capa acuosa se extrajo dos veces con éter y la capa de éter combinada se secó sobre $MgSO_4$, se filtró y se concentró para dar 2-(aminometil)-1,1,1,3,3,3-hexafluoropropan-2-ol como un semisólido (0.87 g, 81% rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) ppm 3.14 (s, 2 H), 3.25 (s, 1 H).

1276



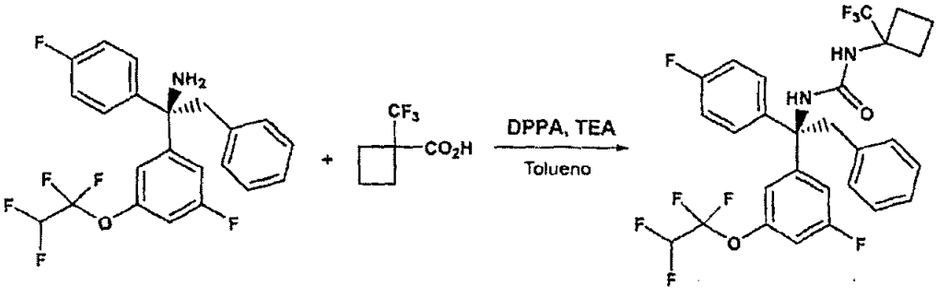

La (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3,3,3-trifluoro-2-hidroxi-2-(trifluorometil)propil)urea fue preparada como se describe en el Procedimiento 12. El producto se purificó por cromatografía ISCO (columna 4 g) al usar hexano/EtOAc (0-20% durante 12 min) para dar la (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3,3,3-trifluoro-2-hidroxi-2-(trifluorometil)propil)urea (Ejemplo 239) como un aceite incoloro (24 mg, 65% rendimiento). CLEM: T.R. = 4.11 min [M+H] 649.10 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 3.60 - 3.90 (m, 4 H), 5.13 (t, J=5.81 Hz, 1 H), 5.50 (s, 1 H), 5.69 - 6.05 (t, J=56 Hz, 1 H), 6.68 (d, J=6.82 Hz, 2 H), 6.81 - 6.95 (m, 3 H), 6.96 - 7.05 (m, 3 H), 7.06 - 7.24 (m, 5 H).

**EJEMPLO 240**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(trifluorometil)ciclobutil)urea**

**Procedimiento 30**

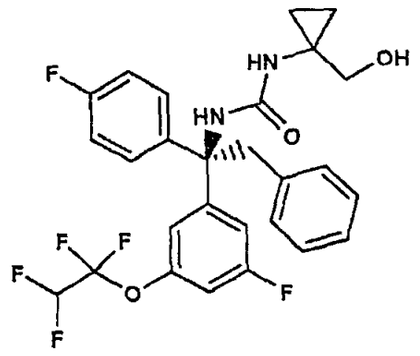


A una solución de ácido 1-(trifluorometil)ciclobutancarboxílico (54 mg, 0.354 mmoles) en tolueno (0.9 ml) se agregó TEA (36 mg, 0.354 mmoles), seguido por DPPA (76.4 ul, 0.354 mmoles). La mezcla de reacción se calentó a 90°C durante 2 h, luego se permitió enfriar hasta temperatura ambiente. La (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (50 mg, 0.117 mmoles), preparada como

se describe en el Procedimiento 3, 4, 5 y 6, se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 4.5 h. La mezcla de reacción se concentró bajo presión reducida y se purificó cromatografía ISCO (columna 12 g, eluyendo con 0-30% hexano/EtOAc durante 18 min). El producto se purificó además por CLAR preparativa (columna Phenomenex AXIA Luna, 30 x 100 mm, relación de flujo 40 ml/min, eluyendo con 40-100% ACN/$H_2O$/0.1% de TFA durante 10 min) para producir (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(trifluorometil)ciclobutil)urea (Ejemplo 240) como un sólido blanco (45 mg, 65% rendimiento). CLEM: T.R. = 4.13 min [M+H] 519.18 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 1.83 - 2.06 (m, 2 H), 2.16 - 2.33 (m, 2 H), 2.33 - 2.51 (m, 2 H), 3.78 (qt, J=13 Hz, 2 H), 4.71 (s, 1 H), 5.02 (s, 1 H), 5.85 (t, J=52 Hz, 1 H), 6.65 - 6.75 (m, 2 H), 6.83 - 7.06 (m, 5 H), 7.05 - 7.23 (m, 5 H).

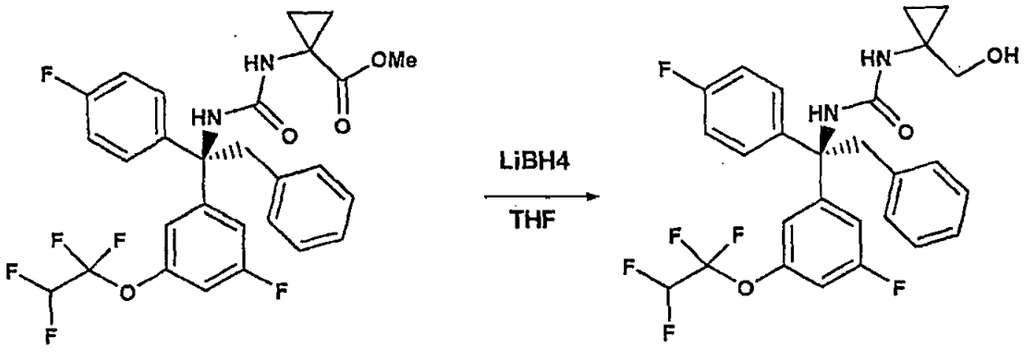
1219

**EJEMPLO 241**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(hidroximatil)ciclopropil)urea**

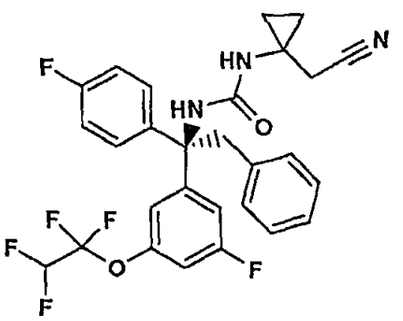
**Procedimiento 31**




A una solución de 1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-ciclopropanocarboxilato de (R)-metilo (112 mg, 0.2 mmoles), preparado por el método descrito en el Procedimiento 30, en THF (0.2 ml) se agregó $LiBH_4$ (0.2 ml, 2 M en THF, 0.4 mmoles) a temperatura ambiente. La mezcla de reacción se agitó durante 14 h, luego se enfrió a 0°C y HCl 1N se agregó. La mezcla de reacción se diluyó con éter. La

capa orgánica se lavó con $H_2O$ y NaCl saturado, se secó sobre $MgSO_4$, se filtró y se concentró para dar un aceite incoloro. El aceite resultante se purificó por cromatografía ISCO (columna 4 g, eluyendo con 0-100% hexano/EtOAc durante 16 min) para producir (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(hidroximatil)ciclopropil)urea (Ejemplo 241) como una espuma blanca (91 mg, 84% rendimiento). CLEM: T.R. = 2.97 min [M+H] 539.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% $CH_3CN/H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 0.61 - 0.81 (m, 4 H), 2.50 (brs, 1 H), 3.31 - 3.50 (m, 2 H), 3.84 (qt, J=12 Hz, 2 H), 4.93 (s, 1 H), 5.84 (t, J=53 Hz, 1 H), 6.53 - 7.05 (m, 8 H), 7.05 - 7.24 (m, 5 H).

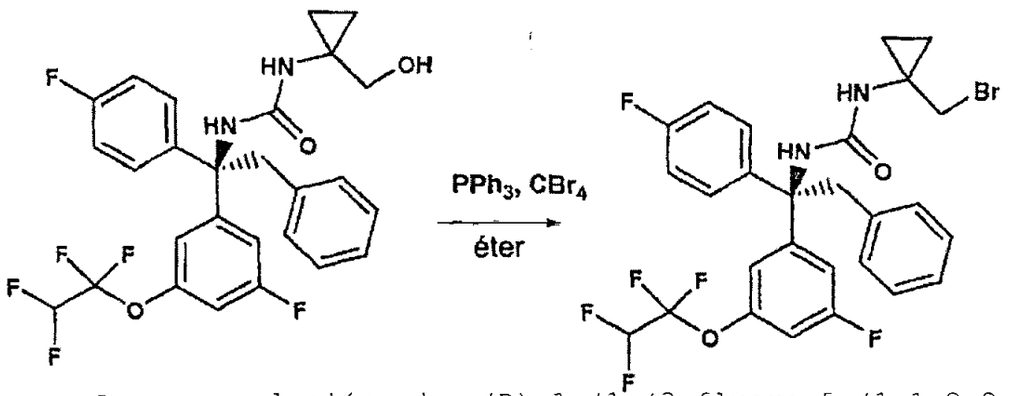
**EJEMPLO 242**




**(R)-1-(1-(cianometil)ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

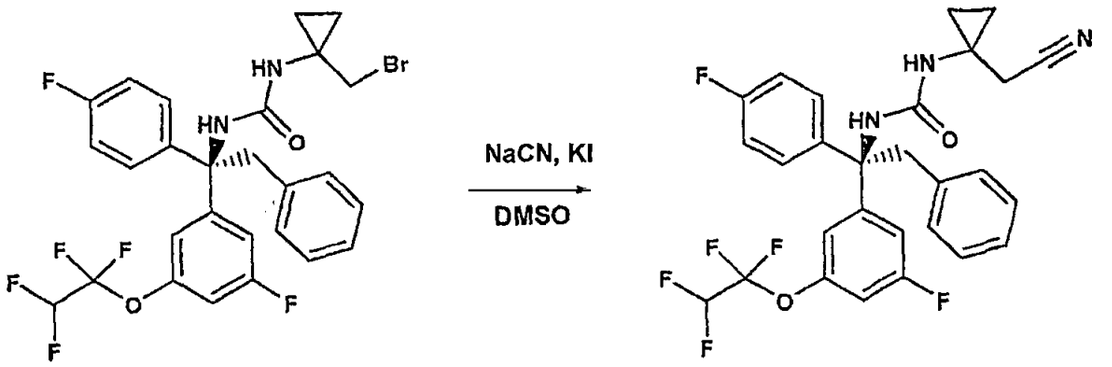
(28)

**Procedimiento 32**




A una solución de (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(hidroximatil)ciclopropil)urea (Ejemplo 241, 43 mg, 0.08 mmoles) en éter (0.4 ml) se agregó $PPh_3$ (48 mg, 0.18 mmoles) y $CBr_4$ (58 mg, 0.18 mmoles) a temperatura ambiente. La mezcla de reacción se agitó durante 14 h y se concentró bajo presión reducida y se purificó cromatografía ISCO (columna 4 g, eluyendo con 0-15% hexano/EtOAc durante 14 min) para producir (R)-1-(1-(bromometil)ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea como un sólido blanco (8 mg, 17% rendimiento). CLEM: T.R. = 4.06 min [M+H] 601.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 0.82 - 1.03 (m, 4 H), 3.47 (qt, J=12 Hz, 2 H), 3.81 (ABqt, J=12 Hz, 2 H), 5.01 (s, 1 H), 5.39 (s, 1 H), 5.86 (t, J=53 Hz, 1 H), 6.61 - 6.78 (m, 2 H), 6.80 - 7.25 (m, 10 H).

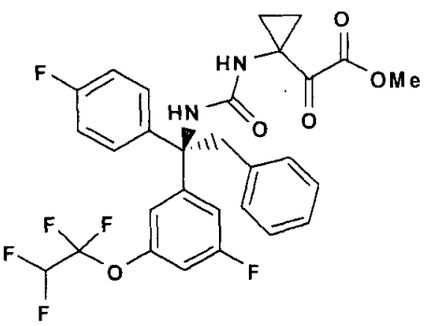
**Procedimiento 33**




A una solución de (R)-1-(1-(bromometil)ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (8 mg, 0.013 mmoles) en DMSO (0.3 ml) se agregó NaCN (18 mg, 0.37 mmoles) y KI (20 mg, 0.12 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se concentró bajo presión reducida y se purificó por CLAR preparativa (columna Phenomenex AXIA Luna, 30x100 mm, relación de flujo 40 ml/min, 30-100% ACN/$H_2O$/0.1% de TFA durante 12 min) para producir (R)-1-(1-(cianometil)ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 242, 5 mg, 63% rendimiento). CLEM: T.R. = 3.88 min [M+H] 548.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 0.76 - 0.91 (m, 4 H), 2.58 (qt, J=17 Hz, 2 H), 3.78 (qt, J=12 Hz, 2 H), 5.49 (s, 1 H), 5.52 (s, 1 H), 5.87

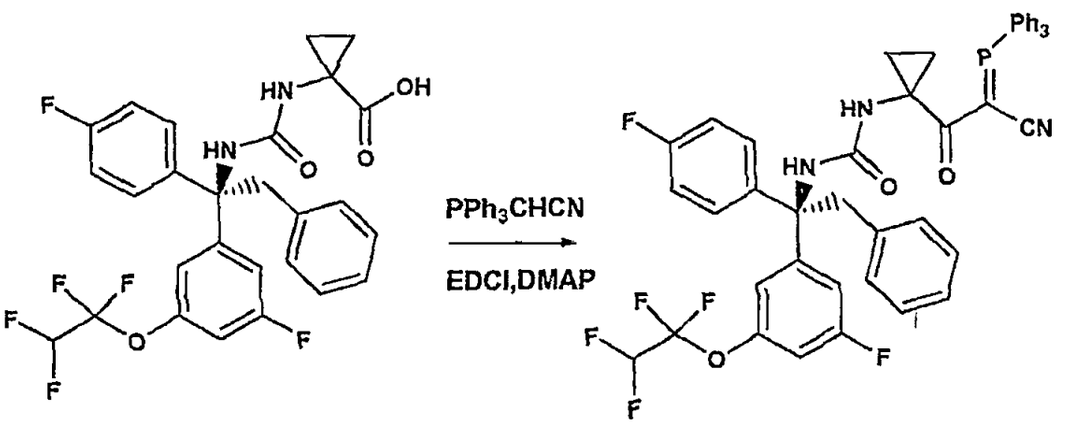
(t, J=53 Hz, 1 H), 6.66 (d, J=6.6 Hz, 2 H), 6.84 - 6.95 (m, 3 H), 6.96 - 7.07 (m, 2 H), 7.07 - 7.26 (m, 5 H).

**EJEMPLO 243**



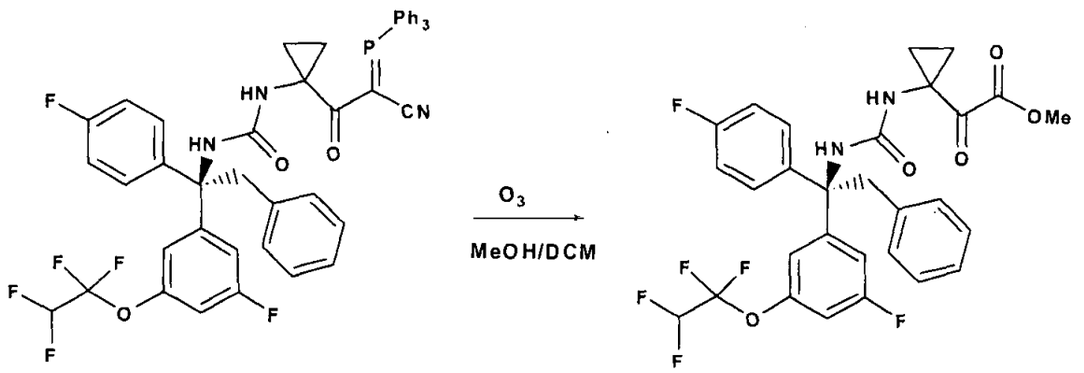
**2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclopropil)-2-oxoacetato de (R)-metilo**

**Procedimiento 34**




A una solución de ácido (R)-1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-ciclopropanocarboxílico (84 mg, 0.153 mmoles), preparado por el método descrito en el Procedimiento 30, en DCM (0.5 ml) se agregó 2-(fenilfosfiniliden)acetonitrilo compuesto con bifenilo (1:1)

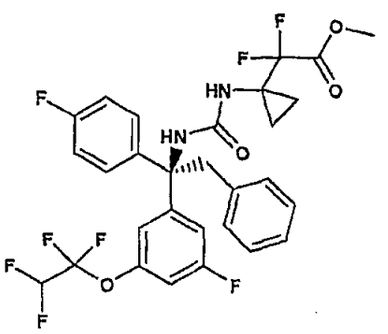
(51 mg, 0.168 mmoles), EDCI (32 mg, 0.168 mmoles) y DMAP (3 mg, 0.024 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 4.5 h, se concentró bajo presión reducida y se purificó cromatografía ISCO (columna 12 g, eluyendo con 0-100% hexano/EtOAc) para producir (R)-1-(1-(2-ciano-2-(fenilphosphinylidene)acetil)ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea compuesto con bifenilo (1:1) como un sólido blanco (53 mg, 42% rendimiento). CLEM: T.R. = 3.49 min [M+H] 836.4 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 50-100% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 0.78 - 1.00 (m, 2 H), 1.34 - 1.49 (m, 2 H), 3.79 - 3.95 (m, 2 H), 5.62 - 5.98 (m, 3 H), 6.67 - 6.94 (m, 7 H), 6.98 - 7.20 (m, 5 H), 7.37 - 7.66 (m, 15 H).




Una solución de (R)-1-(1-(2-ciano-2-(fenilfosfiniliden)acetil)ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea con bifenilo (1:1) (53 mg, 0.063 mmoles) en

DCM/MeOH (0.7 ml/0.3 ml) se enfrió a -78°C. El $O_3$ se burbujeó en la solución hasta que la solución se volvió azul claro. La mezcla de reacción se calentó hasta temperatura ambiente y se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía ISCO (columna 4 g) al usar hexano/EtOAc (0-100%) para dar 2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclopropil)-2-oxoacetato de (R)-metilo (Ejemplo 243) como un sólido blanco (33 mg, 86% rendimiento). CLEM: T.R. = 2.99 min [M+H] 595.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 50-100% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 0.81 - 0.95 (m, 2 H), 1.04 - 1.18 (m, 2 H), 3.63 - 3.88 (m, 5 H), 5.48 (s, 2 H), 5.86 (t, J=53 Hz, 1 H), 6.60 - 6.69 (m, 2 H), 6.80 - 7.02 (m, 5 H), 7.05 - 7.24 (m, 5 H).

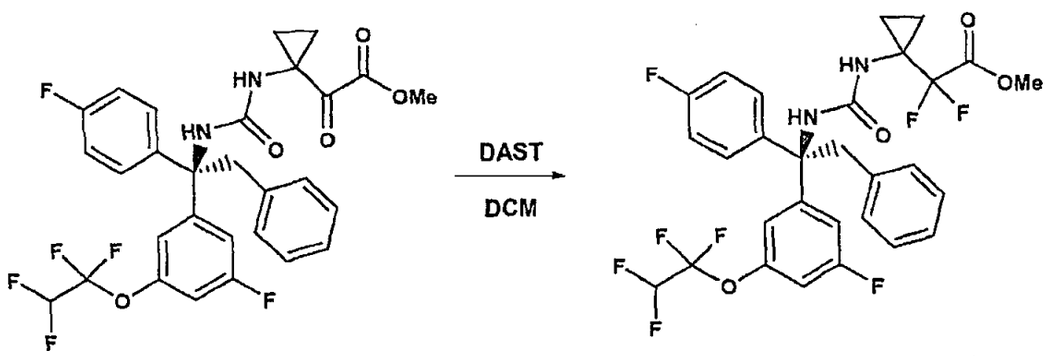
**EJEMPLO 244**



**2,2-difluoro-2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclopropil)acetato de (R)-metilo**

1286

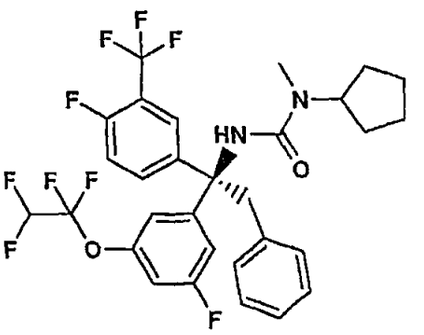
**Procedimiento 35**




A una solución de 2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclopropil)-2-oxoacetato de (R)-metilo (Ejemplo 243, 24 mg, 0.040 mmoles) en DCM (0.5 ml) a 0°C se agregó DAST (40 mg, 0.24 mmoles). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se extinguió por la adición de $NaHCO_3$ saturado (0.5 ml), se concentró bajo presión reducida y se purificó por CLAR preparativa (columna Phenomenex Axia, 30 x 100 mm, relación de flujo 40 ml/min, 30-100% $CH_3CN/H_2O$/0.1% de TFA durante 13 min) para producir 2,2-difluoro-2-(1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclopropil)acetato de (R)-metilo (Ejemplo 244) como un sólido blanco (3 mg, 12% rendimiento). CLEM: T.R. = 2.12 min [M+H] 617.5 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% $MeOH/H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); $^1H$ RMN

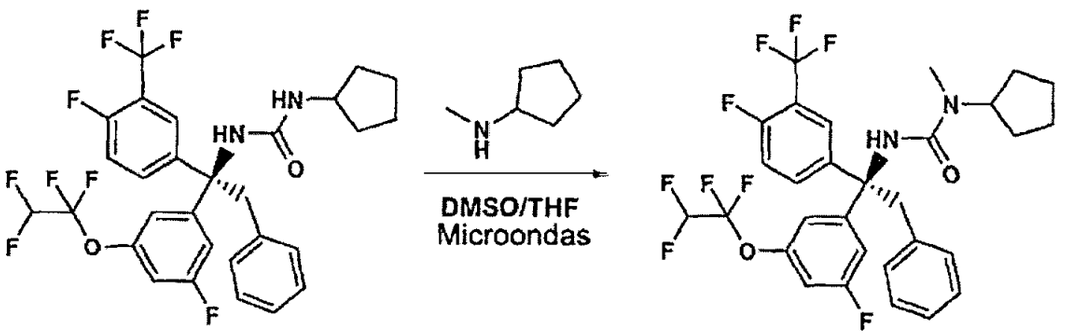
(400 MHz, $CDCl_3$) ppm 0.81 - 0.98 (m, 2 H), 1.21 - 1.35 (m, 2 H), 3.62 - 3.94 (m, 5 H), 4.96 (s, 1 H), 5.57 - 6.08 (m, 2 H), 6.61 - 6.72 (m, 2 H), 6.84 - 7.25 (m, 21 H).

**EJEMPLO 245**



**(R)-1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-1-metilurea**

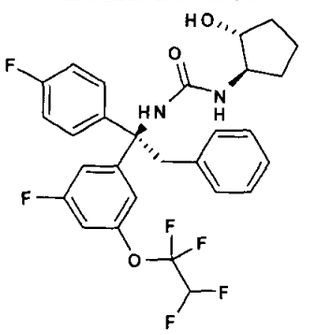
**Procedimiento 36**




A una solución de (R)-1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea (20 mg, 0.033 mmoles), preparada como se describe en el Procedimiento 3, 4, 5, 6 y 2, en DMSO/THF (0.1 ml /0.1 ml) se le agregó N-

metilciclopentanamina (32 mg, 0.33 mmoles). La solución resultante se agitó a 120°C bajo radiación por microondas durante 1800 seg. La mezcla de reacción se filtró y el sólido se lavó con EtOAc. El producto filtrado luego se lavó con $H_2O$, NaCl saturado y se secó sobre $Na_2SO_4$. El solvente orgánico se evaporó bajo presión reducida y el residuo resultante se purificó por CLAR preparativa (Phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para resultar en la (R)-1-ciclopentil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-1-metilurea (Ejemplo 246) como liofilato blanco (13 mg, 65% rendimiento). CLEM: [M+H] 619.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

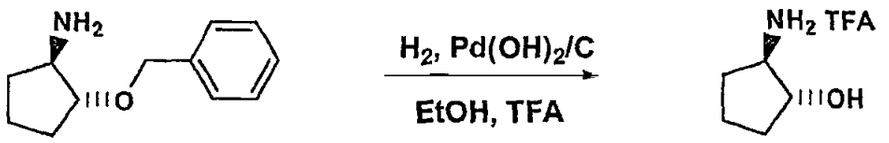
**EJEMPLO 246**



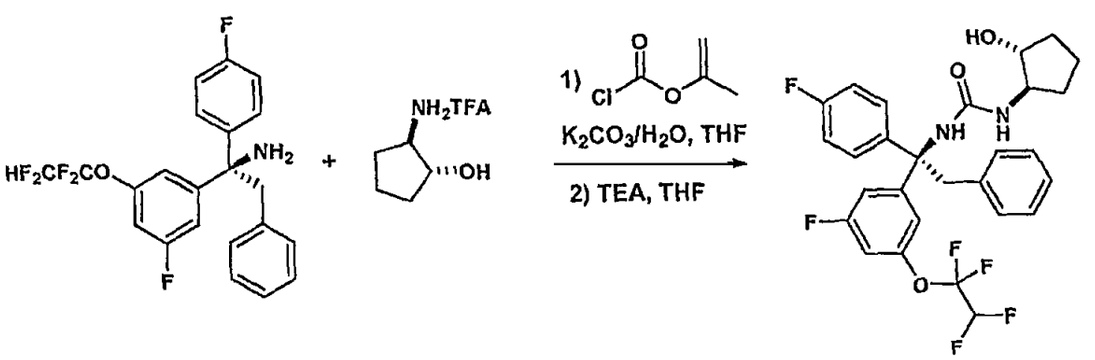

**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1R,2R)-2-hidroxiciclopentil)urea**

1289

**Procedimiento 37**



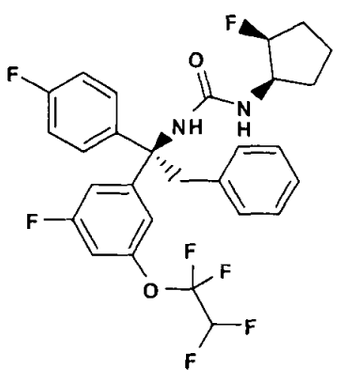

A una solución de (1R,2R)-2-(benciloxi)ciclopentanamina (3.5 g, 18.3 mmoles) en EtOH (20 ml) se agregó TFA (1.6 ml, 21.5 mmoles), seguido por $Pd(OH)_2/C$ (20% en peso, 627 mg). La mezcla de reacción se desgasificó con Ar y se agitó a temperatura ambiente bajo una atmósfera $H_2$ durante 3 días. El sólido resultante se filtró y se enjuagó con EtOH. El producto filtrado se concentró para producir sal TFA de (1R,2R)-2-aminociclopentanol (4.3 g, 100% rendimiento) como un aceite amarillo. $^1$H RMN (400 MHz, DMSO-D6) ppm 1.00 - 1.13 (m, 1 H), 1.39 - 1.57 (m, 2 H), 1.56 - 1.76 (m, 2 H), 1.79 - 1.94 (m, 1 H), 1.94 - 2.10 (m, 1 H), 3.06 - 3.23 (m, 1 H), 3.88 - 4.02 (m, 1 H), 7.84 - 8.07 (m, 2 H).




La 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-

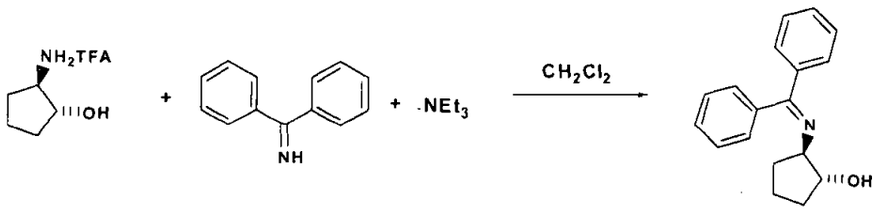
((1R,2R)-2-hidroxiciclopentil)urea (Ejemplo 246) fue preparada como se describe en el Procedimiento 25. CLAR: T.R. = 3.94 min [M+H] 553.08 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 1.07 - 1.35 (m, 1 H), 1.43 - 1.78 (m, 3 H), 1.80 - 1.98 (m, 2 H), 3.42 - 3.60 (m, 1 H), 3.61 - 3.73 (m, 1 H), 3.74 - 3.83 (m, 1 H), 3.83 - 3.96 (m, 1 H), 4.52 - 4.92 (m, 1 H), 5.66 - 6.03 (m, 2 H), 6.64 - 6.77 (m, 2 H), 6.80 - 6.89 (m, 1 H), 6.89 - 7.04 (m, 4 H), 7.04 - 7.22 (m, 4 H).

**EJEMPLO 247**



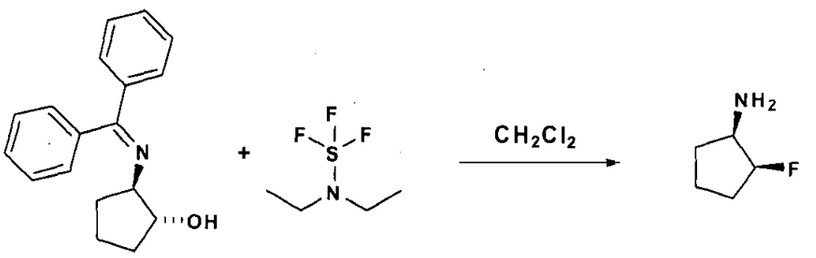
**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1R,2S)-2-fluorociclopentil)urea**

**Procedimiento 38**



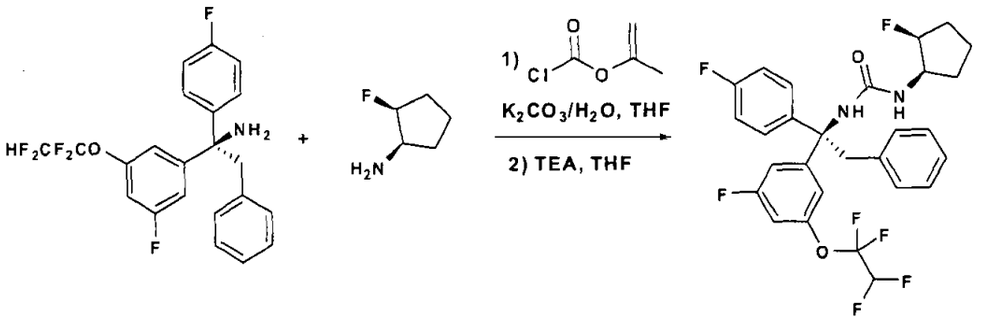

A una solución de sal TFA de (1R,2R)-2-

aminociclopentanol (630 mg, 2.93 mmoles) se agregó difenilmetanimina (490 ul, 2.93 mmoles) y TEA (0.5 ml, 3.58 mmoles) en $CH_2Cl_2$ (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se concentró bajo presión reducida y se purificó cromatografía instantánea ISCO al usar EtOAc y hexano como solvente eluyente para producir (1R,2R)-2-(difenilmetilenamino)ciclopentanol (697 mg, 90% rendimiento) como una goma incolora. CLAR: T.R. = 1.96 min [M+H] 266.13 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 1.49 - 1.64 (m, 2 H), 1.66 - 1.91 (m, 3 H), 2.08 - 2.24 (m, 1 H), 3.55 - 3.71 (m, 1 H), 4.31 - 4.47 (m, 1 H), 7.15 - 7.25 (m, 2 H), 7.29 - 7.53 (m, 6 H), 7.61 - 7.67 (m, 2 H).



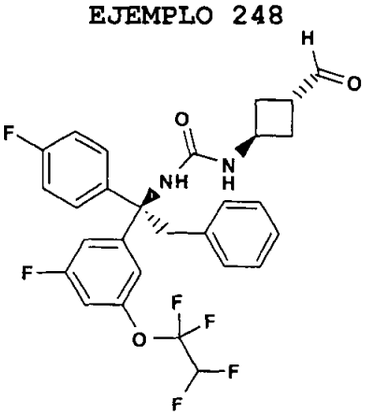

A una solución de (1R,2R)-2-(difenilmetilenamino)ciclopentanol (112 mg, 0.42 mmoles) en $CH_2Cl_2$ (1 ml) a -20°C se agregó gota a gota DAST (67 ul, 0.5 mmoles). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 16 h. La solución se concentró bajo presión reducida para producir la (1R,2R)-2-fluorociclopentanamina cruda (120 mg) la cual se usó en la

siguiente etapa sin purificación adicional.




La 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1R,2S)-2-fluorociclopentil)urea (Ejemplo 247) fue preparada como se describe en el Procedimiento 25. CLEM: T.R. = 4.07 min [M+H] 555.20 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CD_3CN$) δ ppm 1.02 - 1.12 (m, 6 H), 3.15 - 3.33 (m, 2 H), 3.89 (dd, 2 H), 5.10 - 5.24 (m, 1 H), 6.22 (t, 1 H), 6.71 - 6.82 (m, 2 H), 6.93 - 7.00 (m, 1 H), 7.01 - 7.33 (m, 9 H).

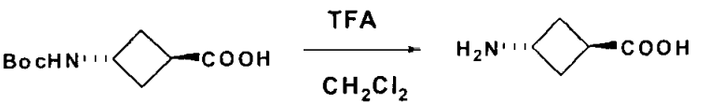
**EJEMPLO 248**



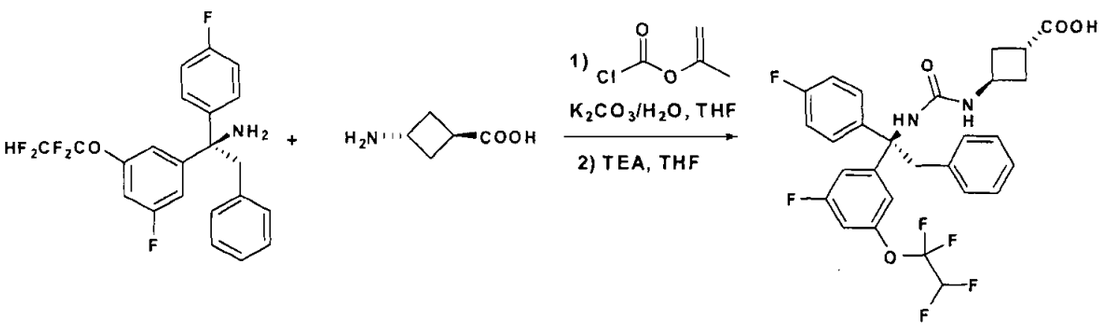

**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1r,3R)-3-formilciclobutil)urea**

1293

**Procedimiento 39**



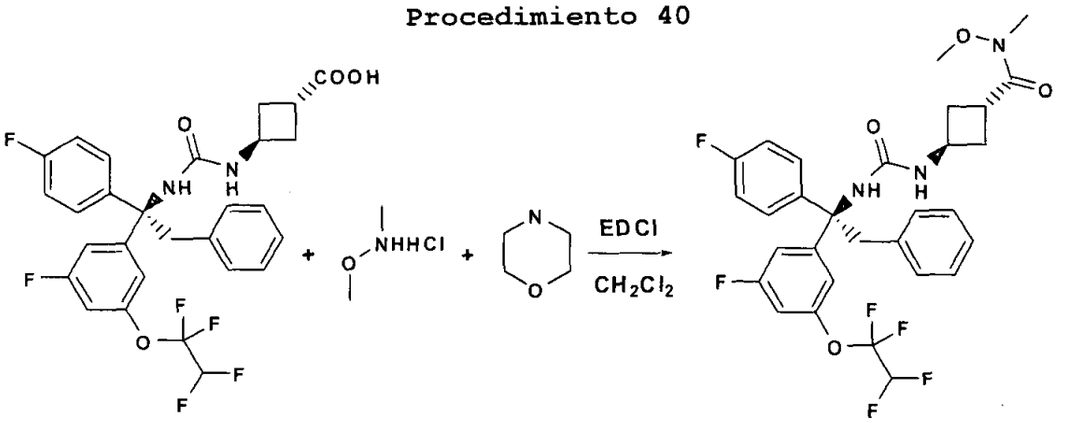

A una suspensión de ácido (1r,3r)-3-(terbutoxicarbonilamino)ciclobutancarboxílico (217 mg, 1 mmoles) en $CH_2Cl_2$ (5 ml) a temperatura ambiente se agregó TFA (0.37 ml, 2.7 mmoles) en una porción, y la mezcla de reacción se agitó a temperatura ambiente durante 16 h, luego se concentró para producir ácido (1r,3r)-3-aminociclobutanocarboxílico (227 mg, 100% rendimiento) como un aceite incoloro. $^1$H RMN (500 MHz, DMSO-D6) δ ppm 2.21 - 2.34 (m, 2 H), 2.35 - 2.46 (m, 2 H), 3.01 - 3.17 (m, 1 H), 3.65 - 3.85 (m, 1 H), 7.90 - 8.13 (m, 3 H).




Al usar el método descrito en Procedimiento 25, el ácido (1*R*,3r)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclobutanocarboxílico se preparó como un sólido blanco (372 mg, 66% rendimiento). CLAR: T.R. = 3.90 min [M+H] 567.69 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene

0.1% de TFA; 4 ml/min, observando a 220 nm).

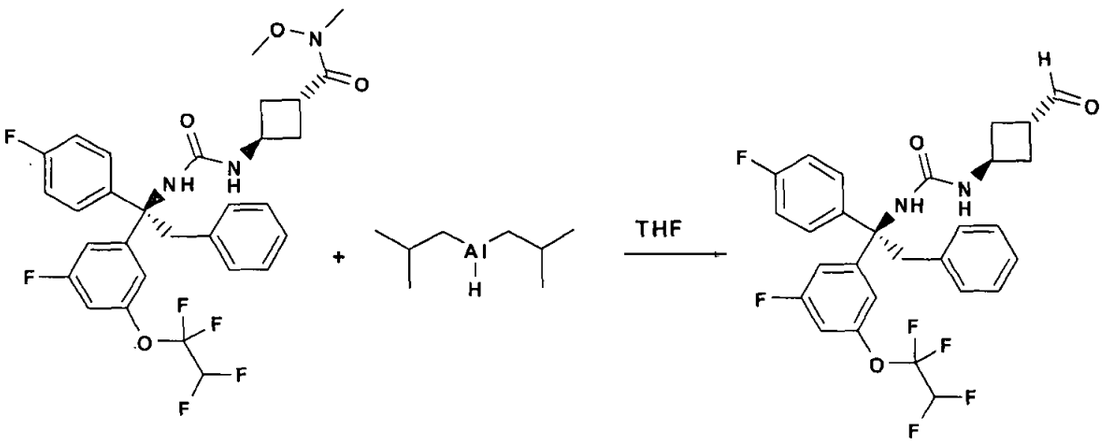
**Procedimiento 40**




A una solución de ácido (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)ciclobutanocarboxílico (180 mg, 0.32 mmoles) en $CH_2Cl_2$ (5 ml) se agregó HCl de N,O-dimetilhidroxiamina (31 mg, 0.32 mmoles) y N-metilmorfolina (32 mg, 0.37 mmoles). La mezcla de reacción se enfrió a -10°C bajo Ar. Después de 5 min, EDCI (61 mg, 0.39 mmoles) se agregó y la mezcla de reacción se permitió llegar a temperatura ambiente y se agitó durante 15 min. La mezcla de reacción se concentró y se purificó Cromatografía instantánea ISCO para producir (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-*N*-metoxi-*N*-metilciclobutanocarboxamida como un sólido blanco (194 mg, 100% rendimiento). CLAR: T.R. = 3.94 min [M+H] 610.72 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN

(400 MHz, DMSO) ppm 2.55 - 2.63 (m, 2 H), 2.94 - 3.10 (m, 2 H), 3.61 - 3.71 (m, 3 H), 3.84 - 4.02 (m, 1 H), 4.13 - 4.21 (m, 3 H), 4.41 (dd, 2 H), 4.58 - 4.75 (m, 1 H), 5.92 - 6.05 (m, 2 H), 6.75 (t, 1 H), 7.24 - 7.33 (m, 2 H), 7.43 - 7.52 (m, 2 H), 7.54 - 7.64 (m, 3 H), 7.64 - 7.83 (m, 5 H).

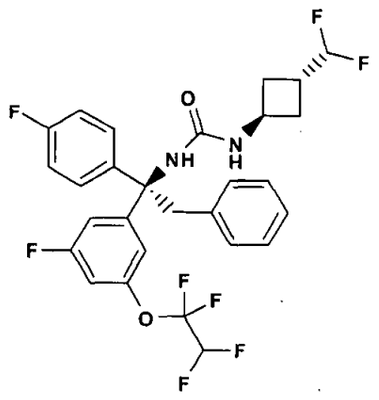
**Procedimiento 41**




A una solución de (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-*N*-metoxi-*N*-metilciclobutanocarboxamida (182 mg, 0.3 mmoles) en THF (2 ml) a -78°C bajo Ar se agregó gota a gota DIBAL-*H* (1.0 M en hexano, 0.75 ml). La mezcla de reacción se agitó a -78°C durante 20 min. Se agregó acetona (1 ml), seguido por tartrato de potasio de sodio acuoso saturado (5 ml) y éter (2 ml). La mezcla resultante de reacción se agitó a temperatura ambiente durante 16 h. La capa acuosa se extrajo con éter (2 x 10 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se

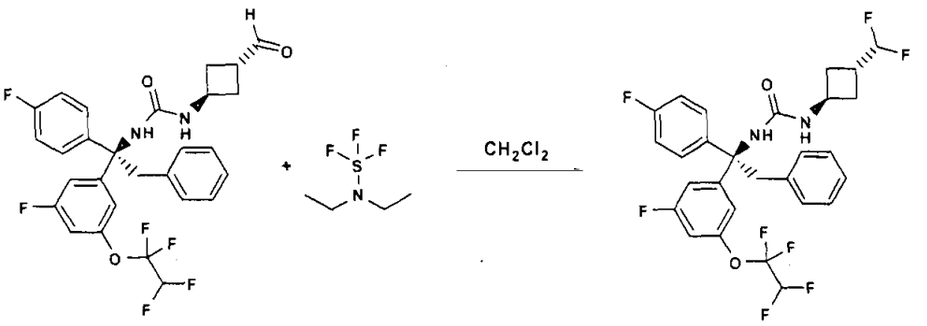
purificó por Cromatografía de vaporización instantánea ISCO al usar EtOAc y hexano como solvente eluyente para producir 1-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1*r*,3*R*)-formilciclobutil)urea (Ejemplo 248) como un sólido blanco (122 mg, 74% rendimiento). CLAR: T.R. = 3.89 min [M+H] 551.10 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 1.73 - 1.88 (m, 2 H), 2.35 - 2.49 (m, 2 H), 2.80 - 2.94 (m, 1 H), 3.64 (dd, 2 H), 3.81 - 3.98 (m, 1 H), 4.95 (d, 1 H), 5.20 - 5.29 (m, 1 H), 5.79 (t, 1 H), 6.56 (d, 2 H), 6.71 - 6.92 (m, 4 H), 6.92 - 7.16 (m, 5 H), 9.58 - 9.70 (m, 1 H).

**EJEMPLO 249**




**1-((1r,3R)-3-(difluorometil)ciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

**Procedimiento 42**

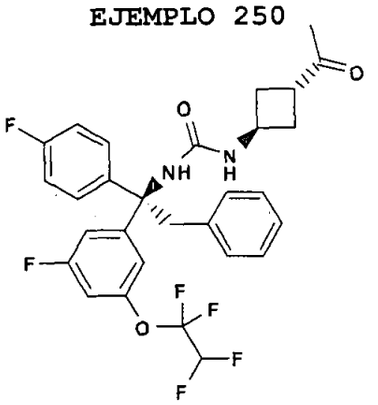


A una solución de 1-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1*r*,3*R*)-formilciclobutil)urea (Ejemplo 248, 43 mg, 0.078 mmoles) en $CH_2Cl_2$ (0.5 ml) a temperatura ambiente se agregó DAST (30 ul , 0.23 mmoles) gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 16 h, se concentró bajo presión reducida y se purificó por CLAR preparativa (phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm). El producto se purificó además por Cromatografía de vaporización instantánea ISCO para producir 1-((1r,3*R*)-3-(difluorometil)ciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 249) como un sólido blanco (18 mg, 40% rendimiento). CLAR: T.R. = 4.03 min [M+H] 573.69 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (500 MHz, $CD_3CN$) δ ppm 1.98 - 2.08 (m, 2 H), 2.24 - 2.39 (m, 2 H), 2.46 - 2.65 (m, 1

1298

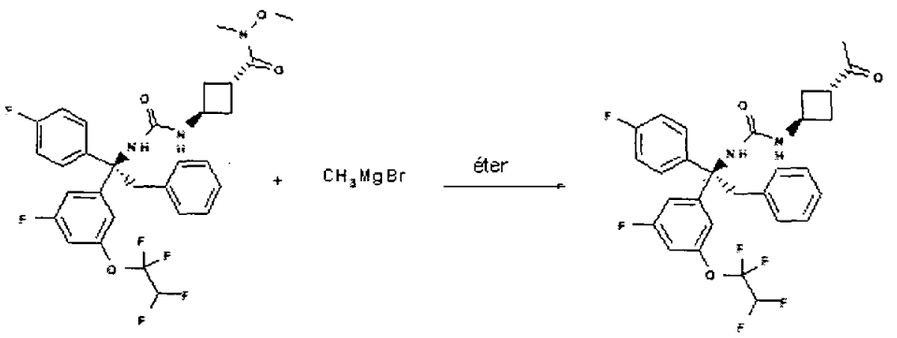
H), 3.85 (dd, 2 H), 4.08 - 4.22 (m, 1 H), 5.45 - 5.56 (m, 1 H), 5.96 (t, 1 H), 6.19 (t, 1 H), 6.65 - 6.78 (m, 2 H), 6.88 - 6.97 (m, 2 H).

**EJEMPLO 250**



**1-((1r,3R)-3-acetilciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

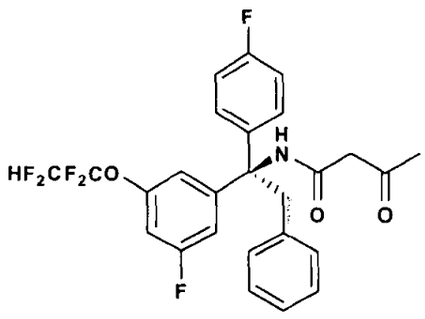
**Procedimiento 43**




A una solución de (1*R*,3*r*)-3-(3-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-*N*-metoxi-*N*-metilciclobutanocarboxamida, preparada como se describe en el Procedimiento 40, (160 mg, 0.26 mmoles) en éter (5 ml) a -40°C, se agregó gota a gota $CH_3MgBr$ (3 M en éter, 0.2 ml). Luego la mezcla de reacción se agitó a 0°C durante 4 h. La reacción se apagó con NaCl

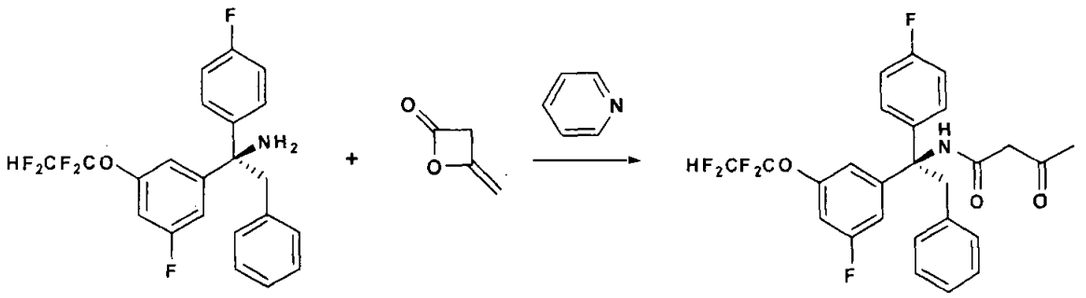
saturado y la capa acuosa se extrajo con éter. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El aceite resultante se purificó por Cromatografía de vaporización instantánea ISCO al usar EtOAc y hexano como solvente eluyente para producir 1-((1r,3*R*)-3-acetilciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 250) como un sólido blanco (32 mg, 22% rendimiento). CLAR: T.R. = 3.90 min [M+H] 565.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CD_3CN$) δ ppm 2.03 - 2.09 (m, 2 H), 2.08 - 2.12 (m, 3 H), 2.41 - 2.54 (m, 2 H), 3.10 - 3.23 (m, 1 H), 3.88 (dd, 2 H), 3.98 - 4.07 (m, 1 H), 5.41 - 5.51 (m, 2 H), 6.21 (t, 1 H), 6.73 - 6.80 (m, 2 H), 6.93 - 7.00 (m, 2 H), 7.02 - 7.10 (m, 3 H), 7.12 - 7.30 (m, 6 H).

**EJEMPLO 251**




**(R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-oxobutanamida**

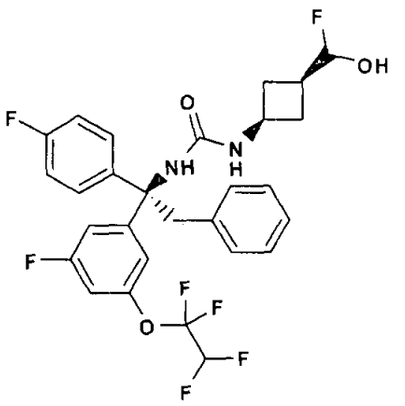
**Procedimiento 44**



A una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (28 mg, 0.07 mmoles), preparada como se describe en el Procedimiento 3, 4, 5 y 6, en DCM (1 ml) se agregó piridina (0.01 ml, 0.12 mmoles). La reacción se enfrió a 0°C, seguido por la adición de 4-metilenoxetan-2-ona (0.01 ml, 0.13 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se concentró. El residuo se purificó por CLAR preparativa (columna Axia luna, 30 x 75 mm, 40-100% ACN/$H_2O$ con 0.1% de TFA durante 10 min, relación de flujo 40 ml/min, observando a 220 nm) para producir (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-oxobutanamida (Ejemplo 251) como un aceite incoloro (23 mg, 58% rendimiento). CLEM: T.R. = 3.71 min [M+H] 510.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 8.23 (1 H, s), 7.04 - 7.20 (5 H, m), 6.96 - 7.02 (2 H, m), 6.87 - 6.92 (3 H, m), 6.61 (2 H, d, J=7.07

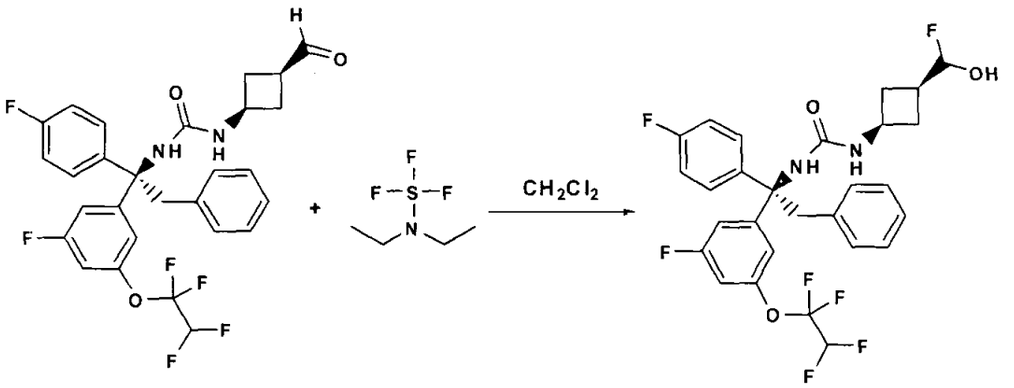
Hz), 5.87 (1 H, t, J=2.78 Hz), 3.94 (1 H, d, J=12.88 Hz), 3.71 (1 H, d, J=12.88 Hz), 3.43 (2 H, s), 2.24 (3 H, s).

**EJEMPLO 252**



**1-((1R,3S)-3-((S)-fluoro(hidroxi)metil)ciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

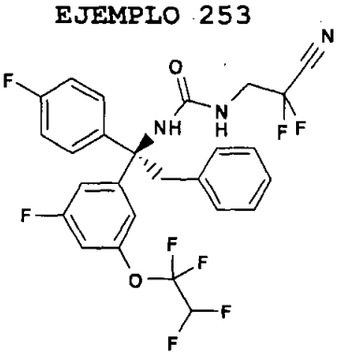
**Procedimiento 45**



A una solución de 1-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1s,3S)-3-formilciclobutil)urea (Ejemplo 248, 35 mg, 0.064 mmoles) en $CH_2Cl_2$ (0.5 ml) se agregó DAST (50 ul, 0.37 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 días, luego se concentró y se purificó por

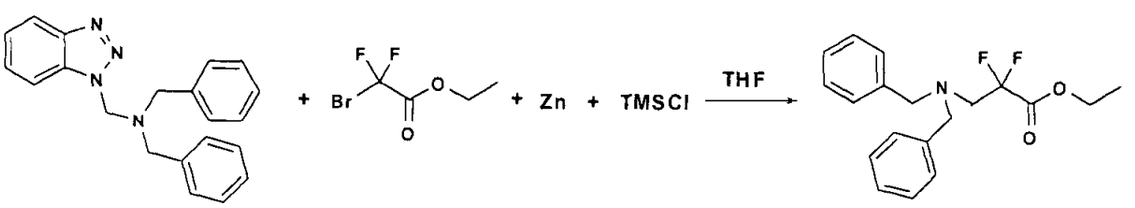
CLAR preparativa para producir 1-((1R,3S)-3-((S)-fluoro(hidroxi)metil)ciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 252) como un sólido amarillo ligero (20 mg, 56% rendimiento). CLEM: T.R. = 1.79 min [M+H] 553.2 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 1.59 - 1.79 (m, 1 H), 1.95 - 2.15 (m, 1 H), 2.52 - 2.77 (m, 2 H), 2.90 - 3.07 (m, 1 H), 3.65 - 3.76 (m, 2 H), 3.99 - 4.16 (m, 1 H), 4.60 - 5.11 (m, 1 H), 5.56 - 6.07 (m, 2 H), 6.57 - 6.67 (m, 2 H), 6.78 - 7.32 (m, 12 H), 10.13 - 10.41 (m, 1 H).

**EJEMPLO 253**



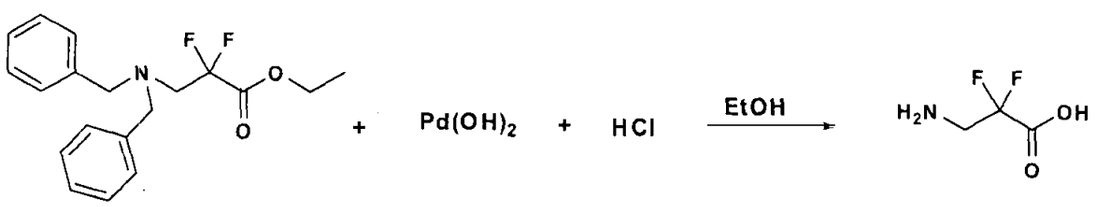
**(R)-1-(2-ciano-2,2-difluoroetil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

**Procedimiento 46**




A una suspensión de polvo de zinc (238 mg, 3.66

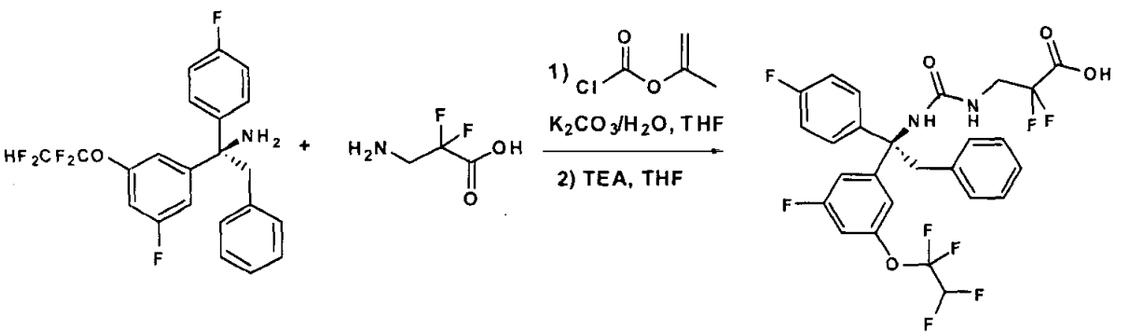
mmoles) en THF (3 ml) bajo Ar se agregó TMSCl (234 ul, 1.83 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 10 min seguido por la adición de bromodifluoroacetato de etilo (260 ul, 2.0 mmoles) gota a gota. Después de 10 min, *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-il)metil)-*N*-bencil-1-fenilmetanaima (600 mg, 1.83 mmoles) en THF (3 ml) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se apagó con 5% $NaHCO_3$ en $H_2O$ (10 ml). El sólido resultante se filtró y se lavó con EtOAc. El producto filtrado se extrajo con EtOAc y las capas EtOAc combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo resultante se purificó por Cromatografía de vaporización instantánea ISCO al usar EtOAc y hexano como solvente eluyente para producir 3-(dibencilamino)-2,2-difluoropropanoato de etilo como un aceite incoloro (577 mg, 56% rendimiento). CLEM: T.R. = 4.09 min [M+H] 334.28 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).




A una solución de 3-(dibencilamino)-2,2-

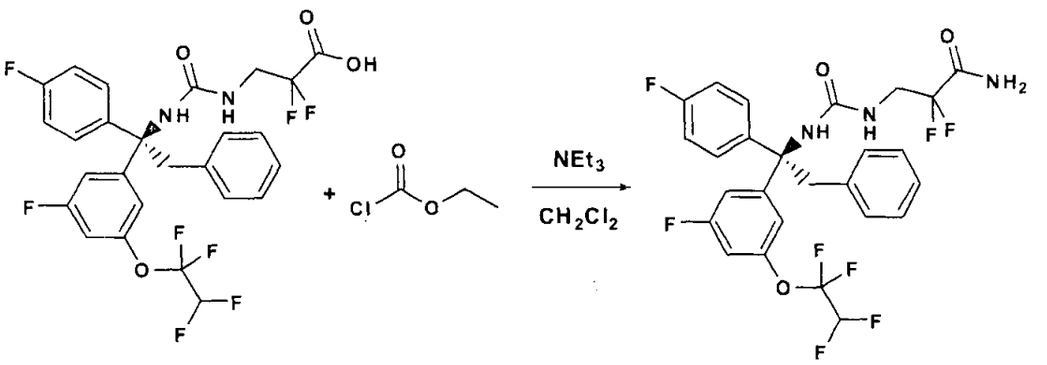
1304

difluoropropanoato de etilo (517 mg, 1.55 mmoles) en EtOH (1 ml) se agregó 0.5 N HCl (1 ml) y $Pd(OH)_2/C$ (20%, 50 mg). La mezcla de reacción se agitó a temperatura ambiente bajo una atmósfera $H_2$ durante 3 días. La mezcla de reacción se filtró y el sólido se enjuagó con agua y éter. La capa acuosa se separó a partir de la capa de éter y se liofilizó para producir ácido etil 3-amino-2,2-difluoropropanoico como un sólido blanco (210 mg, 100 % rendimiento). $^1H$ RMN (400 MHz, DMSO) ppm 3.27 - 3.46 (m, 2 H), 8.06 - 8.64 (m, 3 H).




Al usar el método descrito en el Procedimiento 25, el ácido (*R*)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)propanoico (60 mg, 0.1 mmoles) se preparó como un sólido blanco (62 mg, 54% rendimiento). CLEM: T.R. = 1.97 min [M+H] 577.2 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

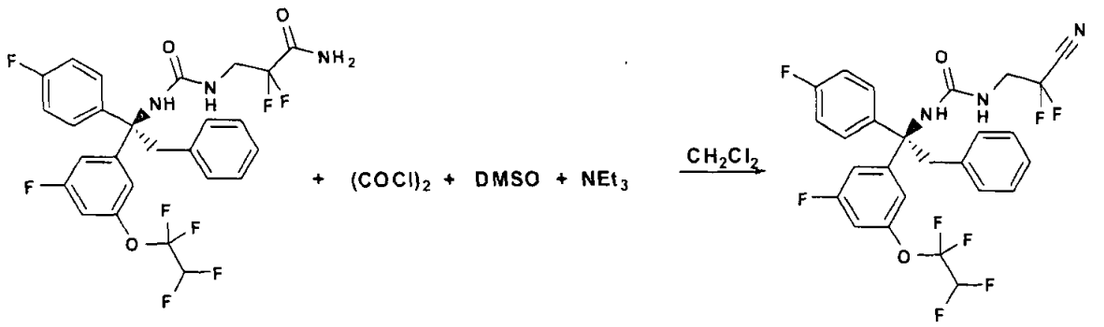
**Procedimiento 47**



A una solución del ácido (*R*)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)propanoico (60 mg, 0.1 mmoles) en $CH_2Cl_2$ (1 ml) a 0°C se agregó clorhidrato de etil carbono (10 ul, 0.1 mmoles), seguido por $NEt_3$ (0.021 ml, 0.15 mmoles) y $NH_3 \cdot H_2O$ (0.1 ml, 2.6 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego se concentró bajo presión reducida y se purificó por CLAR preparativa (Phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para producir (*R*)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)propanamida como un sólido blanco (12 mg, 21% rendimiento). CLEM: T.R. = 3.85 min [M+H] 576.1 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

1306

**Procedimiento 48**

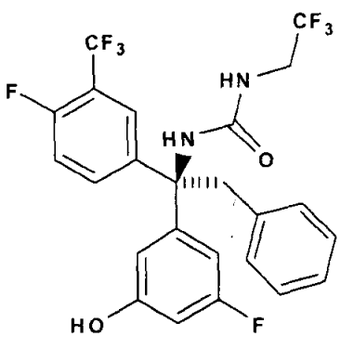



A una solución de (*R*)-2,2-difluoro-3-(3-(1-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)propanamida (12 mg, 0.02 mmoles) en $CH_2Cl_2$ (0.5 ml) a -78°C se agregó DMSO (10 ul, 0.14 mmoles), seguido por la adición de $(COCl)_2$ (2 M en $CH_2Cl_2$, 0.05 mmoles). La mezcla de reacción se agitó a -78°C durante 15 min, luego $NEt_3$ (0.03 ml, 0.2 mmoles) se agregó gota a gota. La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 16 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por CLAR preparativa (Phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para producir (*R*)-1-(2-ciano-2,2-difluoroetil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 253) como un sólido blanco (7 mg, 62% rendimiento). CLEM: T.R. = 4.03 min [M+H] 558.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220

(307)

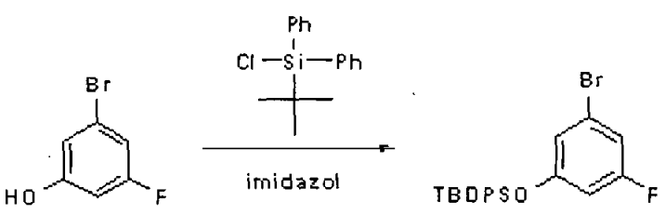
nm). $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 3.71 (d, 2 H), 3.76 - 3.99 (m, 3 H), 4.75 - 4.84 (m, 1 H), 5.13 - 5.27 (m, 1 H), 5.86 (t, 1 H), 6.64 - 6.76 (m, 2 H), 6.86 - 6.96 (m, 3 H), 6.97 - 7.06 (m, 2 H), 7.07 - 7.23 (m, 5 H).

**EJEMPLO 254**




**(*R*)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-hidroxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea**

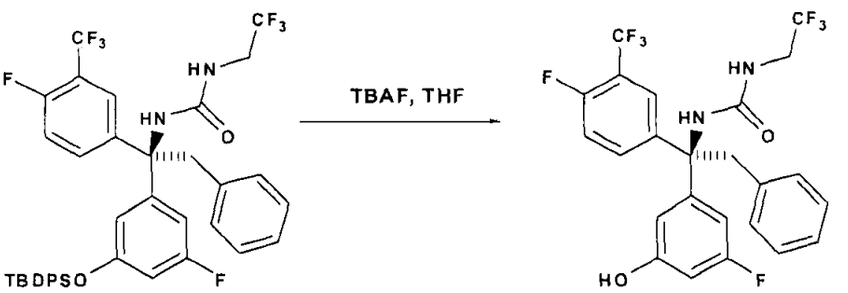
**Procedimiento 49**




A una solución de 3-bromo-5-fluorofenol (5.7 g, 30 mmoles), preparada como se describe en el Procedimiento 3, y imidazol (4.0 g, 60 mmoles, 2 eq) en THF anhidro (100 ml) a 0°C se agregó cloruro de ter-butildifenil-sililo (9.6 ml, 1.3 eq). La mezcla resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se apagó con agua y se extrajo con hexano/EtOAc (1:1). Las capas orgánicas

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combinadas se lavaron con $H_2O$ (2 x) y NaCl saturado (2 x), se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo resultante se purificó por cromatografía de gel de sílice (hexanos/EtOAc) para dar (3-bromo-5-fluorofenoxi)(ter-butil)difenilsilano como un aceite incoloro (7.5 g, rendimiento 58 %).



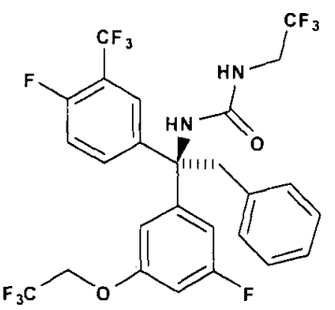

La (R)-1-(1-(3-(ter-butildifenilsililoxi)-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea fue preparada como se describe en el Procedimiento 4, 5, 6 y 10 (85 mg, 37 % de rendimiento general). CLEM: T.R. = 2.71 min [M+H] 757.3 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

A una solución de (R)-1-(1-(3-(ter-butildifenilsililoxi)-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (85 mg, 0.11 mmoles) en THF (1.5 ml) se agregó TBAF (1.0 M en THF, 0.12 ml, 0.12 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 45 min. La

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reacción se diluyó con $CH_2Cl_2$ y se lavó con $NH_4Cl$ saturado, $H_2O$ y NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo resultante se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar (*R*)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-hidroxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 254, 45 mg, rendimiento 77 %). CLEM: T.R. = 2.0 min [M+H] 519.1 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.20 - 7.27 (3 H, m), 7.09 - 7.18 (3 H, m), 6.72 (1 H, d, J=9.60 Hz), 6.66 (3 H, d, J=7.07 Hz), 6.57 (1 H, s), 3.73 - 3.78 (1 H, m), 3.65 - 3.71 (1 H, m), 3.63 (1 H, d, J=8.59 Hz), 3.47 - 3.58 (1 H, m).

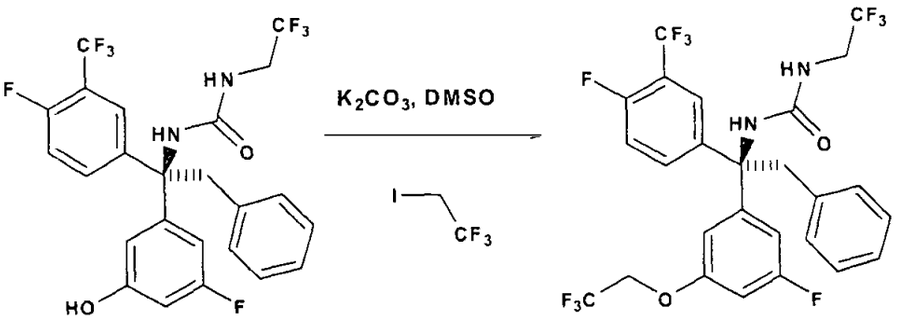
**EJEMPLO 255**




**(*R*)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(2,2,2-trifluoroetoxi)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea**

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**Procedimiento 50**

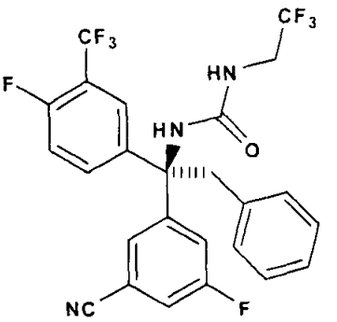



A una solución de (R)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-hidroxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 254, 15 mg, 0.03 mmoles) en DMSO (0.15 ml) se agregó $ICH_2CF_3$ (0.02 ml) y $K_2CO_3$ (20 mg, 0.2 mmoles). La mezcla de reacción se calentó a 70°C durante la noche. La reacción se enfrió hasta temperatura ambiente y se diluyó con $CH_3CN$, se filtró y se purificó por CLAR preparativa (phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para dar (*R*)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(2,2,2-trifluoroetoxi)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 255) como un sólido blanco (10 mg, rendimiento 58%). CLEM: T.R. = 2.18 min [M+H] 601.2 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.33 - 7.43 (2 H, m), 7.21 (1 H, d, J=6.60 Hz), 7.12 - 7.19

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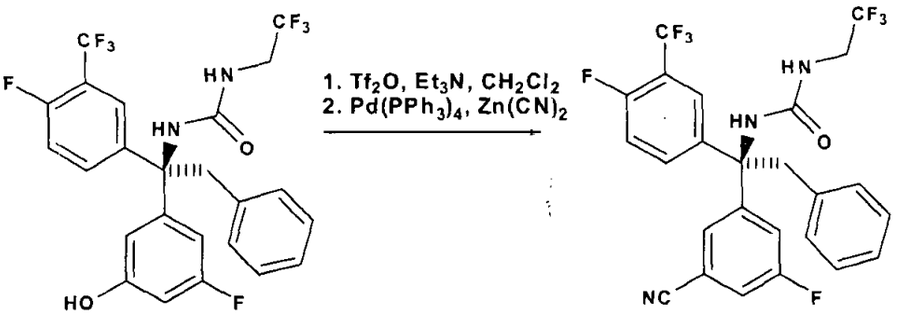
(2 H, m), 6.68 (2 H, d, J=7.70 Hz), 6.54 - 6.63 (3 H, m), 4.19 - 4.30 (2 H, m), 3.73 - 3.84 (4 H, m).

**EJEMPLO 256**



**(*R*)-1-(1-(3-ciano-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea**

**Procedimiento 51**



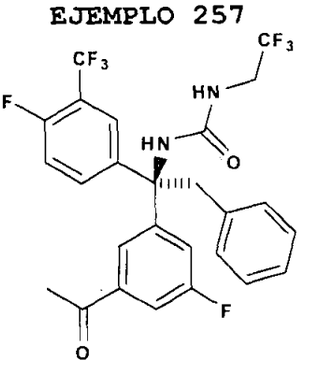

A una solución de (R)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-hidroxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 254, 0.12 g, 0.23 mmoles) en $CH_2Cl_2$ anhidro (2 ml) a 0°C bajo argón se agregó $Et_3N$ (0.05 ml, 0.4 mmoles) seguido por adición gota a gota de anhídrido trifluoroacético (0.05 ml). La mezcla de reacción se agitó a 0°C durante 30 min, se diluyó con $CH_2Cl_2$ (10 ml). La capa orgánica se lavó con $H_2O$, NaCl saturado, se

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secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar trifluorometansulfonato de (R)-3-(1-(4-fluoro-3-(trifluorometil)fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil)ureido)etil)fenilo (65 mg). CLEM: T.R. = 2.34 min [M+H] 651.4 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). A una solución de (R)-3-(1-(4-fluoro-3-(trifluorometil)fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil)ureido)etil)fenil trifluorometansulfonato (65 mg, 0.1 mmoles) en DMF (0.4 ml) se agregó $Zn(CN)_2$ (70 mg) y $Pd(PPh_3)_4$ (cantidad catalítica). La mezcla de reacción se calentó a 105°C en un vial sellado durante 2 h. Después del enfriamiento hasta temperatura ambiente, la solución de reacción se filtró y el sólido se enjuagó con EtOAc. El producto filtrado se lavó con $NaHCO_3$ saturado, $H_2O$, y NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar (R)-1-(1-(3-ciano-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 256, 37 mg, 30% rendimiento durante 2 etapas). CLEM: T.R. = 3.88 min [M+H] 528.2 (columna Phenomenex Luna C18, 4.6 × 30 mm

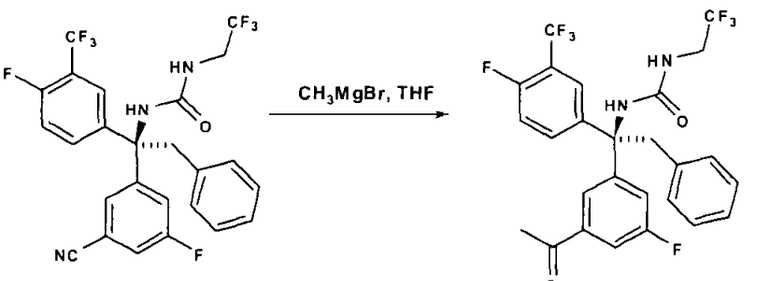
eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.31 (m, 2 H), 7.26-7.13 (m, 4 H), 7.02-6.93 (m, 3 H), 6.66 (d, J=7.7 Hz, 2 H), 5.24 (s, br, 1H), 5.05 (t, J=6.0 Hz, 1 H), 3.80 (AB, J=12.6 Hz, 2 H), 3.74 (m, 2 H).

**EJEMPLO 257**



**(*R*)-1-(1-(3-acetil-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea**

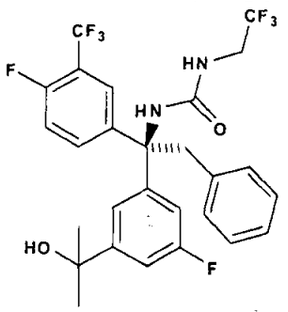
**Procedimiento 52**




A una solución de (S)-1-(1-(3-cianofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 256, 30 mg, 0.06 mmoles) en THF (1 ml) a temperatura ambiente se agregó $CH_3MgBr$ (3.0 M en $Et_2O$, 0.1 ml). La mezcla de reacción se calentó a 48°C - 55°C durante 2.5 h. Después del enfriamiento, se agregó HCl 1N y

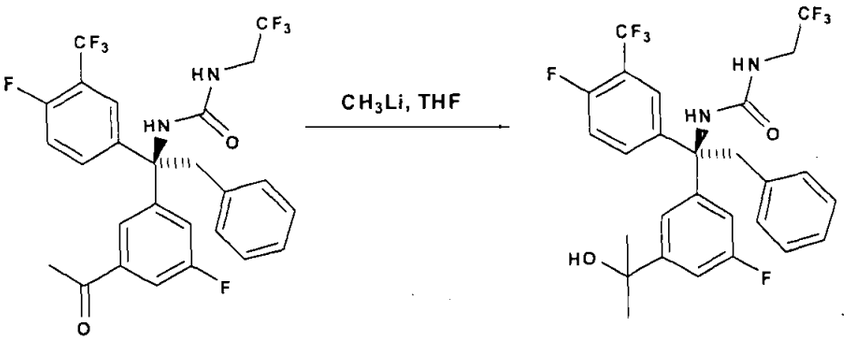
la mezcla de reacción se agitó durante 10 min a temperatura ambiente. La mezcla de reacción se extrajo con EtOAc, se lavó con $H_2O$, NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar la (*R*)-1-(1-(3-acetil-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea pura (Ejemplo 257, 26 mg, rendimiento: 84%). CLEM: T.R. = 3.90 min [M+H] 545.2 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.58 (m, 1 H), 7.53 (m, 1 H), 7.36 (m, 2 H), 7.23 (m, 1 H), 7.16 (m, 4 H), 6.68 (d, J=6.8 Hz, 2 H), 5.43 (s, br, 1 H), 5.17 (m, 1 H), 3.88 (dd, J=23.2, 12.9 Hz, 2 H), 3.78 (m, 2 H), 3.03 (s, 3 H).

**EJEMPLO 258**




**(*R*)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(2-hidroxipropan-2-il)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea**

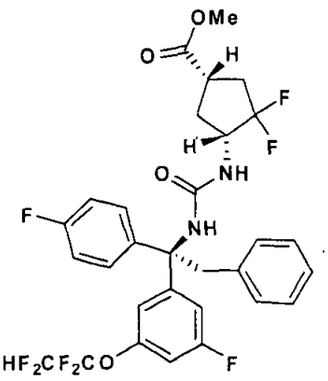
**Procedimiento 53**




A una solución de (R)-1-(1-(3-acetil-5-fluorofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 257, 20 mg, 0.037 mmoles) en THF (1 ml) a 0°C bajo argón se agregó gota a gota $CH_3Li$ (1.4 M en $Et_2O$, 0.04 ml, 0.056 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego se apagó con $NH_4Cl$ saturado y 0.5 N HCl y la capa acuosa se extrajo con EtOAc. Las porciones orgánicas combinadas se lavaron con $H_2O$, NaCl saturado, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos /EtOAc) para dar (*R*)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(2-hidroxipropan-2-il)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 258, 8 mg, rendimiento 39%). CLEM: T.R. = 3.89 min [M+H] 559.4 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4Cl$; 4 ml/min, observando a 220

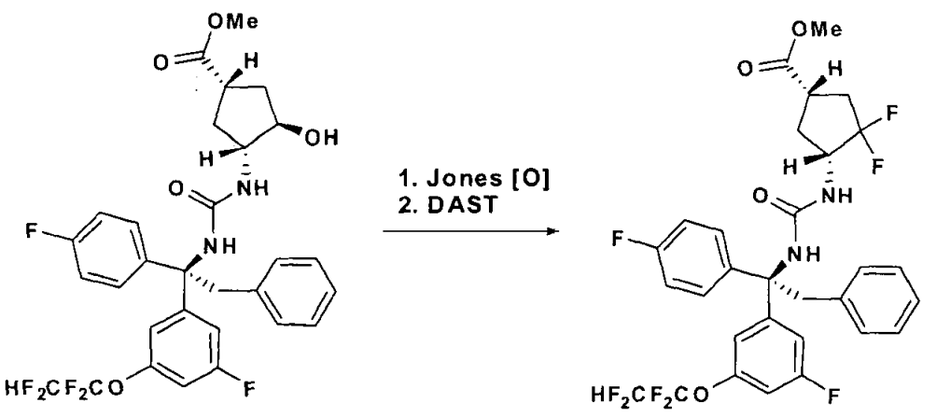
nm). $^1$H RMN (400 MHz, $CDCl_3$) ppm 7.51-7.45 (m, 2 H), 7.21-6.96 (m, 6 H), 6.68 (d, J=6.8 Hz, 2 H), 6.61 (d, J= 9.9 Hz, 1 H), 5.43 (s, br, 1 H), 5.17 (m, 1 H), 4.01 (d, J= 13.2 Hz, 1 H), 3.85-3.62 (m, 3 H), 1.46 (s, 3 H), 1.44 (s, 3 H).

**EJEMPLO 259**



**3,3-difluoro-4-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(ureido)ciclopentanocarboxilato de (1S,4R)-metilo**

**Procedimiento 54**

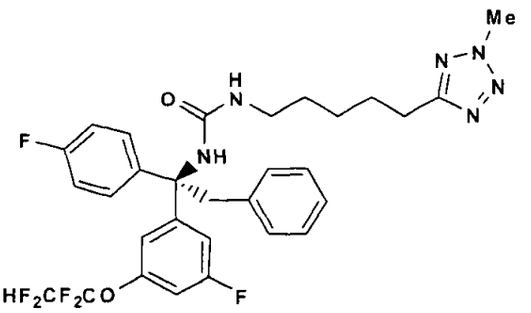



A una solución de 3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-4-hidroxiciclopentanocarboxilato de

(1S,3R,4R)-metilo, se preparó como se describe en el Procedimiento 12, (11 mg, 0.017 mmoles) en acetona (430 µl) se agregó una solución del reactivo Jones (17 µL, solución 1M). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, luego se filtró a través de una almohadilla de celite. La almohadilla se lavó con acetona y el producto filtrado se concentró bajo presión reducida. El residuo se disolvió en EtOAc y la solución se lavó con $H_2O$. La capa orgánica se separó y la capa acuosa se extrajo además con EtOAc (3 x). Los orgánicos combinados se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se disolvió en $CH_2Cl_2$ (17 ml) y se agregó DAST (6.5 ml) a temperatura ambiente. La mezcla de reacción se agitó durante la noche, luego se apagó con NaCl saturado. La capa acuosa se extrajo con $CH_2Cl_2$ (3 x). Las capas orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó por CLAR preparativa (Phenoma Luna AXIA 10A, C18, eluyendo con MeCN/$H_2O$ que contiene 0.1% de TFA, observando a 220 nm) para proporcionar 3,3-difluoro-4-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetra-fluoroetoxi)fenil)-1-(4-fluorofenil)-2-)ureido)ciclopentanocarboxilato de (1S,4R)-metilo (Ejemplo 259, 9 mg, 85% rendimiento) como una película. $^1H$ RMN (500 MHz, $CDCl_3$) δ 7.16-7.07 (m, 6 H), 7.00-6.83 (m, 6 H), 6.62 (d, $J$ = 10 Hz, 2 H), 5.93-5.68 (m, 1 H), 5.37 (s, 1 H), 3.77

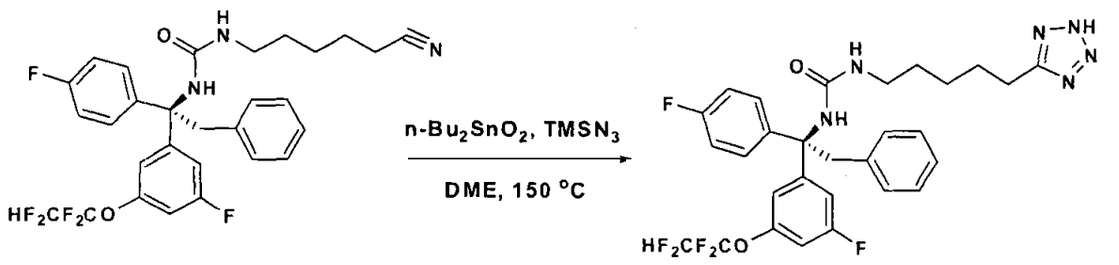
(d, $J$ = 10 Hz, 1 H), 3.64 (s, 3 H), 3.68-5.58 (m, 2 H), 2.90-2.84 (m, 1 H), 2.47-2.26 (m, 3 H), 1.60-1.53 (m, 1 H); CL/EM: T.R. = 3.97 min [M+H] 631.4 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm).

**EJEMPLO 260**




**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(5-(2-metil-2H-tetrazol-5-il)pentil)urea**

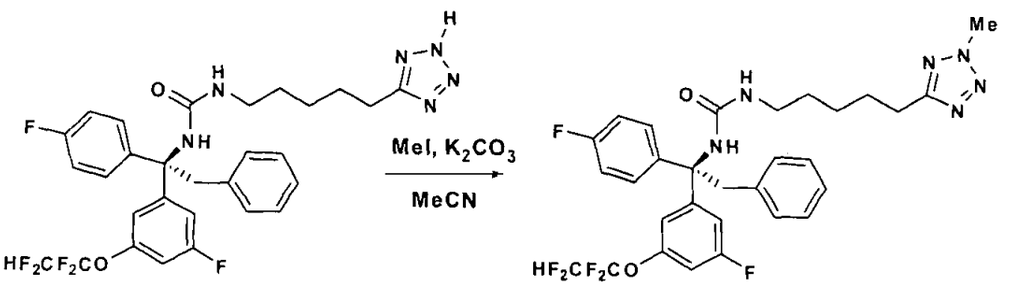
**Procedimiento 55**




A una solución de (R)-1-(5-cianopentil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea, preparado por el método descrito en el Procedimiento 12 (45 mg, 0.080 mmoles) en DME (161 µl) a temperatura ambiente se agregó $TMSN_3$ (0.013 ml, 0.16 mmoles),

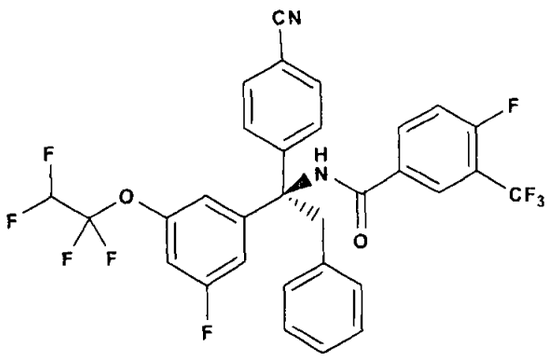
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seguido por n-$Bu_2SnO_2$ (2 mg, 0.008 mmoles). La mezcla de reacción se calentó a 150°C durante 10 min. bajo radiación por microondas. Una cantidad adicional de $TMSN_3$ (0.013 ml, 0.16 mmoles) y n-$Bu_2SnO_2$ (2 mg, 0.008 mmoles) se agregó, y la mezcla de reacción se calentó a 150°C durante 10 minutos adicionales bajo radiación por microondas. La mezcla de reacción se concentró y el residuo se disolvió en MeOH y se purificó por CLAR preparativa (Phenoma Luna AXIA 10A, C18, eluyendo con MeCN/$H_2O$ que contiene 0.1% de TFA, observando a 220 nm) para proporcionar (R)-1-(5-(2H-tetrazol-5-il)pentil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (23 mg, 47% rendimiento) como un sólido blanco. $^1H$ RMN (500 MHz, MeOH-$d_4$) δ 7.18-6.89 (m, 11 H), 6.71 (d, J=5 Hz, 2 H), 6.37-6.16 (m, 1 H), 3.93 (d, J=15 Hz, 1 H), 3.81 (d, J=15.0 Hz, 1 H), 3.08 (t, J=5 Hz, 2 H), 2.94 (t, J=5 Hz, 2 H), 1.83-1.76 (m, 2 H), 1.55-1.48 (m, 2 H), 1.41-1.35 (m, 2 H); CL/EM: T.R. = 3.736 min [M+H] 607.3 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm).



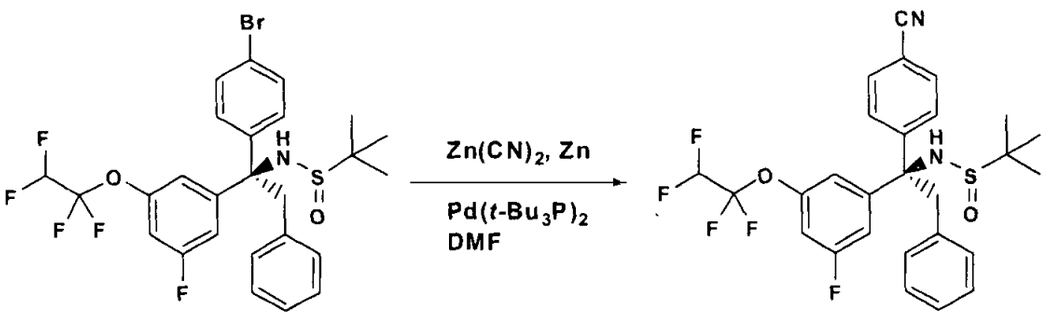
A una solución de (R)-1-(5-(2H-tetrazol-5-il)pentil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (12 mg, 0.019 mmoles) en MeCN (115 µL) a temperatura ambiente se agregó $K_2CO_3$ (3.2 mg, 0.023 mmoles) seguido por MeI (1.5 µl, 0.023 mmoles). La mezcla de reacción se calentó a 80°C durante la noche. La mezcla de reacción se apagó por la adición de $H_2O$ y la capa acuosa se extrajo con EtOAc (3 x). Las capas orgánicas combinadas se concentraron y el residuo se disolvió en MeOH y se purificó por CLAR preparativa (Phenoma Luna AXIA 10A, C18, eluyendo con MeCN/$H_2O$ que contiene 0.1% de TFA, observando a 220 nm) para proporcionar (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(5-(2-metil-2H-tetrazol-5-il)pentil)urea (Ejemplo 260, 2 mg, 18% rendimiento) como un sólido blanco. $^1$H RMN (500 MHz, $CDCl_3$) ppm 7.17-7.08 (m, 5 H), 6.99-6.85 (m, 5 H), 6.67 (d, *J* = 5 Hz, 2 H), 5.98-5.75 (m, 1 H), 4.23 (s, 3 H), 3.82 (d, *J* = 15 Hz, 1 H), 3.68 (d, *J* = 15 Hz, 1 H), 3.10-3.07 (m, 2 H), 2.85-2.82 (m, 2 H), 1.77-1.71 (m, 2 H), 1.46-1.40 (m, 2 H), 1.32-1.26 (m, 2 H); CL/EM: T.R. = 3.218 min [M+H] 621.2 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm).

**EJEMPLO 261**



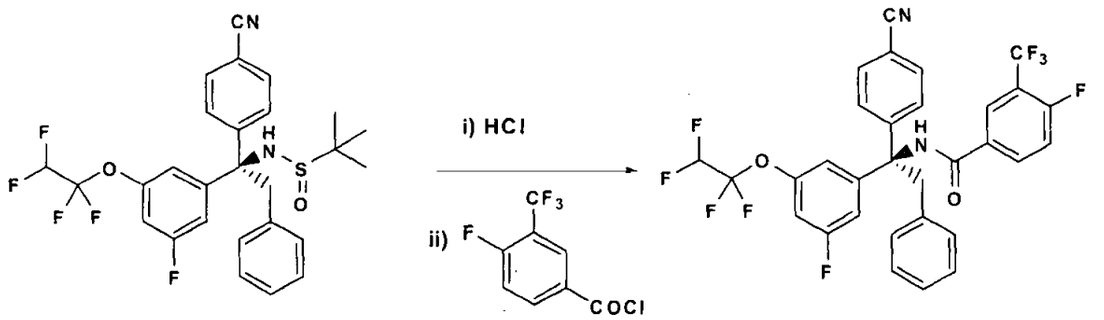
**(R)-N-(1-(4-cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 56**




A una solución de (1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (2.44 g, 4.13 mmoles), preparada como se describe en el Procedimiento 3, 4, 5 y 6, en DMF (20 ml) donde se agregó cianuro de zinc (970 mg, 8.27 mmoles) y polvo de zinc (81 mg, 1.24 mmoles). La mezcla de reacción se desgasificó con Ar y se colocó bajo nitrógeno. La paladiobistributilfosfina (41 mg, 0.20 mmoles) se agregó y la mezcla de reacción se calentó a 60°C durante 16 h. La mezcla de reacción se apagó con bicarbonato de sodio

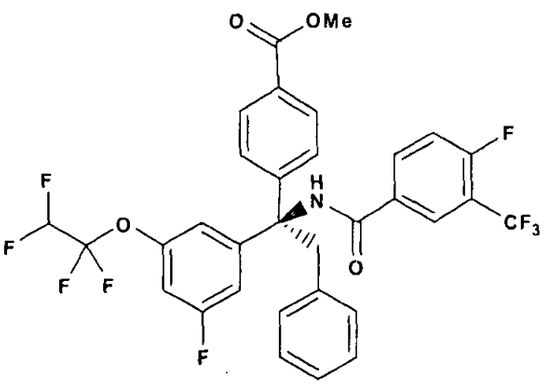
saturado y se extrajo con acetato de etilo. Los extractos orgánicos combinados se secaron sobre $Mg_2SO_4$, se filtraron y se concentraron para proporcionar N-((R)-1-(4-cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como un sólido blanco (2.08 g, 93% rendimiento). CL/EM: T.R. = 2.25 min [M+H] 537 (columna Chromolith Performance 18e 4.6 x 100 mm, 10-90% $CH_3OH/H_2O$ con 0.1% de TFA gradiente durante 2 min, 5 ml/min, observando a 220 nm).




Siguiendo el procedimiento 6 y 7, la (R)-N-(1-(4-cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 261) se preparó como un polvo blanco (380 mg, 89% rendimiento). CL/EM: T.R. = 2.33 min [M+H] 623 (columna Chromolith Performance 18e 4.6 x 100 mm, 10-90% $CH_3OH/H_2O$ con 0.1% de TFA gradiente durante 2 min, 5 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 7.91 (1 H, d, J=6.60 Hz), 7.81 - 7.86 (1 H, m), 7.67 (2 H, d, J=8.24 Hz), 7.38 (2 H, d, J=8.25 Hz), 7.24 ($CHCl_3$)

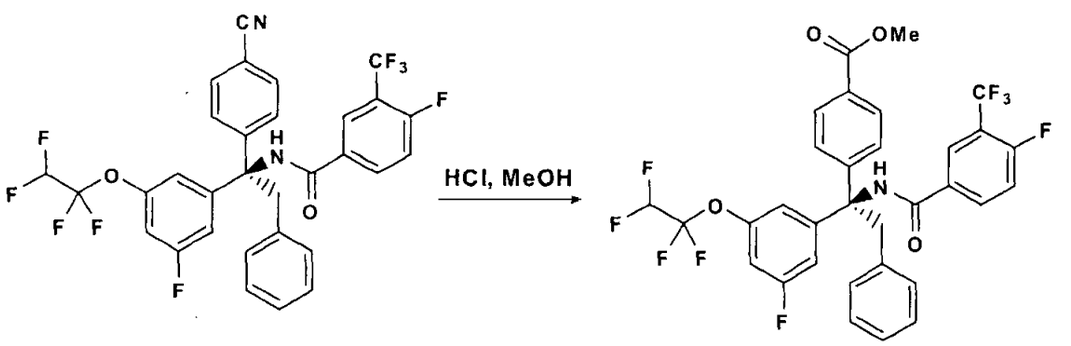
7.24 - 7.31 (2 H, m), 7.18 (2 H, t, J=7.42 Hz), 7.05 (1 H, m), 6.90 (2 H, m), 6.64 - 6.75 (3 H, m), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 3.90 (2 H, s).

**EJEMPLO 262**



**4-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)benzoato de (R)-metilo**

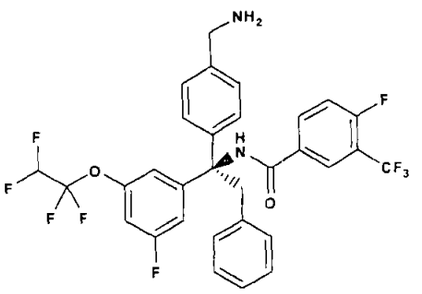
**Procedimiento 57**




La (R)-N-(1-(4-Cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 261, 118 mg, 0.19 mmoles) se disolvió en metanol (10 ml). El gas de

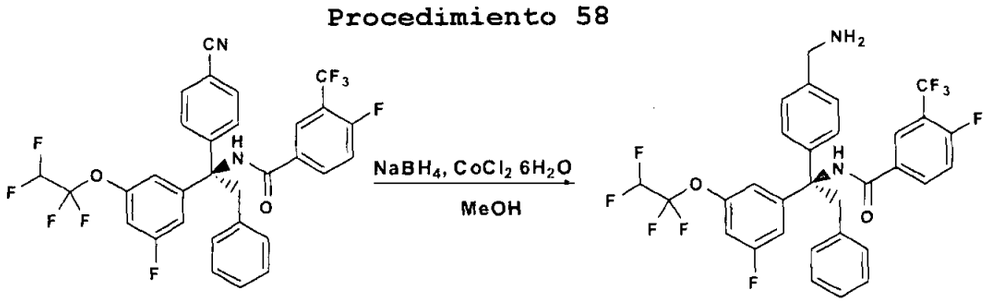
cloruro de hidrógeno se burbujeó en la solución durante 5 min y la mezcla de reacción se agitó a 55°C durante 22 h. Luego el gas de cloruro de hidrógeno se burbujeó en la mezcla nuevamente durante 4 min. Después de agitar durante 22 h adicionales, la reacción se apagó con $NaHCO_3$ saturado y la mezcla se extrajo con acetato de etilo. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron para producir un sólido blanco. El sólido resultante se purificó por Cromatografía de vaporización instantánea ISCO (12 g gel de sílice; 0-50% acetato de etilo/gradiente de hexanos durante 12 min., 30 ml/min) para proporcionar 4-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)benzoato de (R)-metilo (Ejemplo 262) como un sólido blanco (92 mg, 74% rendimiento). CL/EM: T.R. = 2.37 min [M+H] 656 (columna Chromolith Performance 18e 4.6 x 100 mm, 10-90% $CH_3OH/H_2O$ con 0.1% de TFA gradiente durante 2 min, 5 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 8.02 (2 H, d, J=8.25 Hz), 7.92 (1 H, d, J=6.60 Hz), 7.77 - 7.88 (2 H, m), 7.21 - 7.30 (3 H, m), 7.24 (s, $CHCl_3$), 7.15 (2 H, t, J=7.42 Hz), 6.89 - 7.00 (3 H, m), 6.64 - 6.72 (3 H, m), 5.87 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 4.03 (1 H, d, J=13.19 Hz), 3.93 (3 H, s), 3.86 (1 H, d, J=13.19 Hz).

**EJEMPLO 263**



**(R)-N-(1-(4-(aminometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 58**

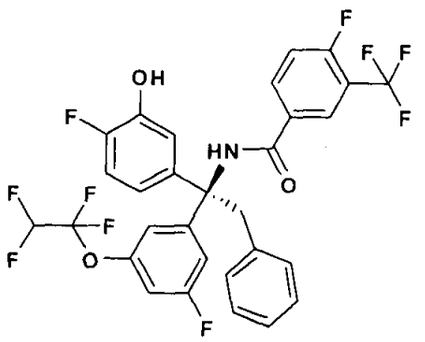



A una solución de (R)-N-(1-(4-Cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 261, 59 mg, 0.095 mmoles) en metanol (2 ml) se agregó hexahidrato de cloruro de cobalto (45 mg, 0.19 mmoles), seguido por borohidruro de sodio (36 mg, 0.95 mmoles). La mezcla de reacción se agitó durante 13 h, luego se apagó con HCl (1.0 M, 2 ml) y se agitó durante 1h adicional. La mezcla de reacción se diluyó con hidróxido de amonio saturado luego se extrajo con acetato de etilo. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron para producir un sólido blanco.

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El sólido resultante se purificó por CLAR preparativa (columna YMC ODS-A s-5 20 x 100 mm; 50-90% MeOH/$H_2O$ con 0.1% de TFA gradiente durante 10 min., 20 ml/min, observando a 220 nm) para proporcionar (R)-N-(1-(4-(aminometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-(trifluorometil)benzamida (Ejemplo 263) como un sólido blanco (39 mg, 56% rendimiento). CL/EM: T.R. = 1.65 min [M+H] 627 (columna Chromolith Performance 18e 4.6 x 100 mm, 10-90% $CH_3OH/H_2O$ con 0.1% de TFA gradiente durante 2 min, 5 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 8.06 (2 H, br s), 7.81 (1 H, d, J=6.05 Hz), 7.67 - 7.77 (1 H, m), 7.34 (2 H, d, J=7.70 Hz), 7.18 - 7.27 (3 H, m), 7.24 ($CHCl_3$, s), 7.13 (2 H, t, J=7.42 Hz), 6.90 (1 H, d, J=8.25 Hz), 6.72 - 6.81 (3 H, m), 6.66 (2 H, d, J=7.15 Hz), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 4.01 (2 H, br s), 3.77 - (2 H, dd, *J*=29.1 Hz, *J*=13.2 Hz).

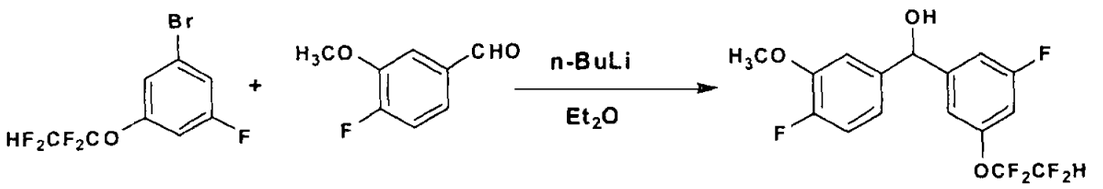
**EJEMPLO 264**




**(R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

1325

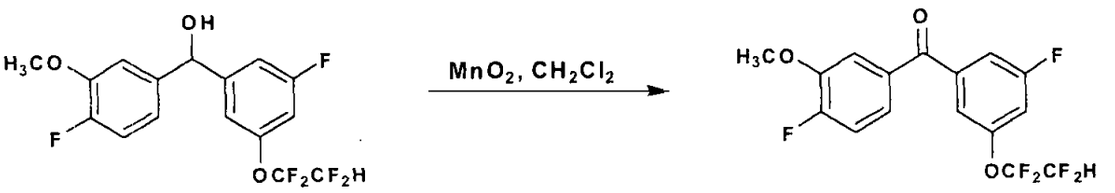
**Procedimiento 59a**




A una solución de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno, preparada como se describe en el Procedimiento 3, (1.00 g, 3.44 mmoles) en éter dietílico en (10 ml) a -72°C se agregó 2.5 M n-BuLi (1.37 ml, 3.44 mmoles) gota a gota. Durante el termino de la adición, la mezcla de reacción se agitó durante 15 minutos a -72°C, luego 4-fluoro-3-metoxibenzaldehído (0.53 g, 3.44 mmoles) se agregó mientras la temperatura de la mezcla de reacción se mantuvo debajo de -52°C. La mezcla de reacción se agitó durante 3 h a -72°C. La mezcla de reacción se apagó por la adición de HCl 1N y la porción acuosa se extrajo con EtOAc (2 x). Las capas orgánicas combinadas se lavaron con NaCl saturado, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El residuo se purificó por ISCO al usar un gradiente de 0-50% EtOAc/hexano como eluyente para producir (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanol (0.83 g, 66% rendimiento). CLAR: T.R. = 3.85 min (columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene ácido fosfórico al 0.1% durante 4 minutos gradiente, relación de flujo 4 ml/min, observando a 220 nm); $^1H$ RMN ($CDCl_3$): 7.05 -

6.8 (m, 6 H), 5.87 (tt, J=2.8, 52.9Hz), 5.75 (s, 1 H), 3.85 (s, 3 H).

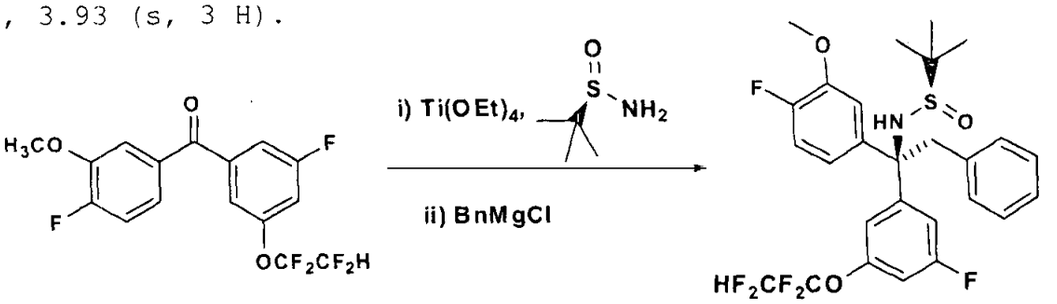
**Procedimiento 59b**




A una solución de (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanol (0.58 g, 1.57 mmoles) en $CH_2Cl_2$ (5 ml) se agregó dióxido de manganeso activado (0.80 g, 7.86 mmoles). La mezcla de reacción se agitó durante la noche a temperatura ambiente. El dióxido de manganeso adicional (0.80 g, 7.86 mmoles) se agregó y la reacción se agitó a temperatura ambiente durante otra noche. La mezcla de reacción se diluyó con $CH_2Cl_2$ y se filtró a través de celite y el sólido se lavó con $CH_2Cl_2$. El producto filtrado se concentró bajo presión reducida para producir (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (0.56 g, 98% rendimiento). CLAR: T.R. = 4.048 minutos (columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene ácido fosfórico al 0.1% durante 4 minutos gradiente, relación de flujo 4 ml/min, observando a 220 nm); CLEM: [M+H] 365.2 (columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene 0.1% de TFA durante 2 minutos gradiente, relación de flujo 5 ml/min, observando a 220 nm); $^1H$ RMN (400

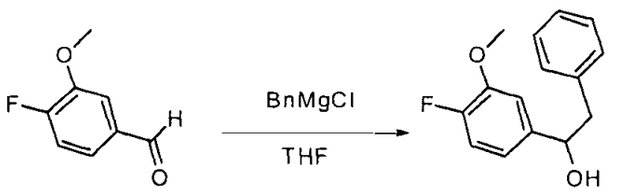
1326

MHz, $CDCl_3$): 7.5-7.1 (m, 6 H), 5.92 (tt, J=2.2, 53.6Hz, 1 H), 3.93 (s, 3 H).




La (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-metilpropano-2-sulfinamida puede también prepararse por los métodos descritos en los procedimientos 59c, 59d, 59e y 59f.

**Procedimiento 59c**

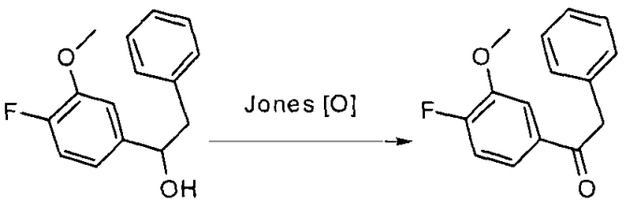



A una solución de 4-fluoro-3-metoxibenzaldehído (25 g, 162 mmoles) en THF (150 ml) se agregó una solución de cloruro de bencil magnesio (solución 2M en THF, 122 ml, 243 mmoles) en THF (50 ml). La mezcla de reacción se calentó a 50°C durante 2 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y se apagó por la adición de $NH_4Cl$ saturado. La mezcla de reacción se extrajo con EtOAc (3 x) y las capas orgánicas combinadas se lavaron con NaCl saturado, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó por Cromatografía de vaporización instantánea ($SiO_2$, eluyendo con 0-40%

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EtOAc/hexano) para producir 1-(4-fluoro-3-metoxifenil)-2-feniletanol como un aceite amarillo (24 g, 60% rendimiento). $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 7.27-7.32 (m, 2 H), 7.21-7.27 (m, 1 H), 7.16 (d, J=7 Hz, 2 H), 7.01 (dd, J=11, 8 Hz, 1 H), 6.92 (dd, J=8, 2 Hz, 1 H), 6.82 (ddd, J=8, 4, 1 Hz, 1 H), 4.80-4.88 (m, 1 H), 4.66 (d, J=6 Hz, 1 H), 3.84 (s, 3 H), 2.91-3.04 (m, 2 H).

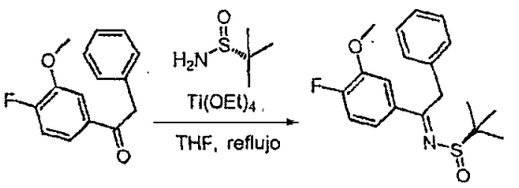
**Procedimiento 59d**




A una solución de 1-(4-fluoro-3-metoxifenil)-2-feniletanol (23.7g, 40.6 mmoles) en acetona (240 ml) se agregó Reactivo Jones (64 ml) a temperatura ambiente. La mezcla de reacción se agitó durante la noche, se apagó por la adición de isopropanol y se diluyó con EtOAc. La porción orgánica se lavó con HCl 1N (2 x), se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida para producir el 1-(4-fluoro-3-metoxifenil)-2-feniletanona (15 g, 66% rendimiento). CLEM: T.R. = 3.250 min [M+H] 245.1 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm); $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 7.62 (dd, J=8, 1 Hz, 1 H), 7.60-7.55 (m, 1 H), 7.35-7.29 (m, 2 H),

7.26-7.23 (m, 3 H), 7.10 (dd, J=10, 8 Hz, 1 H), 4.24 (s, 2 H), 3.89 (s, 3 H).

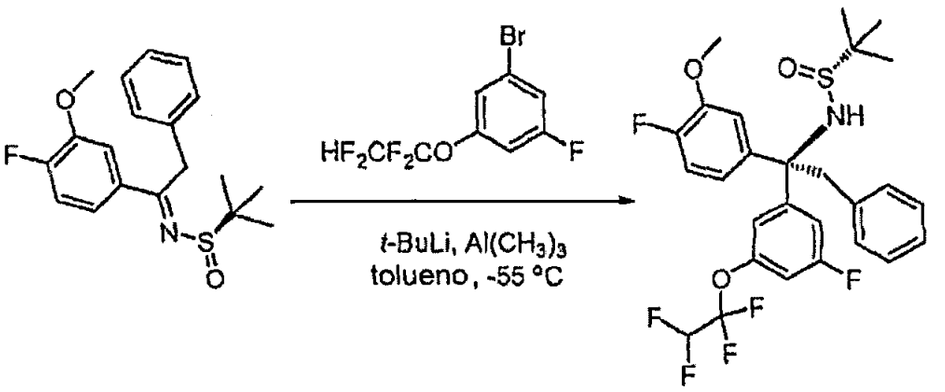
**Procedimiento 59e**




A una solución de 1-(4-fluoro-3-metoxifenil)-2-feniletanona (13 g, 53 mmoles) se disolvió en THF (266 ml) se agregó (R)-2-metilpropano-2-sulfinamida (7.8 g, 64 mmoles) a temperatura ambiente, seguido por $Ti(OEt)_4$ (17 ml, 80 mmoles). La mezcla de reacción se calentó a reflujo durante 48 h, luego se permitió enfriar hasta temperatura ambiente. La mezcla de reacción se concentró bajo presión reducida y el residuo se diluyó con $Et_2O$. El $H_2O$ se agregó y el sólido se filtró y se lavó con $Et_2O$. El producto filtrado se lavó con $H_2O$, se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por Cromatografía de vaporización instantánea ($SiO_2$, eluyendo con 0-100% EtOAc/hexano) para producir (R,E)-N-(1-(4-fluoro-3-metoxifenil)-2-feniletiliden)-2-metilpropano-2-sulfinamida (12 g, 67% rendimiento). CLEM: T.R. = 3.655 min [M+H] 348.2 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm); $^1H$ RMN (500 MHz, $CDCl_3$) $\delta$ ppm 7.60-7.53 (m, 1 H), 7.43-7.36 (m, 1 H), 7.29-7.15 (m, 5 H), 7.03 (dd,

J=11, 8 Hz, 1 H), 4.75 (d, J=15Hz, 1 H), 4.54 (d, J=15Hz, 1 H), 3.84 (s, 3 H), 1.34 (s, 9 H).

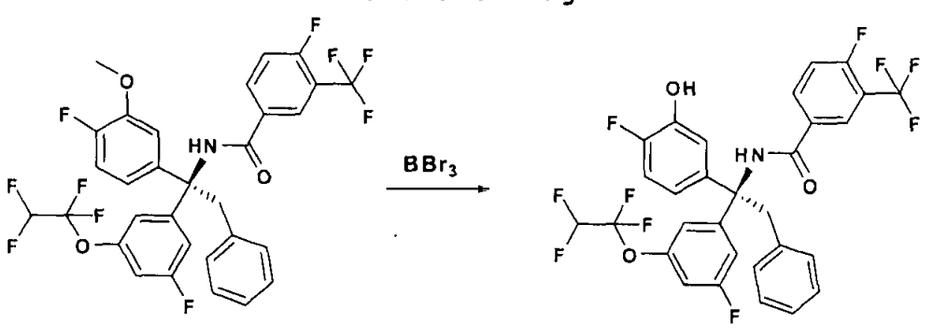
**Procedimiento 59f**




A una solución de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (357 mg, 1.23 mmoles) en tolueno (1.5 ml) a -60°C se agregó n-BuLi (2.5 M en hexano, 352 ml, 0.88 mmoles). La mezcla de reacción se agitó durante 1.5 h a -20°C hasta -55°C. En un vial separado, a una solución a -78°C de (R,E)-N-(1-(4-fluoro-3-metoxifenil)-2-feniletilidene)-2-metilpropano-2-sulfinamida (122 mg, 0.35 mmoles) en tolueno (1 ml) se agregó $Al(CH_3)_3$ (210 ml, 0.42 mmoles). La solución resultante se agitó durante 10-15 min, luego se agregó a la mezcla de (3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)litio. La mezcla de reacción combinada se agitó a -55°C durante la noche y luego se diluyó con EtOAc. La porción orgánica se lavó con $H_2O$ y la porción acuosa se extrajo con EtOAc (3 x). Las porciones orgánicas combinadas se concentraron bajo presión reducida y el residuo se purificó por CLAR preparativa (Phenomenex Luna AXIA 100A,

C18, 5 μ; 10%-90% ACN/$H_2O$ que contiene 0.1% de TFA, observando a 220 nm) para producir (R)-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (83 mg, 42% rendimiento). CLEM: T.R. = 3.49 min [M+H] 560.1 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm); $^1H$ RMN (500 MHz, $CDCl_3$) δ 7.21-7.12 (m, 3 H), 7.08 (dd, J=11, 8 Hz, 1 H), 7.00-6.94 (m, 1 H), 6.91-6.81 (m, 4 H), 6.72-6.62 (m, 2H), 5.99-5.70 (m, 1 H), 4.36 (s, 1 H), 3.96 (d, J=13 Hz, 1 H), 3.77 (s, 3 H), 3.55 (d, J=13 Hz, 1 H), 1.21 (s, 9 H).

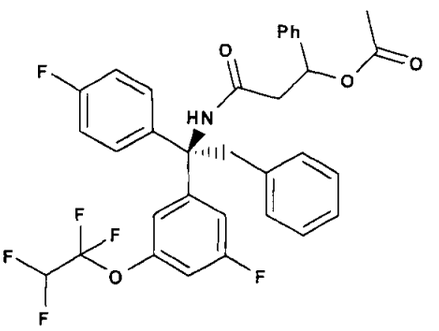
**Procedimiento 59g**




A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida, preparada como se describe en el Procedimiento3, 59a-f, 6 y 7, (2.8 g, 4.43 mmoles) en $CH_2Cl_2$ (15 ml) se agregó $BBr_3$ (12 ml, 12 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 2 h y se apagó por la adición de hielo. La mezcla de reacción

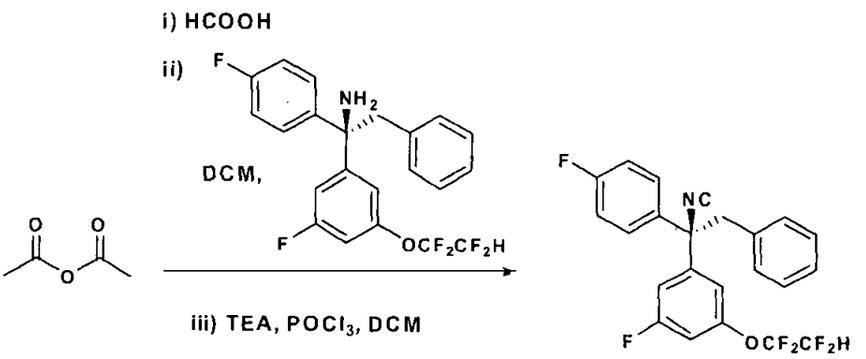
se diluyó con EtOAc y se lavó con $NaHCO_3$ saturado, NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró para resultar (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264) como un aceite claro (2.9 g, 100 % rendimiento). CLEM: T.R. = 4.176 min [M+H] 632.2 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

**EJEMPLO 265**



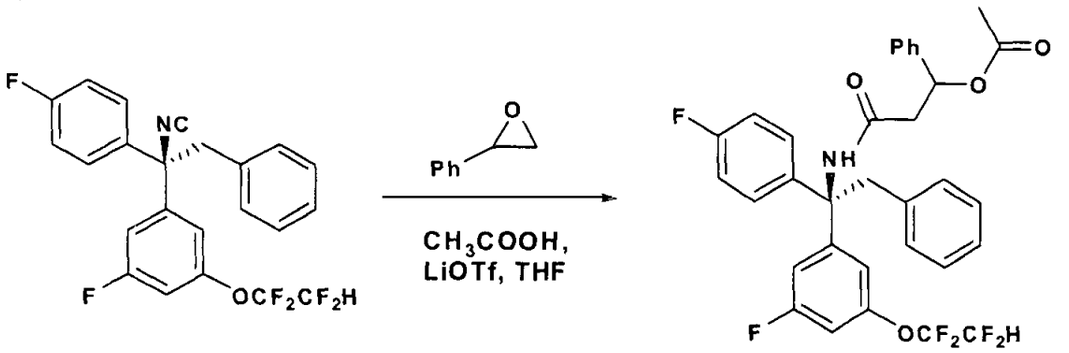
**Acetato de 3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-3-oxo-1-fenilpropilo**

**Procedimiento 60**



Una solución de anhídrido acético (10 ml, 106 mmoles) y ácido fórmico (6 ml, 159 mmoles) se calentó a 60°C durante 3 h, luego se enfrió hasta temperatura ambiente. Un alícuota de la solución resultante (0.623 ml) se agregó a una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina preparada como se describe en el Procedimiento 3, 4, 5 y 6 (83 mg, 0.2 mmoles) en DCE (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, luego se concentró bajo presión reducida para producir un aceite claro. El aceite resultante se disolvió en DCM y se purificó cromatografía ISCO (12 g) con 0-30% EtOAc en hexano para producir (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)formamida como un sólido blanco (72 mg, 81 % rendimiento). CLEM: T.R. = 2.02 min [M-NHCOH] 409.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). A 0°C una solución de (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)formamida (72 mg, 0.16 mmoles) en DCM (2 ml) se agregó trietilamina (0.06 ml, 0.43 mmoles) y $POCl_3$ (0.016 ml, 0.18 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con EtOAc (15 ml). La capa orgánica se lavó con $NaHCO_3$ saturado y

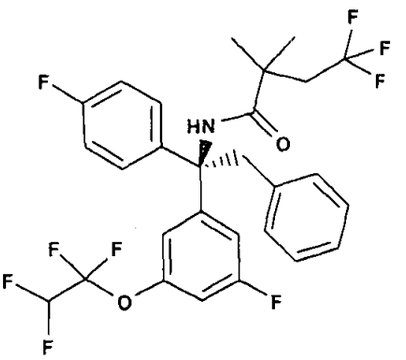
NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía ISCO (12 g) con 0-30% EtOAc en hexano para producir (R)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(1,1,2,2-tetrafluoroetoxi)benceno como un sólido blanco (60 mg, 87 % rendimiento). CLEM: T.R. = 2.10 min [M-NC] 409.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 3.56 - 3.65 (m, 2 H), 5.74 - 6.01 (m, 1 H), 6.84 (d, J=7.03 Hz, 2 H), 6.94 (d, J=7.03 Hz, 3 H), 7.04 - 7.10 (m, 2 H), 7.16 - 7.26 (m, 3 H), 7.32 (dd, J=9.01, 5.05 Hz, 2 H).




A una solución de 2-feniloxirano (0.009 ml, 0.08 mmoles) en THF (1.5 ml) se agregó LiOTf (12 mg, 0.08 mmoles), (R)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(1,1,2,2-tetrafluoroetoxi)benceno (30 mg, 0.07 mmoles) y ácido acético (0.004 ml, 0.08 mmoles) en sucesión. La mezcla de reacción se calentó a reflujo durante 3 h. La reacción se

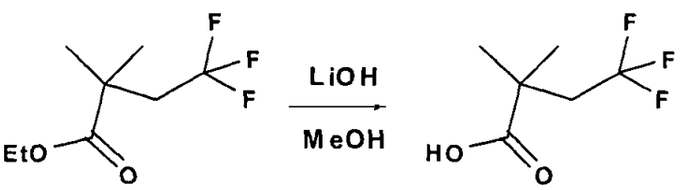
permitió enfriar hasta temperatura ambiente y se diluyó con EtOAc (15 ml). La capa orgánica se lavó con NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. La mezcla cruda resultante se purificó por CLAR preparativa columna YMC ODS S5 30 x 100 mm 30-100% MeOH (90% en agua, 0.1%TFA) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm para producir acetato de 3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-3-oxo-1-fenilpropilo (Ejemplo 265) como un sólido blanco (26 mg, rendimiento 62%, mezcla diaestereomérica 1:1 RR:RS). CLEM: T.R. = 2.19 min [M+H] 616.3 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.27 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); 1H RMN (400 MHz, $CDCl_3$) $\delta$ ppm 1.96 (d, J=4.95 Hz, 3 H), 3.01 (ddd, J=14.30, 6.87, 3.02 Hz, 1 H), 3.14 (td, J=8.94, 5.22 Hz, 1 H), 3.523 (d, J=13.2 Hz, 0.5 H), 3.62 (m, 0.5 H), 3.72 (m, 0.5 H), 3.82 (d, J=13.2 Hz, 0.5 H), 5.30 - 5.34 (m, 1 H), 5.74 - 5.97 (m, 1 H), 6.46 - 6.53 (m, 2 H), 6.60 (d, J=10.45 Hz, 1 H), 6.67 - 6.72 (m, 1 H), 6.80 - 7.31 (m, 13 H).

**EJEMPLO 266**



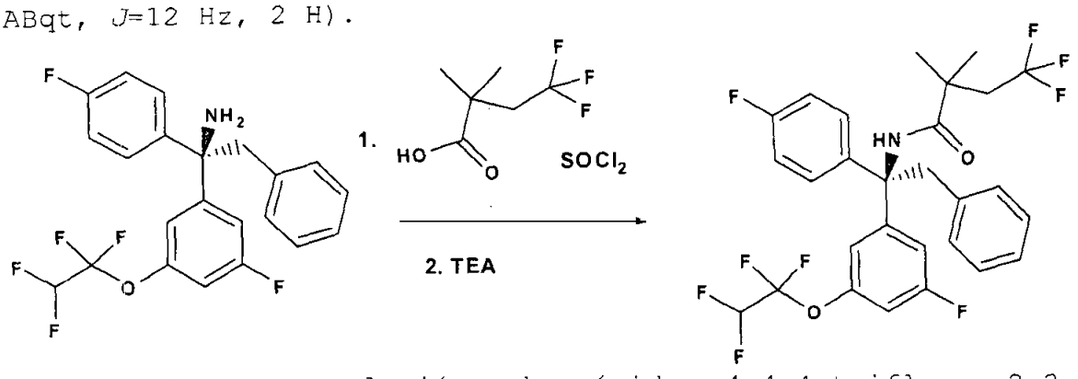
**(R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,2-dimetilbutanamida**

**Procedimiento 61**




A una solución de 4,4,4-trifluoro-2,2-dimetilbutanoato de etilo (426 mg, 2.15 mmoles) en MeOH (15 ml) se agregó una solución de LiOH en $H_2O$ (2 N, 5.35 ml, 10.75 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró y la mezcla resultante se diluyó con DCM y se lavó con 3 N HCl. La capa acuosa se extrajo dos veces con DCM. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para producir el ácido 4,4,4-trifluoro-2,2-dimetilbutanoico como un aceite incoloro (370 mg, 100% rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) ppm 1.35 (s, 6 H), 2.48

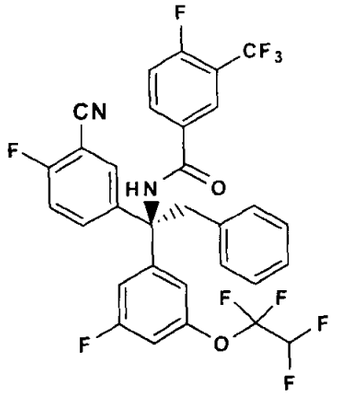
(ABqt, J=12 Hz, 2 H).




A una solución de ácido 4,4,4-trifluoro-2,2-dimetilbutanoico (30 mg, 0.176 mmoles) en DCE (1 ml) se agregó $SOCl_2$ (21 mg, 0.176 mmoles) y la mezcla resultante se puso a reflujo durante 2 h. Después del enfriamiento hasta temperatura ambiente, TEA se agregó (82 ul, 0.59 mmoles), seguido por la adición de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina, preparada como se describe en el Procedimiento 3, 4, 5 y 6, (25 mg, 0.059 mmoles). La mezcla de reacción se calentó a reflujo durante la noche, se concentró y el residuo se purificó por CLAR preparativa (columna Axia, 30 x 100 mm, 40 ml/min, 40-100% ACN/$H_2O$/0.1% de TFA durante 12 min) para dar (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,2-dimetilbutanamida (Ejemplo 266) como un aceite café (8 mg, 24% rendimiento). CLEM: T.R. = 2.13 min [M+H] 578.3 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) ppm 1.28 (s, 6

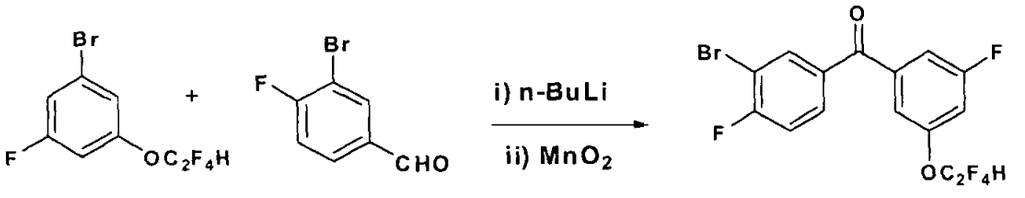
H), 2.21 - 2.51 (m, 2 H), 3.77 (ABqt, *J*=13 Hz, 2 H), 5.83 (t, *J*=53 Hz, 1 H), 6.37 (s, 1 H), 6.65 - 6.74 (m, 2 H), 6.75 - 6.95 (m, 3 H), 6.94 - 7.09 (m, 4 H), 7.09 - 7.31 (m, 3 H).

**EJEMPLO 267**



**N-(1-(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 62**

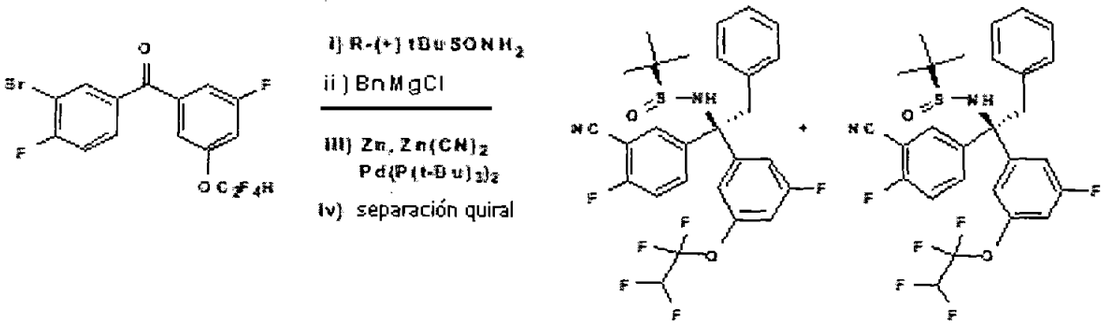


A una solución de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (5.0 g, 17 mmoles) en éter (40 ml) a -78°C se agregó una solución de n-butillitio (6.9 ml, 2.5 M,17 mmoles). La mezcla de reacción se agitó durante 15 minutos y se agregó una solución de 3-bromo-4-fluorobenzaldehído (3.5 g, 17 mmoles) en éter (10 ml). La reacción se agitó a -78°C durante 2 h, luego se apagó con $NH_4Cl$ saturado y se calentó hasta temperatura ambiente. La

capa de éter se separó y se secó sobre sulfato de magnesio, se filtró y se concentró para producir (3-bromo-4-fluorofenil)(4-fluoro-2-(1,1,2,2-tetrafluoroetoxi)fenil)metanol como un aceite color ámbar (6.5 g, 92% rendimiento). El producto se usó en la siguiente etapa sin purificación adicional. A una solución de (3-bromo-4-fluorofenil)(4-fluoro-2-(1,1,2,2-tetrafluoroetoxi)fenil)metanol (29.5 g, 71.3 mmoles) en diclorometano (600 ml) se agregó $MnO_2$ (30 g, 345 mmoles). La mezcla de reacción se agitó durante 6 h, luego otros 30 g de $MnO_2$ se agregó y la reacción se continuó agitando durante la noche. La adición $MnO_2$ se repitió dos veces y la reacción se agitó durante un total de 48 h cuando la reacción se completó. La suspensión se filtró a través de una almohadilla de celite, el producto filtrado se concentró y el residuo se purificó por Cromatografía de vaporización instantánea ISCO para producir (3-bromo-4-fluorofenil)(4-fluoro-2-(1,1,2,2-tetrafluoroetoxi)fenil)metanona como un aceite amarillo (60% rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) $\delta$ ppm 8.06 (1 H, d, $J$=6.59 Hz), 7.76 (1 H, ddd, $J$=6.48, 4.50, 2.20 Hz), 7.38 - 7.44 (2 H, m), 7.21 - 7.29 (2 H, m), 6.09 - 5.83 (1 H, t).

Alternativamente, las siguientes condiciones pueden usarse para oxidar 3-bromo-4-fluorofenil)(4-fluoro-2-(1,1,2,2-tetrafluoroetoxi)fenil)metanol hasta (3-bromo-4-fluorofenil)(4-fluoro-2-(1,1,2,2-

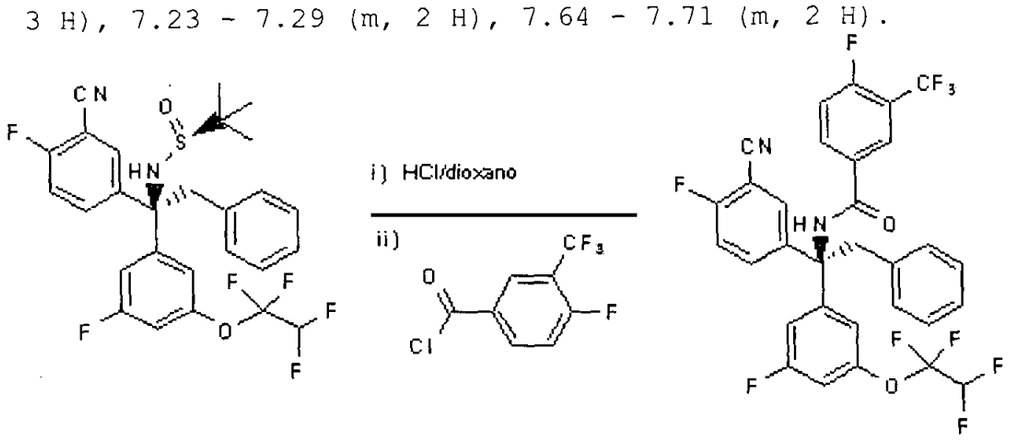
tetrafluoroetoxi)fenil)metanona: A una solución de (3-bromo-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanol (3.6 g, 8.67 mmoles) en $CH_2Cl_2$ (53.0 ml) se agregó dicromato de piridinio (4.89 g, 13.01 mmoles), y tamiz molecular activado (8.67g, ~1g/mmoles). La mezcla espesa resultante se agitó a temperatura ambiente durante 2 h. El celite (5g) se agregó a la mezcla de reacción y la solución espesa se agitó durante 15 minutos luego se filtró. El producto filtrado se concentró in vacuo. El residuo se disolvió en 20% de EtOAc en Heptanos se filtró a través de 50 ml de Columna de filtración SPE isoluta (parte # 120-1028F) sobre $Na_2SO_4$ para dar una solución amarilla pálida clara. Los solventes se retiraron in vacuo para dar un líquido amarillo el cual se purificó por Cromatografía de gel de sílice ISCO (80g, 60 ml/min observación a 254 nm de elución con heptano:EtOAc).




La N-(1-(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida fue preparada como se describe en el Procedimiento 5 y 6. La mezcla de diaestereómeros de N-(1-

(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida se separó por CLAR quiral preparativa (columna Chiralpak AD 20µ, 5 × 50 cm, eluyendo con 60% IPA/Heptano con relación de flujo 50 ml/min). La (R)-N-((S)-1-(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (0.224 g, 18% rendimiento) se eluyó a un tiempo de retención de 19 min. CLEM: T.R. = 2.23 min, Pureza 71% [M+H] 555.3 (columna 2 min Chromolith Performance RP 4.6 x 100 mm, eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA con relación de flujo 5 ml/min, observando a 220 nm); CLAR quiral analítica: T.R. = 4.01 min (columna Chiralpak AD 10µ 4.6 x 250 mm, elución isocrática con 50% IPA/Heptano con relación de flujo 1mL/min, observando a 254 nm); $^1$H RMN (400 MHz, $CDCl_3$) ppm 1.23 (s, 9 H), 3.55 (d, *J*=12.3 Hz, 1 H), 3.97 (d, *J*=12.3 Hz, 1 H), 5.89 (t, J=53.17Hz, 1H) 6.85 (d, *J*=6.6 Hz, 2 H), 6.94 (s, 1 H), 7.00 (d, *J*=8.3 Hz, 1 H), 7.12 - 7.22 (m, 4 H), 7.24 - 7.29 (m, 2 H), 7.37 (d, *J*=4.8 Hz, 1 H). La (R)-N-((R)-1-(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (0.266 g, 22% rendimiento) se eluyó a un tiempo de retención de 41 min. CLEM: T.R. = 2.23 min, Pureza 84% [M+H] 555.3 (columna 2 min Chromolith Performance RP 4.6 x 100 mm, eluyendo con 10-90%

MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA con relación de flujo 5 ml/min, observando a 220 nm); CLAR quiral analítica: T.R. = 10.09 min (columna Chiralpak AD 10µ 4.6 x 250 mm, elución isocrática con 50% de IPA/Heptano con relación de flujo 1mL/min, observando a 254 nm); $^1$H RMN (400 MHz, $CDCl_3$. ppm 1.18 - 1.25 (m, 9 H), 3.59 (d, *J*=12.3 Hz, 1 H), 3.99 (d, *J*=12.3 Hz, 1 H), 4.30 (s, 1 H), 5.87 (t, 1H) 6.64 - 6.71 (m, 2 H), 6.90 (d, *J*=7.0 Hz, 3 H), 7.15 - 7.22 (m, 3 H), 7.23 - 7.29 (m, 2 H), 7.64 - 7.71 (m, 2 H).

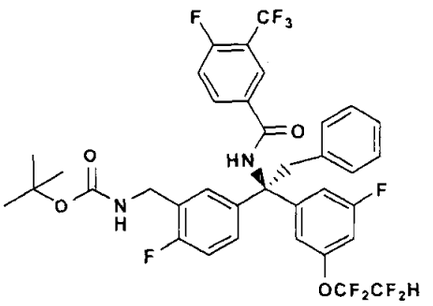



La (R)-N-(1-(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 267) fue preparada como se describe en el Procedimiento 6 y 7. CLEM: T.R. = 2.342 min [M+H] 641.3 (columna 2 min Chromolith Performance RP 4.6 x 100 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA con relación de flujo 5 ml/min. observando a 220 nm); CLAR: T.R. = 4.358 min, Pureza 95% (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA con relación

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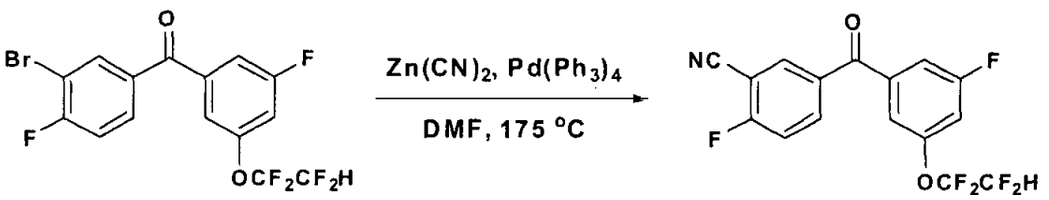
de flujo 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 3.76 - 3.81 (m, 2 H), 5.89 (t, *J*=53.1Hz, 1 H), 6.68 - 6.73 (m, 3 H), 6.81 - 6.85 (m, 2 H), 6.99 (d, *J*=8.3 Hz, 1 H), 7.19 - 7.30 (m, 6 H), 7.54 - 7.58 (m, 2 H), 7.82 - 7.86 (m, 1 H), 7.92 (d, *J*=6.6 Hz, 1 H).

**EJEMPLO 268**



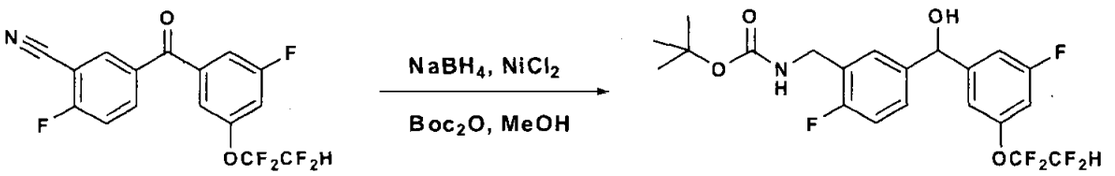

**2-fluoro-5-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)bencilcarbamato de (R)-ter-butilo**

**Procedimiento 63**




Una mezcla de (3-bromo-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona, preparada como se describe en el Procedimiento 3 y 62, (2.0 g, 4.84 mmoles), cianuro de zinc (568 mg, 4.84 mmoles) y tetraquis(trifenilfosina)paladio (559 mg, 0.48 mmoles) en DMF se calentó a 175°C bajo radiación por microondas durante 10 minutos. La mezcla de reacción se permitió enfriar hasta

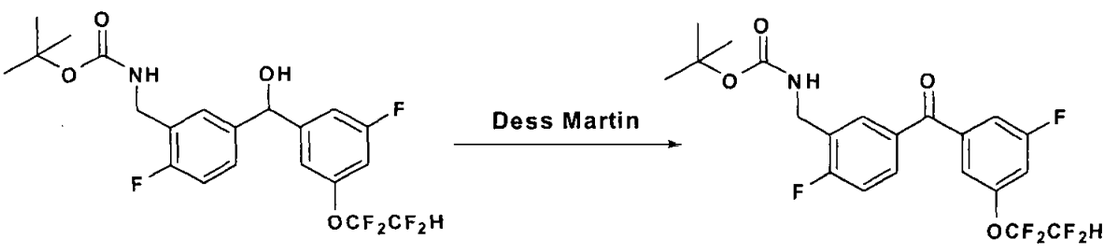
temperatura ambiente, se vació en $H_2O$ y la capa acuosa se extrajo con EtOAc. La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró. El producto crudo se purificó por cromatografía ISCO (columna 12 g, 0-20% EtOAc/hexano) para producir 2-fluoro-5-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benzoil)benzonitrilo como un aceite incoloro (1.5 g, 86% rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 8.11 (m, 2 H), 7.41 (m, 3 H), 7.27 (m, 1 H), 5.97 (m, 1 H).




A una solución de 2-fluoro-5-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benzoil)benzonitrilo (1.30 g, 3.62 mmoles), $BOC_2O$ (1.68 ml, 7.24 mmoles) y cloruro de níquel (II) (0.47 g, 3.62 mmoles) en MeOH a 0°C se agregó borohidruro de sodio (0.96 g, 25.3 mmoles). La mezcla de reacción se agitó a 0°C durante 30 minutos y luego a temperatura ambiente durante 6 h. La mezcla de reacción se filtró a través de celite y el producto filtrado se concentró. El residuo se diluyó con EtOAc y la solución se lavó con $NaHCO_3$ saturado. La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró para producir 2-fluoro-5-((3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(hidroxi)metil)bencilcarbamato de terbutilo como un aceite incoloro, transparente (1.43 g, 85% rendimiento). Este producto se usó en la siguiente etapa sin

1349

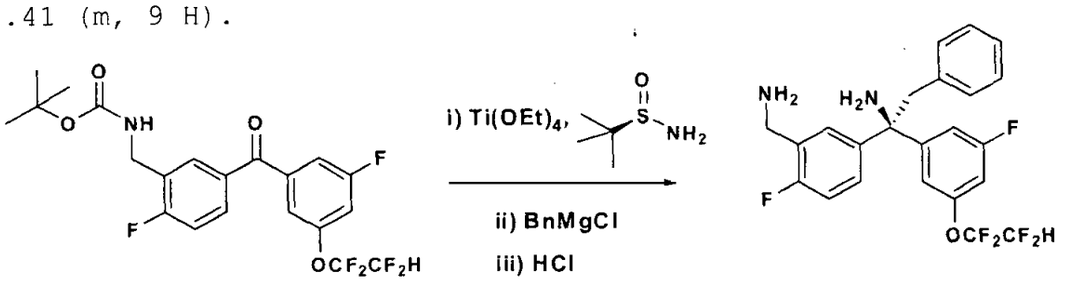
purificación adicional. $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.32 (m, 1 H), 7.22 (m, 1 H), 7.03 (m, 3 H), 6.87 (d, *J*=8.84 Hz, 1 H), 5.90 (m, 2 H), 4.98 (br. s., 1 H), 4.31 (d, *J*=5.05 Hz, 2 H).



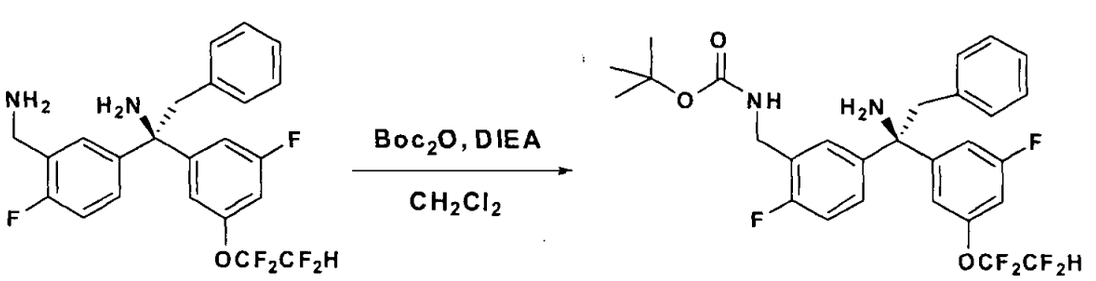

A una solución de 2-fluoro-5-(hidroxi(3-(1,1,2,2-tetrafluoroetoxi)-5-(trifluorometil)fenil)metil)bencilcarbamato de ter-butilo (1.43 g, 2.77 mmoles) en $CH_2Cl_2$ (25 ml) se agregó 1,1,1-tris(acetiloxi)-1,1-dihidro-1,2-benziodoxol-3-(1H)-ona (1.77 g, 4.16 mmoles) a temperatura ambiente. El agua (0.2 ml) en $CH_2Cl_2$ (1 ml) luego se agregó a la mezcla de reacción y la solución resultante se agitó a temperatura ambiente durante 3 h, luego el sólido se filtró y el producto filtrado se concentró. El residuo se purificó por cromatografía ISCO (12 g columna, 0-30% EtOAc/hexano) para producir 2-fluoro-5-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benzoilo) de ter-butilo como un aceite incoloro, transparente (915 mg, 64% rendimiento). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.85 (d, *J*=7.07 Hz, 1 H), 7.73 (m, 1 H),

1345

7.40 (m, 2 H), 7.18 (m, 2 H), 7.00 (m, 1 H), 5.96 (m, 1 H), 1.41 (m, 9 H).



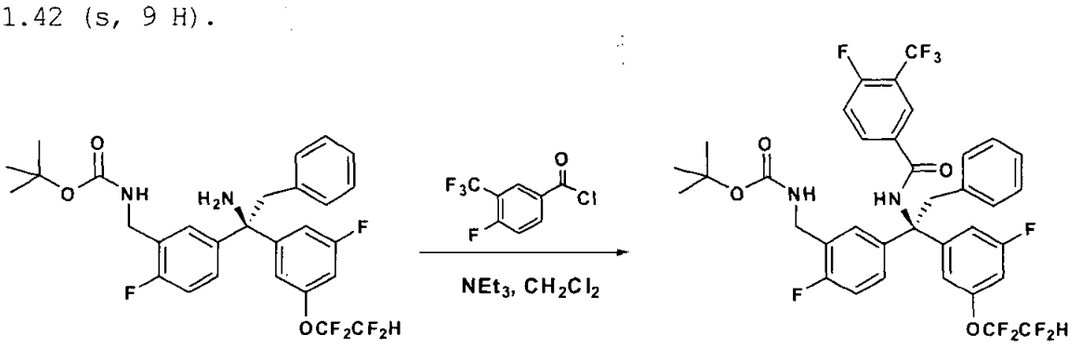

Siguiendo el procedimiento 5 y 6, el 5-((1R)-1-(1,1-dimetiletilsulfinamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-fluorobencilcarbamato de ter-butilo se preparó y se aisló por cromatografía ISCO (columna 40 g, eluyendo con 0-40% EtOAc/hexano). Siguiendo el procedimiento 6, la (R)-1-(3-(aminometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)-fenil)-2-feniletanamina se preparó como un aceite incoloro (214 mg, 40% rendimiento). $^1$H RMN (500 MHz, $CDCl_3$) $\delta$ ppm 7.32 (d, $J$=5.50 Hz, 1 H), 7.19 (m, 4 H), 6.98 (br. s., 3 H), 6.84 (d, $J$=7.70 Hz, 1 H), 6.72 (d, $J$=6.60 Hz, 2 H), 5.86 (t, $J$=53.06 Hz, 1 H), 3.85 (br. s., 2 H), 3.50 (m, 2 H).




A una solución de (R)-1-(3-(aminometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-

1346

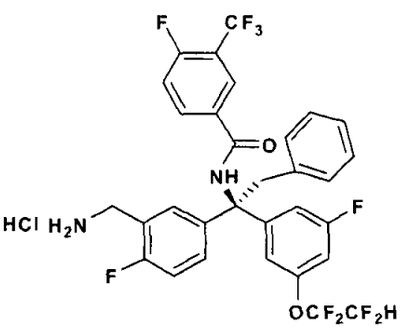
2-feniletanamina (229 mg, 0.50 mmoles) a 0°C en $CH_2Cl_2$ (5 ml) se agregó DIEA (0.11 ml, 0.61 mmoles) y $(Boc)_2O$ (0.12 ml, 0.50 mmoles). La mezcla de reacción se agitó a 0°C durante 1.5 h y luego se vació en $NH_4Cl$ saturado y la capa acuosa se extrajo con EtOAc. La fase orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo resultante se purificó por cromatografía en columna ISCO (12 g, 0-30% EtOAc/hexano) para producir 5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-fluorobencilcarbamato de (R)-ter-butilo como una espuma blanca (202 mg, 72% rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 3.49 (s, 2 H), 7.34 (m, 1 H), 7.17 (m, 4 H), 6.97 (m, 3 H), 6.83 (d, J=8.84 Hz, 1 H), 6.73 (d, J=6.32 Hz, 2 H), 5.86 (m, 1 H), 4.86 (br. s., 1 H), 4.31 (d, J=4.55 Hz, 2 H), 3.49 (s, 2 H), 1.42 (s, 9 H).




El 2-fluoro-5-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)bencilcarbamato de (R)-ter-Butilo (Ejemplo 268) se preparó como un aceite incoloro (220 mg, 91% rendimiento) al usar el método descrito en el procedimiento 7. CLEM: T.R. = 3.47 min [M+H-17] 538 (Phemonenex Luna C18, 50 x 4.6 mm, 4 min gradiente, eluyendo con 105 - 90% MeOH/$H_2O$ que contiene 0.1%TFA, observando a 220 nm); $^1H$ RMN (400

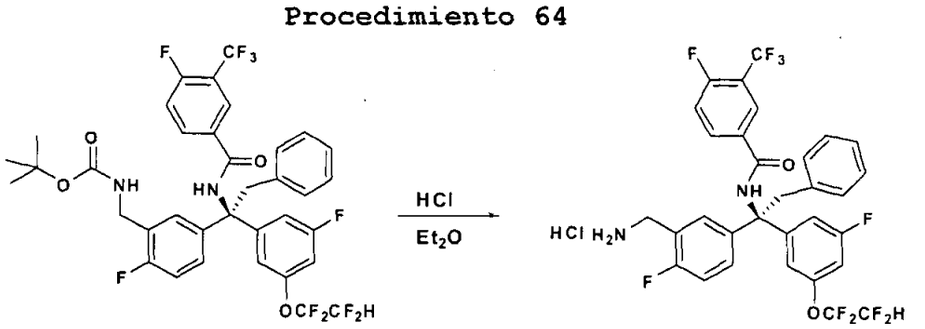
MHz, $CDCl_3$) δ ppm 7.97 (d, J=5.31 Hz, 1 H), 7.84 (br. s., 1 H), 7.24 (m, 2 H), 7.15 (m, 3 H), 6.96 (m, 5 H), 6.71 (m, 3 H), 5.86 (m, 1 H), 4.84 (br. s., 1 H), 4.27 (t, J=6.19 Hz, 2 H), 4.02 (m, 1 H), 3.79 (d, J=13.14 Hz, 1 H), 1.37 (s, 9 H).

**EJEMPLO 269**



**Clorohidrato de (R)-N-(1-(3-(aminometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

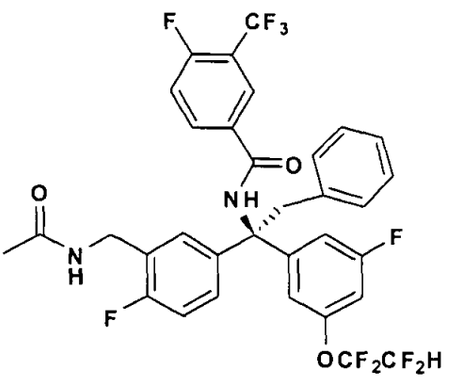
**Procedimiento 64**



A una solución de 5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-fluorobencilcarbamato de (R)-ter-butilo (222 mg, 0.30 mmoles) en DCM (5 ml) a temperatura ambiente se agregó 2 M HCl en éter dietílico (1.49 ml, 1.49 mmoles). La mezcla de reacción se agitó durante 2 h, luego se concentró bajo presión

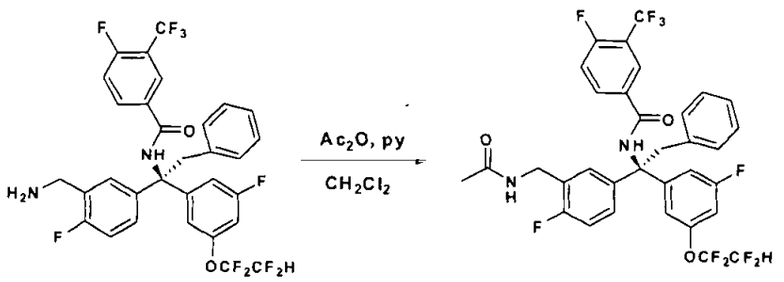
reducida para producir clorohidrato de (R)-N-(1-(3-(aminometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 269) como una espuma blanca (216 mg, 100%). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.95 (m, 1 H), 7.84 (m, 1 H), 7.19 (m, 4 H), 6.91 (m, 3 H), 6.70 (d, *J*=7.07 Hz, 2 H), 5.88 (m, 1 H), 4.24 (t, *J*=5.31 Hz, 1 H), 4.06 (m, 1 H), 3.79 (m, 2 H).

**EJEMPLO 270**



**(R)-N-(1-(3-(acetamidometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

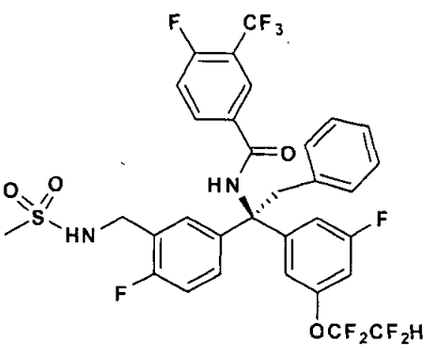
**Procedimiento 65**




A una solución de clorohidrato de (R)-N-(1-(3-(aminometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-

tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 269, 30 mg, 0.04 mmoles) en DCM (2 ml) a temperatura ambiente se agregó piridina (7.8 µl, 0.1 mmoles) seguido por anhídrido acético (4.6 µl, 0.05 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se vació en HCl 1N y la capa acuosa se extrajo con EtOAc. La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo resultante se purificó por cromatografía en columna ISCO (4 g, 0-50% EtOAc/hexano) para producir (R)-N-(1-(3-(acetamidometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 270) como una espuma blanca (21 mg, 100%). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.98 (dd, J=6.57, 2.02 Hz, 1 H), 7.86 (dt, J=8.53, 2.18 Hz, 1 H), 7.25 (m, 2 H), 7.13 (m, 3 H), 6.99 (m, 5 H), 6.81 (s, 1 H), 6.69 (m, 2 H), 5.87 (m, 2 H), 4.38 (m, 2 H), 4.04 (d, J=13.14 Hz, 1 H), 3.75 (d, J=13.14 Hz, 1 H), 1.92 (s, 3 H).

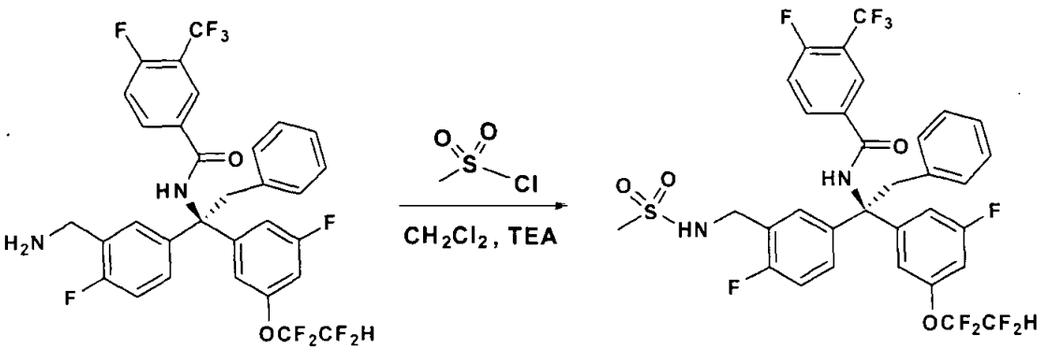
**EJEMPLO 271**




**(R)-4-fluoro-N-(1-(4-fluoro-3-(metilsulfonamidometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

(350

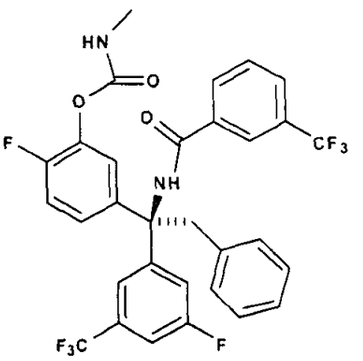
**Procedimiento 66**




A una solución de clorohidrato de (R)-N-(1-(3-(aminometil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 269, 30 mg, 0.04 mmoles) en DCM (2 ml) a temperatura ambiente se agregó TEA (6.8 µl, 0.05 mmoles) seguido por cloruro de metansulfonilo (3.4 µl, 0.04 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y luego se vació en HCl 1N. La capa acuosa se extrajo con $CH_2Cl_2$ y las capas orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna ISCO (4 g, 0-40% EtOAc/hexano) para producir (R)-4-fluoro-N-(1-(4-fluoro-3-(metilsulfonamidometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 271) como una película clara incolora (12 mg, 41%). $^1$H RMN (400 MHz, $CDCl_3$) 7.95 (dd, *J*=6.57, 2.02 Hz, 1 H), 7.86 (m, 1 H), 7.22 (m, 7 H), 7.07 (t, *J*=8.97 Hz, 1 H), 6.93 (m, 3 H), 6.71 (m, 3 H), 5.88 (m, 1 H),

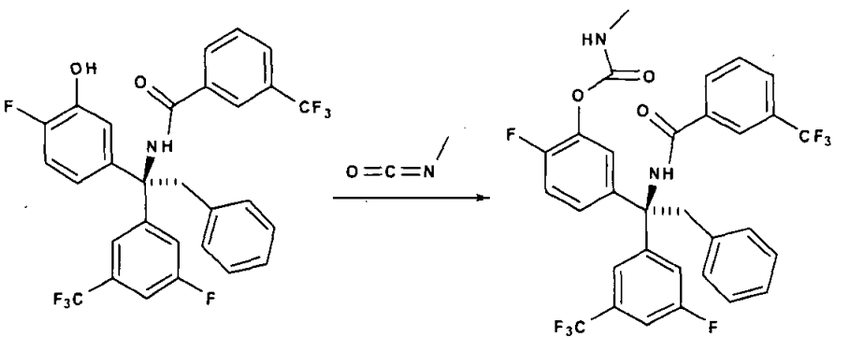
4.55 (t, *J*=6.32 Hz, 1 H), 4.30 (t, *J*=5.81 Hz, 2 H), 3.97 (m, 1 H), 3.83 (m, 1 H), 2.81 (s, 3 H).

**EJEMPLO 272**



**Metilcarbamato de (*R*)-2-fluoro-5-(1-(3-fluoro-5-(trifluorometil)fenil)-2-fenil-1-(3-(trifluorometil)benzamido)etil)fenilo**

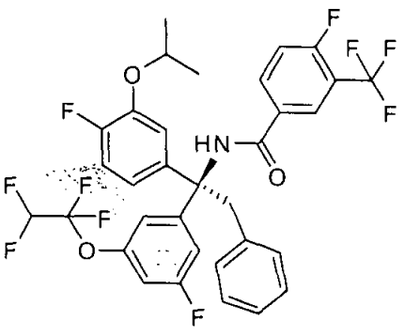
**Procedimiento 67**



Una solución de (R)-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida, se preparó como se describe en el Ejemplo 264, (15 mg, 0.027 mmoles), metilisocianato (0.01 ml), y $Et_3N$ (0.02 ml) en $CH_2Cl_2$ (0.3 ml) se calentó a 80°C bajo radiación por microondas durante 10 min. Después del enfriamiento, la mezcla de reacción se

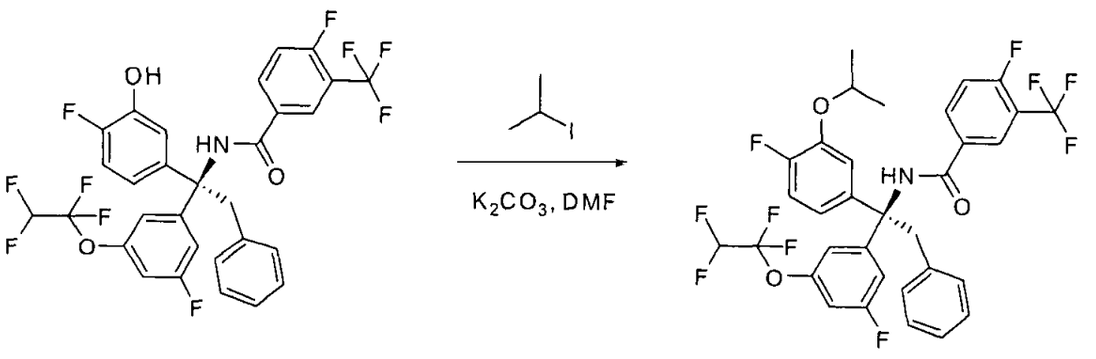
diluyó con EtOAc y la capa orgánica se lavó con $H_2O$, NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se purificó por Cromatografía de vaporización instantánea ISCO (gel de sílice, hexanos/EtOAc) para producir metilcarbamato de (*R*)-2-fluoro-5-(1-(3-fluoro-5-(trifluorometil)fenil)-2-fenil-1-(3-(trifluorometil)-benzamido)-etil)fenilo (Ejemplo 272, 11 mg, rendimiento: 61%). CLEM: T.R. = 2.13 min [M+H] 623.3 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

**EJEMPLO 273**



**(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

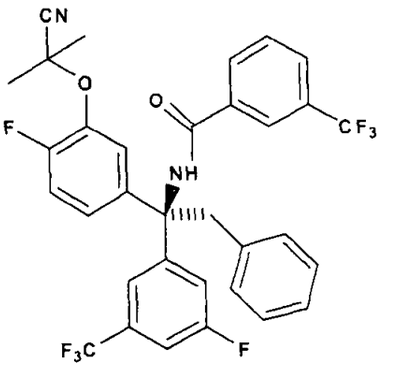
**Procedimiento 68**



A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264, 2.70 g, 4.27 mmoles) en DMF (6 ml) se agregó $K_2CO_3$ (1.47 g, 10.69 mmoles), seguido por yoduro de isopropilo (0.64 ml, 6.40 mmoles). La mezcla de reacción se agitó a 60°C durante 16 h. La mezcla de reacción se filtró y el sólido se lavó con EtOAc. El producto filtrado se lavó con $H_2O$, NaCl saturado, se secó sobre $Na_2SO_4$ y se concentró bajo presión reducida. El residuo se purificó por Columna de gel de sílice ISCO al usar 0 hasta 50% de EtOAc en hexano como solventes de elución para producir (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 273) como un polvo blanco (2.4 g, 83% rendimiento). CLEM: T.R. = 4.05 min [M+H] 674.1 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CD_3OD$) $\delta$ ppm 7.95 - 8.00 (2 H, m), 7.42 - 7.47 (1 H, m), 7.19 (1 H, t, *J*=7.47 Hz), 7.12 (3 H, t, *J*=7.25 Hz), 6.99 - 7.07 (3 H, m), 6.71 - 6.81 (4 H, m), 6.14 - 6.41 (1 H, m), 4.26 - 4.32 (1 H, m, *J*=6.15, 6.15, 6.15, 6.15 Hz), 4.12 (1 H, d, *J*=13.18 Hz), 3.85 (1 H, d, *J*=12.74 Hz), 1.23 (3 H, d, *J*=6.15 Hz), 1.17 (3 H, d, *J*=6.15 Hz).

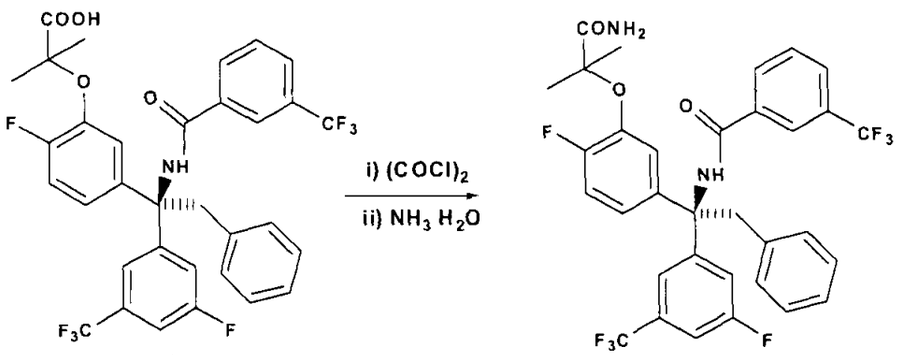
1354

**EJEMPLO 274**



**(*R*)-N-(1-(3-(1-amino-2-metil-1-oxopropan-2-iloxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

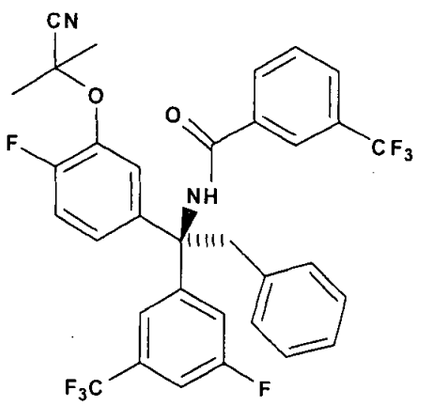
**Procedimiento 69**




A 0°C una solución de ácido (R)-2-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil)fenil)-2-fenil-1-(3-(trifluorometil)benzamido)etil)fenoxi)-2-metilpropanoico, preparada como se describe en el Procedimiento 68 y 23, (60 mg, 0.092 mmoles, rendimiento 91%) en $CH_2Cl_2$ se agregó DMF (1 gota), seguido por la adición de $(COCl)_2$ (0.02 ml). La mezcla de reacción se agitó a 0°C durante 30 min, luego se concentró y se secó in vacuo. El residuo resultante se disolvió en THF

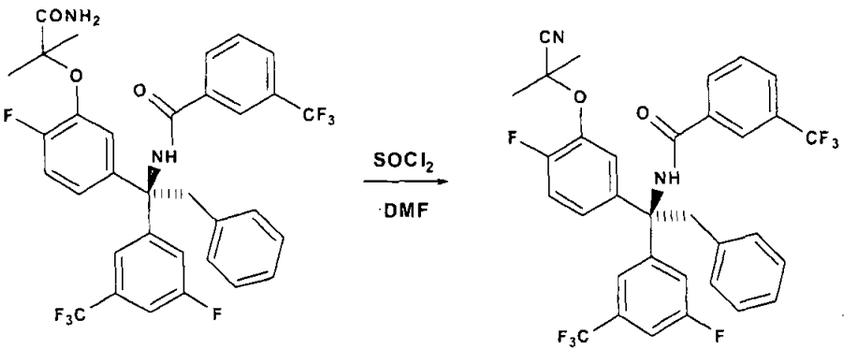
(1 ml) y se enfrió a 0°C seguido por la adición de $NH_4OH$ concentrado (3 ml). La mezcla resultante se agitó a temperatura ambiente durante 1 h, luego se concentró bajo presión reducida. El residuo se diluyó con $CH_2Cl_2$ y la capa orgánica se lavó con $H_2O$, NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar la (*R*)-N-(1-(3-(1-amino-2-metil-1-oxopropan-2-iloxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida pura (Ejemplo 274, 40 mg, rendimiento: 67%). CLEM: T.R. = 2.15 min [M+H] 651.2 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

**EJEMPLO 275**



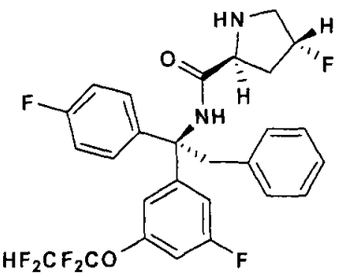

**(*R*)-N-(1-(3-(2-cianopropan-2-iloxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

**Procedimiento 70**



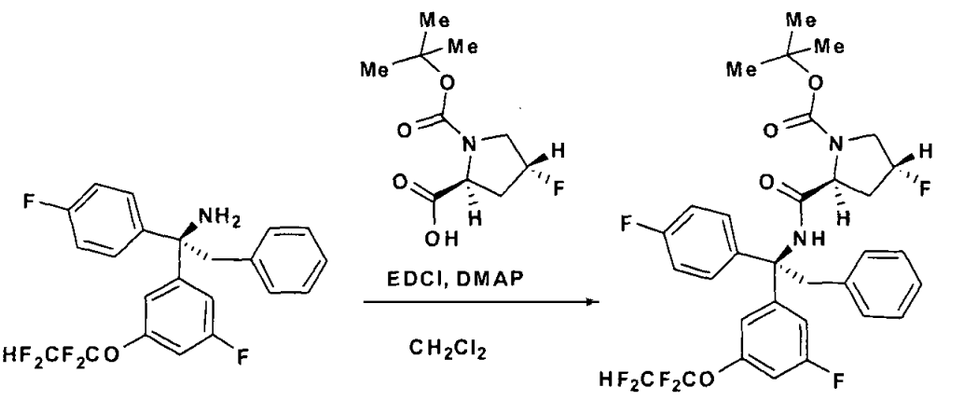

A una solución de (R)-N-(1-(3-(1-amino-2-metil-1-oxopropan-2-iloxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 274, 30 mg, 0.046 mmoles) en DMF (1 ml) a temperatura ambiente se agregó cloruro de tionilo (3 gotas). La mezcla de reacción se agitó durante 40 min y se diluyó con $H_2O$ y EtOAc. La capa orgánica se lavó con $H_2O$, $NaHCO_3$ saturado, $H_2O$ y NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó por Cromatografía de vaporización instantánea (gel de sílice, hexanos/EtOAc) para dar la (*R*)-N-(1-(3-(2-cianopropan-2-iloxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida pura (Ejemplo 275, 16 mg, rendimiento: 55%). CLEM: T.R. = 2.21 min [M+H] 633.3 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

**EJEMPLO 276**



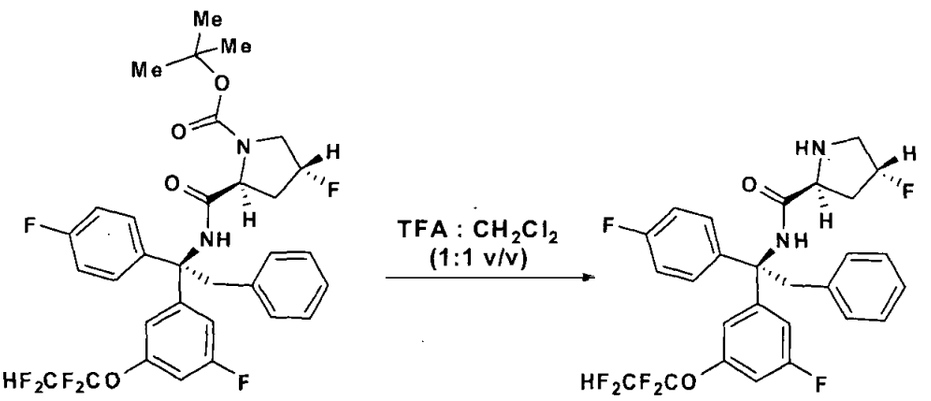
**(2S,4R)-4-fluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)-fenil)-1-(4-fluorofenil)-2-feniletil)pirrolidina-2-carboxamida**

**Procedimiento 71**




A una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (42 mg, 0.1 mmoles), preparada como se describe en el Procedimiento 3, 4, 5 y 6, y ácido (2S,4R)-1-(ter-butoxicarbonil)-4-fluoropirrolidina-2-carboxílico (23 mg, 0.1 mmoles) en $CH_2Cl_2$ (1 ml) se agregó EDCI (25 mg, 0.1 mmoles) y DMAP (16 mg, 0.1 mmoles). La mezcla de reacción se agitó durante la noche y se concentró hasta sequedad bajo una

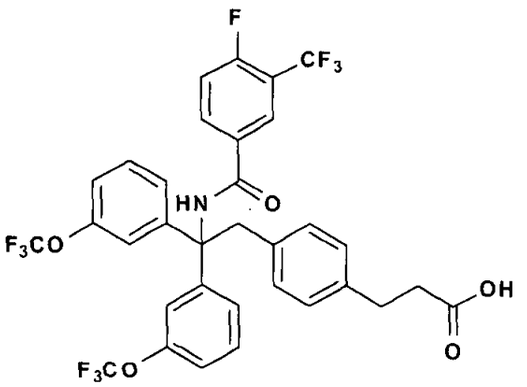
corriente de argón. El residuo resultante se disolvió en MeOH y se purificó por CLAR preparativa (Phenoma Luna AXIA 10A, C18, eluyendo con 10-90% MeCN/$H_2O$ que contiene 0.1% de TFA, observando a 220 nm) para proporcionar 4-fluoro-2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilcarbamoil)pirrolidina-1-carboxilato de (2S,4R)-ter-butilo (40 mg, 64% rendimiento) como un sólido blanco. $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 8.30 (s, 1H), 7.13-7.03 (m, 5H), 6.95-6.90 (m, 2H), 6.80-6.78 (m, 2H), 6.70 (bs, 1H), 6.51-6.47 (m, 2H), 5.88-5.67 (m, 1H, $-CF_2H$), 5.10 (app d, J=50 Hz, 1H, -CFH), 4.48-4.45 (m, 1H), 3.89-3.78 (m, 2H), 3.70 (d, J=10 Hz, 1HO, 3.29-3.18 (m, 1H), 2.79-2.55 (m, 2H), 2.25-2.11 (m, 1H), 1.32 (s, 9H); CL/EM: T.R. = 3.746 min [M+H] 641.2 Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm.




El 4-fluoro-2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilcarbamoil)pirrolidina-1-carboxilato de (2S,4R)-ter-butilo (18

mg, 0.03 mmoles) se disolvió en una solución de $CH_2Cl_2$ (1 ml)/ TFA (1 ml) a temperatura ambiente. La mezcla de reacción se agitó durante la noche y se concentró hasta sequedad bajo una corriente de argón. El residuo resultante se disolvió en MeOH y se purificó por CLAR preparativa (Phenoma Luna AXIA 10A, C18, eluyendo con 10% - 90% MeCN/$H_2O$ que contiene 0.1% de TFA, observando a 220 nm) para proporcionar (2S,4R)-4-fluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)-fenil)-1-(4-fluorofenil)-2-feniletil)pirrolidina-2-carboxamida (Ejemplo 276) como un sólido blanco (13 mg, 83% rendimiento). $^1H$ RMN (500 MHz, MeOH-$d_4$) δ ppm 7.22-7.13 (m, 7H), 7.07-6.96 (m, 7H), 6.68 (d, J=5 Hz, 2H), 6.40-6.18 (m, 1H, $-CF_2H$), 5.43 (app d, J=50 Hz, 1H, -CFH), 4.55-4.51 (m, 1H), 4.01 (d, J=10 Hz, 1H), 3.92 (d, J=15 Hz, 1H), 3.65-3.49 (m, 2H), 2.72-2.64 (m, 1H), 2.10-1.96 (m, 1H); CL/EM: T.R. = 3.310 min [M+H] 541.2 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm).

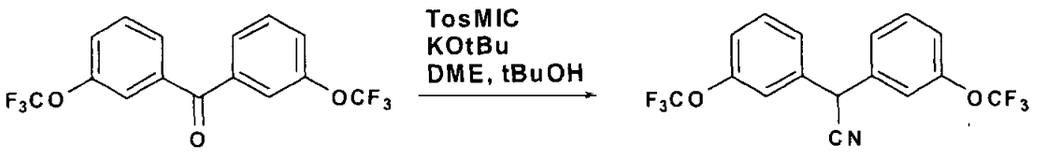
**EJEMPLO 277**




**Acido 3-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenil)propanoico**

1360

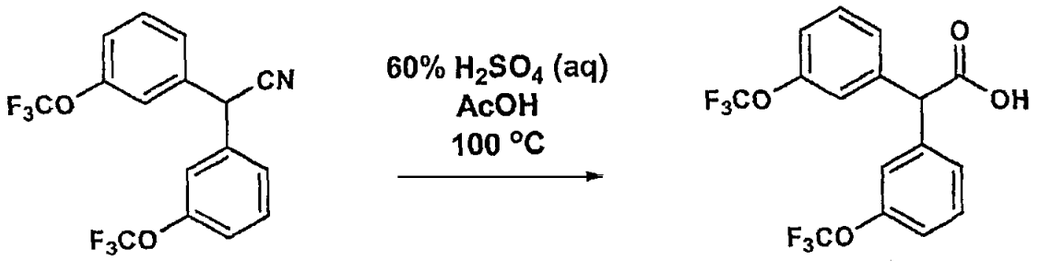
**Procedimiento 72**




A 0°C a una solución de bis(3-(trifluorometoxi)fenil)metanona (3 g, 8.6 mmoles), preparada como se describe en el Procedimiento 11, en DME (60 ml) se agregó 1-(isocianometilsulfonil)-4-metilbenceno (3.3 g, 17.1 mmoles) y tBuOK (25.7 ml, 1.0 M de solución en tBuOH, 25.7 mmoles). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 18 h. El $H_2O$ (100 ml) se agregó a la mezcla de reacción y la capa acuosa se extrajo con DCM (3 × 100 ml). Las capas orgánicas combinadas se lavaron con NaCl saturado (50 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó por cromatografía ISCO (150 g) al usar hexano/EtOAc (0-5% durante 30 min, 5-20% durante 20 min) para dar 2,2-bis(3-(trifluorometoxi)fenil)acetonitrilo como un aceite amarillo a un tiempo de retención de 46 min (1.4 g, 45% rendimiento). CLAR: T.R. = 4.13 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm). RMN: 400 MHz $^1H$ ($CDCl_3$) 7.45 ppm, 2 H, t, $J$=8.13 Hz; 7.30 ppm, 2 H, d, $J$=7.91 Hz; 7.23 ppm, 2 H, d, $J$=9.23 Hz; 7.17 ppm, 2 H, s; 5.17 ppm, 1 H, s.

1361

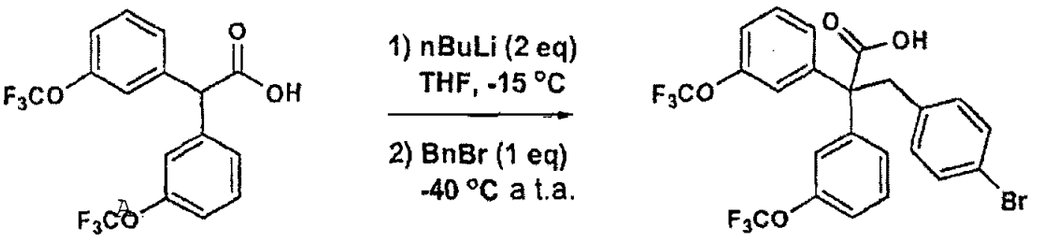
**Procedimiento 73**




A una solución de 2,2-bis(3-(trifluorometoxi)fenil)acetonitrilo (1.0 g, 2.8 mmoles) en AcOH (15 ml) se agregó 60% $H_2SO_4$ (ac.) (10 ml) y la mezcla de reacción se calentó a 100°C durante 10 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y se extrajo con tolueno (2 x 25 ml). Las porciones orgánicas combinadas se lavaron con $H_2O$ (25 ml) y NaCl saturado (25 ml), luego se extrajo con 0.5 N NaOH (50 ml y 10 ml). Los extractos orgánicos combinados en donde se hacen ácidos al usar HCl concentrado luego se extrajo con tolueno (2 x 25 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida para dar ácido 2,2-bis(3-(trifluorometoxi)fenil)acético (700 mg, 67% rendimiento) como un aceite color canela pálido. CLEM: T.R. = 1.99 min [M+H] 381.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) $\delta$ ppm 5.05 (s, 1 H), 7.14 - 7.19 (m, 4 H), 7.25 (d, *J*=7.47 Hz, 2 H), 7.37 (t, *J*=7.69 Hz, 2 H).

1362

**Procedimiento 74**

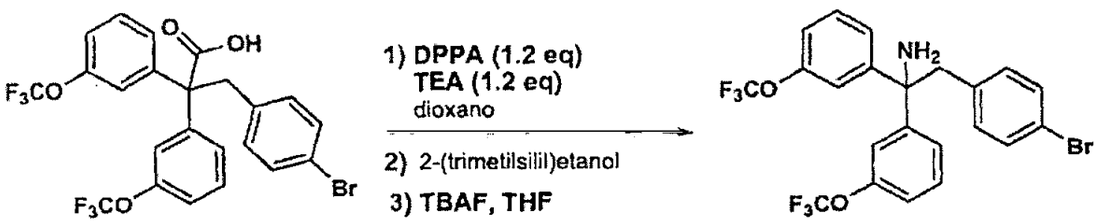



una solución de ácido 2,2-bis(3-(trifluorometoxi)fenil)acético (198 mg, 0.52 mmoles) en THF (3.5 ml) a -15°C se agregó gota a gota una solución 1.6 M de nBuLi en hexanos (0.65 ml, 1.04 mmoles). La mezcla de reacción se agitó durante 45 min. La solución se enfrió a -40°C y una solución de bromuro de bencilo (130 mg, 0.52 mmoles) en THF (0.6 ml) se agregó gota a gota. El baño de hielo se retiró y la mezcla de reacción se permitió entibiar hasta temperatura ambiente. La reacción se apagó por la adición de $NH_4Cl$ saturado (5 ml) y se extrajo con $Et_2O$ (3 x 5 ml). Las porciones orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó por cromatografía de sílice, eluyendo con 30% EtOAc/hexano que contiene 1% AcOH para dar el ácido 3-(4-bromofenil)-2,2-bis(3-(trifluorometoxi)fenil)propanoico (232 mg, 81% rendimiento) como un aceite incoloro transparente. CLEM: T.R. = 1.93 min [M+H] 549.0 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% $MeOH/H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) $\delta$ ppm

1363

3.62 (s, 2 H), 6.53 (d, *J*=8.35 Hz, 2 H), 7.04 (s, 2 H), 7.10 (d, *J*=7.91 Hz, 2 H), 7.13 - 7.19 (m, 4 H), 7.30 (t, *J*=8.13 Hz, 2 H).

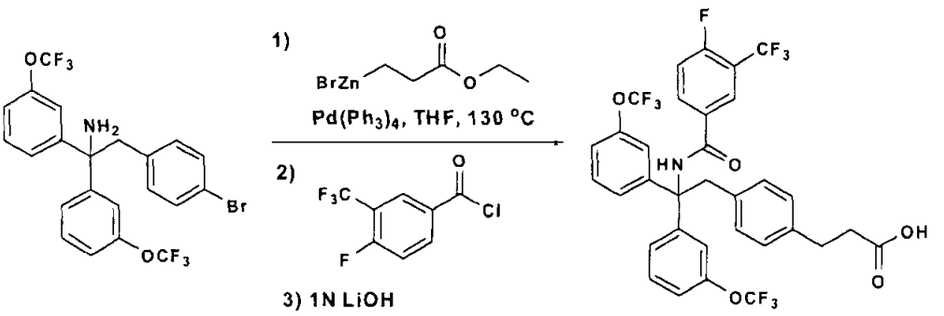
**Procedimiento 75**




A una solución del ácido 3-(4-bromofenil)-2,2-bis(3-(trifluorometoxi)fenil)propanoico (224 mg, 0.41 mmoles) en dioxano (5 ml) se agregó tamiz molecular 4 Å (aprox. 100 mg), trietilamina (0.068 ml, 0.49 mmoles) y azida de difenilfosforilo (0.11 ml, 0.49 mmoles) y la mezcla de reacción se agitó durante 45 minutos. El 2-(Trimetilsilil)etanol (0.176 ml, 1.23 mmoles) se agregó y la mezcla de reacción se calentó a reflujo durante 1 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y se concentró bajo presión reducida. El residuo se diluyó con $Et_2O$ (10 ml) y se lavó con $NH_4Cl$ saturado (5 ml), $NaHCO_3$ saturado (5 ml) y NaCl saturado (5 ml). La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo se diluyó con THF (5 ml) y se enfrió en un baño de hielo, luego una solución 1M de fluoruro de tetrabutilamonio en THF (0.80 ml, 0.80 mmoles) se agregó gota a gota. La mezcla de reacción se permitió entibiar hasta

temperatura ambiente y se agitó durante 3 h. La mezcla de reacción se diluyó con $CH_2Cl_2$ (5 ml) y se lavó con $H_2O$ (5 ml) y NaCl saturado (5 ml). La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó en cromatografía de sílice ISCO con elución a 0 hasta 50% EtOAc/hexano para dar 2-(4-bromofenil)-1,1-bis(3-(trifluorometoxi)fenil)etanamina (78 mg, 37% rendimiento) como un aceite incoloro transparente. CLEM: T.R. = 1.87 min [M-$NH_2$] 505.0 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) $\delta$ ppm 1.68 (bs, 2 H), 3.46 (s, 2 H), 6.57 (d, *J*=8.35 Hz, 2 H), 7.10 (d, *J*=8.35 Hz, 2 H), 7.18 (s, 2 H), 7.21 - 7.26 (m, 4 H), 7.32 (t, *J*=8.13 Hz, 2 H).

**Procedimiento 76**



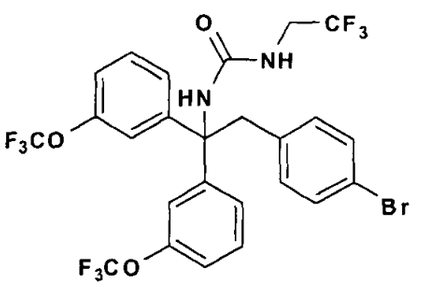

A una solución de 2-(4-bromofenil)-1,1-bis(3-(trifluorometoxi)fenil)etanamina (26 mg, 0.050 mmoles) en THF (0.5 ml) se agregó una solución 0.5M de bromuro de 3-etoxi-3-oxopropilzinc en THF (0.18 ml, 0.090 mmoles) seguido por tetraquis(trifenilfosfina)paladio(0) (3 mg, 5 mol%). La

mezcla de reacción se calentó a 130°C bajo radiación por microondas durante 0.5 h. La mezcla de reacción se filtró a través de gel de sílice y se eluyó con THF. Los solventes se retiraron bajo presión reducida y el residuo se disolvió en $CH_2Cl_2$ (0.5 ml) luego trietilamina (0.020 ml, 0.15 mmoles) se agregó seguido por cloruro de 4-fluoro-3-(trifluorometil)benzoilo (0.020 ml, 0.13 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 h luego se diluyó con $Et_2O$ (10 ml) y la capa orgánica se lavó con $NH_4Cl$ saturado (2 ml), $NaHCO_3$ saturado (2 ml) y NaCl saturado (2 ml). La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por placa CCD preparativa, eluyendo con 20% EtOAc/hexano para dar 3-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenil)propanoato de etilo (11 mg, 31% rendimiento) como un aceite incoloro, transparente. CLEM: T.R. = 2.26 min [M+H] 731.93 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

A una solución de 3-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenil)propanoato de etilo (11 mg, 0.015 mmoles) en THF (0.75 ml) se agregó 1 N LiOH (0.15 ml) y metanol (0.30 ml). La mezcla de reacción se calentó a 50°C durante 0.5 h. Los solventes se retiraron bajo una corriente

de nitrógeno luego HCl 1N (2 ml) se agregó al residuo y la mezcla se extrajo con $CH_2Cl_2$ (2 x 5 ml). Los orgánicos combinados se secaron sobre $Na_2SO_4$, se filtraron y los volátiles se removieron. El residuo resultante se purificó en gel de sílice ISCO eluyendo con 0 hasta 10% $MeOH/CH_2Cl_2$ para dar el ácido 3-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenil)propanoico (Ejemplo 277) como un aceite incoloro, transparente (9 mg, 85% rendimiento). CLEM: T.R. = 2.18 min [M+H] 704.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% $MeOH/H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) $\delta$ ppm 2.55 (t, *J*=7.69 Hz, 2 H), 2.82 (t, *J*=7.69 Hz, 2 H), 3.83 (s, 2 H), 6.54 (d, *J*=8.35 Hz, 2 H), 6.60 (s, 1 H), 6.93 (d, *J*=7.91 Hz, 2 H), 6.97 (s, 2 H), 7.08 - 7.14 (m, 4 H), 7.17 - 7.23 (m, 1 H), 7.28 - 7.33 (m, 2 H), 7.73 - 7.77 (m, 1 H), 7.83 - 7.86 (m, 1 H).

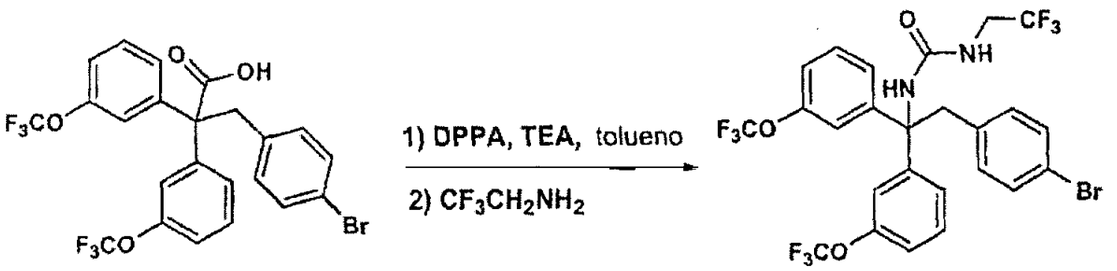
**EJEMPLO 278**




**1-(2-(4-bromofenil)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea**

(302)

**Procedimiento 77**

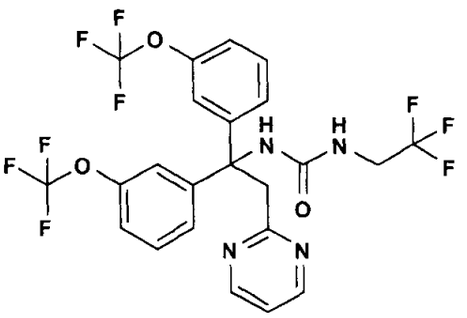



A una solución del ácido 3-(4-bromofenil)-2,2-bis(3-(trifluorometoxi)fenil)propanoico (260 mg, 0.47 mmoles) en tolueno (10 ml) se agregó azida de fenilfosforilo (0.409 ml, 1.9 mmoles) seguido por trietilamina (0.264 ml, 1.9 mmoles). La mezcla de reacción se calentó a reflujo durante 1 h, luego trifluoroetilamina se agregó y la mezcla de reacción se calentó a reflujo durante otra 1 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y se diluyó con EtOAc (30 ml) y se lavó sucesivamente con $NH_4Cl$ saturado (10 ml), $NaHCO_3$ saturado (10 ml) y NaCl saturado (20 ml). La capa orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró bajo presión reducida. El producto crudo se purificó en una columna de gel de sílice ISCO (12 g) con elución a 0 hasta 20% EtOAc/hexano durante 20 min, luego se purificó además por una columna de CLAR preparativa YMC ODS S5 30 x 100 mm 40-100% MeOH/$H_2O$ (90% en agua, 0.1% de TFA) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm para producir 1-(2-(4-bromofenil)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 278) como un sólido blanco (200 mg, rendimiento

1369

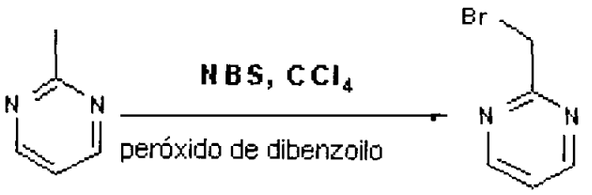
65%). CLEM: T.R. = 2.24 min [M+H] 645.0 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.476 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 3.68 - 3.77 (m, 2 H), 3.81 (s, 2 H), 4.80 (t, *J*=6.15 Hz, 1 H), 5.15 (s, 1 H), 6.52 (d, *J*=7.91 Hz, 2 H), 6.97 (s, 2 H), 7.09 - 7.17 (m, 4 H), 7.23 - 7.27 (m, 3 H), 7.34 (t, *J*=7.91 Hz, 2 H).

**EJEMPLO 279**



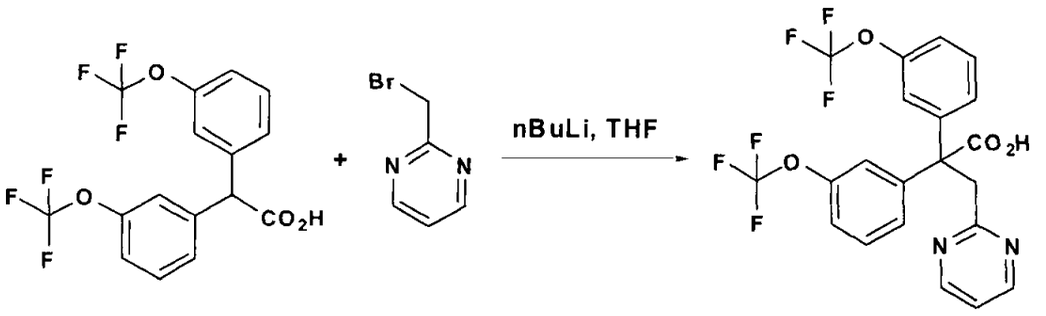
**1-(2-(pirimidin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea**

**Procedimiento 78**



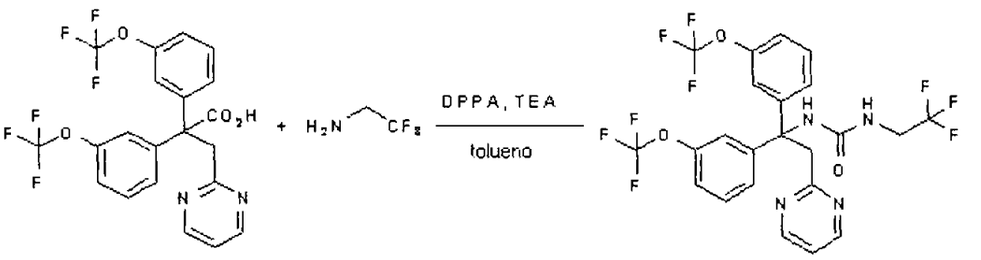

A una solución de 2-metilpirimidina (2.0 g, 21.3 mmoles) en $CCl_4$ (80 ml) se agregó peróxido de benzoilo (80

mg, 0.33 mmoles). La mezcla de reacción se calentó a reflujo, luego NBS (4.5 g, 25.56 mmoles) se agregó en porciones durante 3.5 h. El reflujo se mantuvo durante 18 h y la mezcla de reacción se permitió enfriar hasta temperatura ambiente, se filtró a través de una almohadilla de celite y el celite se enjuagó con éter (200 ml). La capa orgánica se concentró y el residuo se purificó por cromatografía ISCO (120 g columna) al usar hexano/EtOAc (0-80% durante 30 min) para dar 2-(bromometil)pirimidina como un aceite amarillo a un tiempo de retención de 18 min (412 mg, 11% rendimiento). RMN: 400 MHz $^1H$ ($CDCl_3$) 8.76 ppm, 2 H, d, $J$=5.27 Hz; 7.23 ppm, 1 H, m; 4.62 ppm, 2 H, d, $J$=2.20 Hz.




A -15°C una solución del ácido 2,2-bis(3-(trifluorometoxi)fenil)acético preparada como se describe en el Procedimiento 73 (607 mg, 1.6 mmoles) en THF (6 ml) se agregó nBuLi (1.6 ml, 2M en hexano, 3.2 mmoles). La mezcla se agitó a -15°C durante 45 min. La 2-(Bromometil)pirimidina (412 mg, cruda) en THF (1 ml) se agregó y la mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 18 h, luego se apagó con $NH_4Cl$ saturado. La

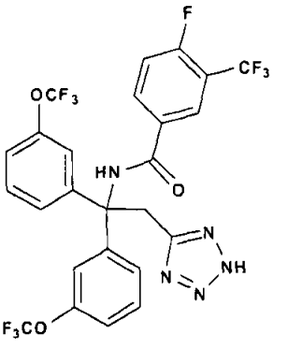
capa acuosa se extrajo con EtOAc (3 × 50 ml). La capa orgánica combinada se secó sobre $MgSO_4$, se filtró y se concentró para dar ácido 3-(pirimidin-2-il)-2,2-bis(3-(trifluorometoxi)fenil)propanoico como un sólido amarillo (437 mg, 58% crudo). Este sólido crudo se llevó a cabo en la siguiente etapa sin purificación adicional.




A una mezcla del ácido 3-(pirimidin-2-il)-2,2-bis(3-(trifluorometoxi)fenil)propanoico (20 mg, 0.042 mmoles) y azida de difenilfosforilo (70 mg, 0.254 mmoles) en tolueno (1.5 ml) se agregó TEA (88 µl, 0.63 mmoles) gota a gota y la mezcla de reacción se calentó a 110°C durante 20 min. La 2,2,2-Trifluoroetanamina (7 µl, 0.084 mmoles) se agregó y la mezcla de reacción se agitó a 110°C durante 1 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y se diluyó con EtOAc (25 ml). La capa orgánica se lavó con $H_2O$ (25 ml), HCl 1N (25 ml) y $NaHCO_3$ saturado (25 ml), se secó sobre $MgSO_4$, se

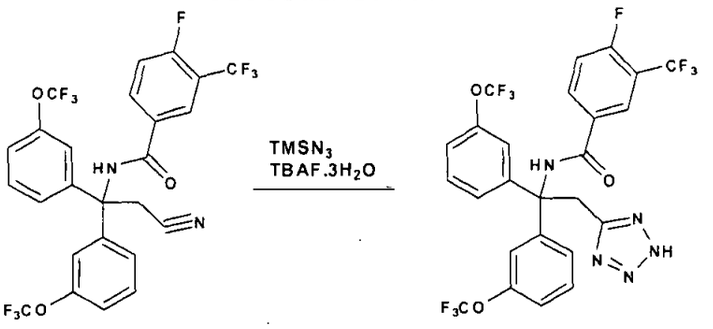
filtró y se concentró bajo presión reducida. El residuo se purificó por CLAR preparativa (columna Shimadzu-YMC-Sunfire 5µ, 30 × 100 mm eluyendo con 40-100% MeOH (90% en $H_2O$, 0.1%TFA) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm). El producto se eluyó en un tiempo de retención de 9.42 min se aisló como un aceite transparente, y se purificó además por CCD Prep (Uniplate, Gel de sílice GF, 20 x 20 cm, 1000 Microns) al usar Hexano/EtOAc (1/2) para producir 1-(2-(pirimidin-2-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 279) como un sólido blanco (4 mg, 16% rendimiento). CLEM: T.R. = 1.867 min [M+H] 568.87 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA, 5 ml/min, observando a 220 nm); CLAR: T.R. = 3.973 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 8.52 ppm, 2 H, d, *J*=4.83 Hz; 7.98 ppm, 1 H, s; 7.33 ppm, 5 H, m; 7.23 ppm, 2 H, s; 7.08 ppm, 3 H, t, *J*=5.05 Hz; 4.61 ppm, 1 H, t, *J*=6.37 Hz; 3.85 ppm, 2 H, s; 3.77 ppm, 2 H, ddd, *J*=15.71, 9.12, 9.01 Hz.

**EJEMPLO 280**



**N-(2-(2H-tetrazol-5-il)-1,1-bis(3-trifluorometoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida**

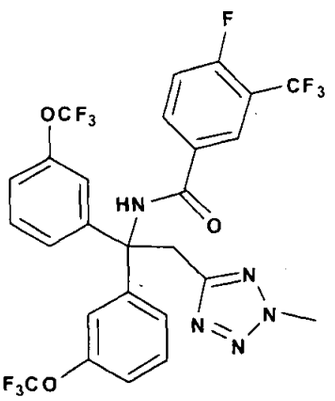
**Procedimiento 79**




La N-(2-ciano-1,1-bis(3-(trifluorometoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida fue preparada como se describe en el Procedimiento 11, 18, 6 y 7. CLEM: T.R. = 4.04 min [M+H] 581.16 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). Una mezcla de N-(2-ciano-1,1-bis(3-(trifluorometoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (70 mg, 0.12 mmoles), $TMSN_3$ (0.025 ml. 1.6 eq) y TBAF·$3H_2O$ (19 mg, 0.5 eq) se calentó en un tubo sellado a 110°C durante 24 h. Después de permitir enfriar

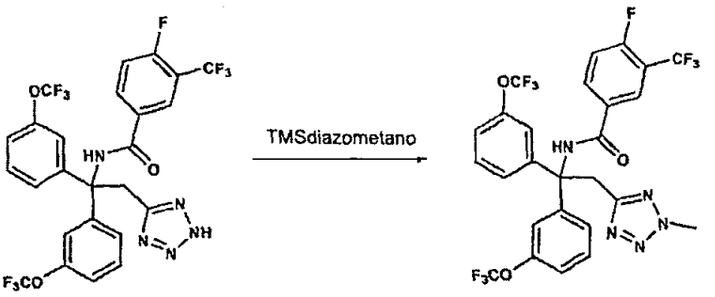
hasta temperatura ambiente, el residuo se disolvió en $CH_2Cl_2$, y se purificó Cromatografía de vaporización instantánea ISCO (gel de sílice, $CH_2Cl_2$/MeOH) para dar N-(2-(2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 280, 54 mg, rendimiento: 72%). CLEM: T.R. = 3.91 min [M+H] 624.06, [M+Na] 647.06 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

**EJEMPLO 281**




**4-fluoro-N-(2-(2-metil-2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(trifluorometil)benzamida**

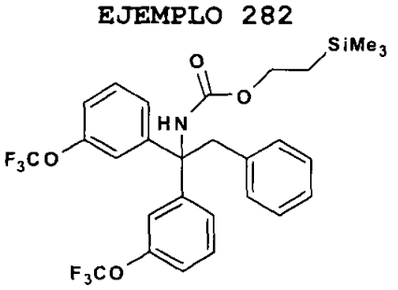
**Procedimiento 80**




A una solución de N-(2-(2H-tetrazol-5-il)-1,1-

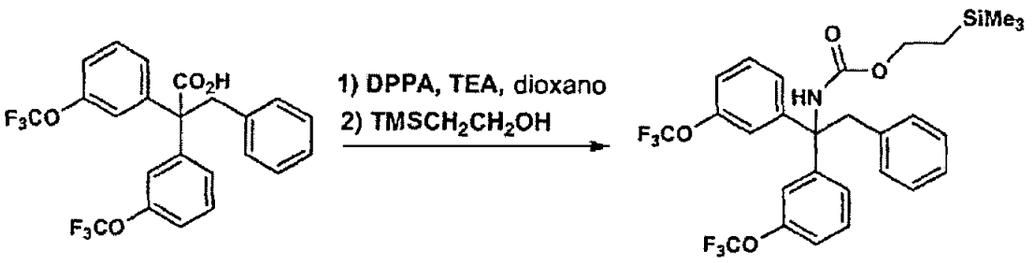
bis(3-(trifluorometoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (18 mg, 0.029 mmoles) en THF (0.4 ml) y MeOH (0.1 ml) a temperatura ambiente se agregó (diazometil)trimetilsilano (0.02 ml, solución 2.0 M). La solución resultante se agitó a temperatura ambiente durante 20 min. Los solventes se evaporaron y residuo resultante se purificó por Cromatografía de vaporización instantánea ISCO (gel de sílice, hexano/EtOAc) para dar 4-fluoro-N-(2-(2-metil-2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 281, 11 mg, rendimiento: 60%). CLEM: T.R. = 4.06 min [M+H] 638.23, [M+Na] 661.26 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

**EJEMPLO 282**




**2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etilcarbamato de 2-(trimetilsilil)etilo**

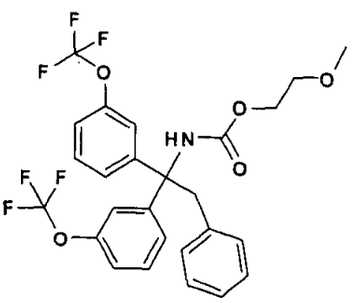
**Procedimiento 81**




A una solución de ácido 3-fenil-2,2-bis(3-

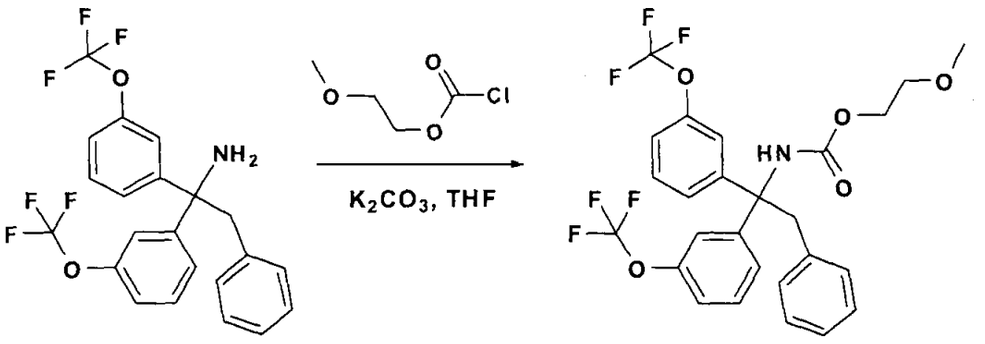
(trifluorometoxi)fenil)propanoico (0.055 g, 0.117 mmoles) en 1,4-dioxano (2 ml) se agregó trietilamina (0.014 g, 20 µL, 0.14 mmoles), tamiz molecular 4Å (0.05 g), azida de fenilfosforilo (0.040 g, 31 µL, 0.14 mmoles) y trimetilsililetanol (0.042 g, 50 µL, 0.35 mmoles ). La mezcla de reacción se agitó durante 1 h a temperatura ambiente, luego se calentó a 75°C durante 1.5 h. La mezcla de reacción fría se diluyó con EtOAc y se filtró a través de celite. El producto filtrado se concentró bajo presión reducida y se purificó ISCO cromatografía de gel de sílice al usar un gradiente de 0-20% EtOAc/hexano como eluyente para producir 2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etilcarbamato de 2-(trimetilsilil)etilo (Ejemplo 282) como una banda incolora (0.037 g, 54% rendimiento). CLAR: T.R. = 4.828 min (Phenomenex Luna C18 5µ columna 4.6 x 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% PPA durante 4 minuto gradiente, observando a 220nm). El ión no molecular se obtuvo. $^1H$ RMN (400 MHz, $CDCl_3$): 7.32 (t, J=8.1 Hz, 2H), 7.18-7.11 (m, 7H), 6.99 (s, 2H), 6.65 (d, J=7.1 Hz, 2H), 5.35 (s, 1H), 4.08 (t, J=8.8Hz, 2H), 3.78 (s, 2H), 0.88 (br, 2H), 0.00 (s, 9H).

**EJEMPLO 283**



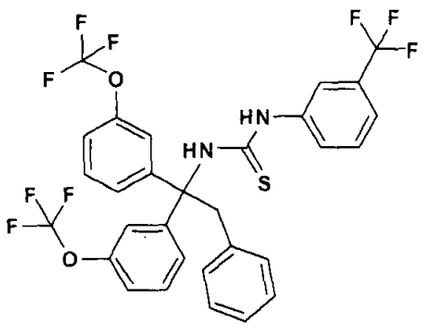

**2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etilcarbamato de 2-metoxietilo**

**Procedimiento 82**



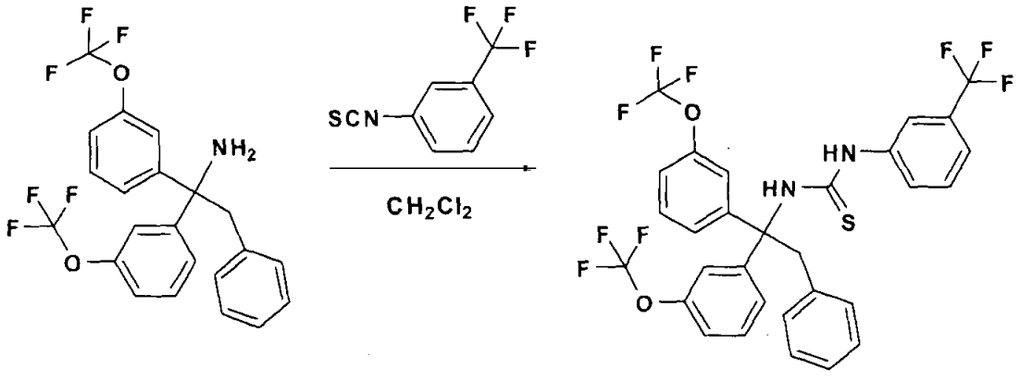

A una solución de 2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etanamina (20 mg, 0.045 mmoles) en THF (6 ml) se agregó $K_2CO_3$ 1M (20 mg en 0.1 ml), seguido por clorhidrato de 2-metoxietilo carbono (0.106 ml, 0.91 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 16 h. El producto crudo se purificó por CLAR preparativa (phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para proporcionar 2-metoxietil 2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etilcarbamato (Ejemplo 283) como liofilato blanco (12 mg, 51% rendimiento). CLEM: T.R. = 4.19 min [M+H] 544.2 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm.

**EJEMPLO 284**



**1-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(3-(trifluorometil)fenil)tiourea**

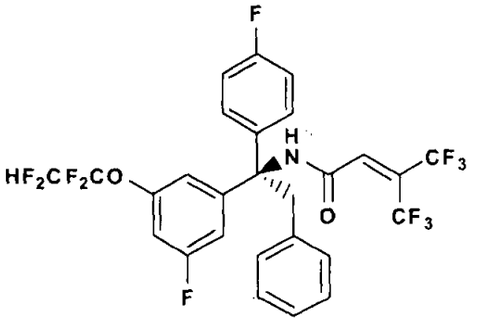
**Procedimiento 83**




A una solución de bis(3-(trifluorometoxi)fenil)metanamina (20 mg, 0.057 mmoles) en $CH_2Cl_2$ (0.1 ml) se agregó 1-isotiocianato-3-(trifluorometil)benceno (35 mg, 0.17 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró y el residuo se purificó por CLAR preparativa (phenomenex AXIA Luna 75 X 30 mm, columna 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para resultar 1-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(3-

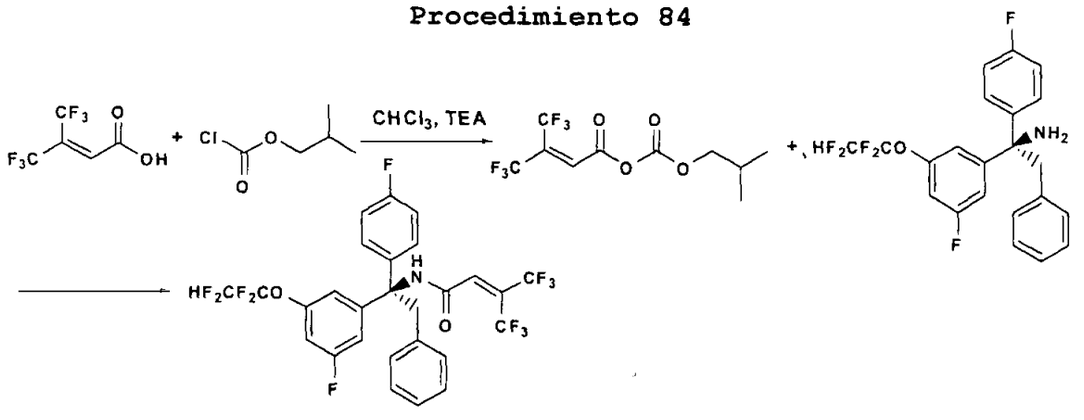
(trifluorometil)fenil)tiourea (Ejemplo 284) como liofilato blanco (30 mg, 81%). CLEM: T.R. = 4.51min [M+H] 645.14 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).

**EJEMPLO 285**



**(R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)but-2-enamida**

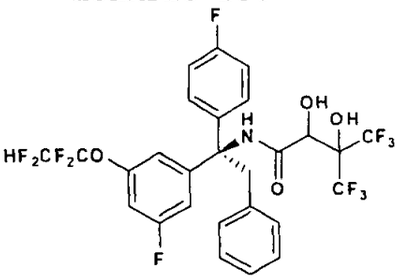
**Procedimiento 84**



A 0°C bajo argón a una solución de ácido 4,4,4-trifluoro-3-(trifluorometil)crotónico (29 mg, 0.14 mmoles) y TEA (25 µl, 0.18 mmoles) en $CHCl_3$ (0.5 ml) se agregó cloroformiato de isobutilo (18 µl, 0.14 mmoles). La mezcla de

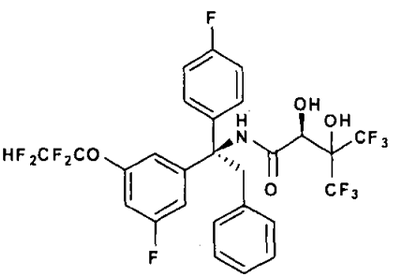
reacción se agitó a 0°C durante 10 min. Una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina, preparada como se describe en el Procedimiento 3, 4, 5 y 6, (50 mg, 0.12 mmoles) en $CHCl_3$ (0.5 ml) se agregó y la reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró y se purificó por columna CLAR preparativa Shimadzu-YMC Sunfire 5µ, 30 × 100 mm eluyendo con 40-100% MeOH (90% en $H_2O$, 0.1% de TFA) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm. La (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)but-2-enamida (Ejemplo 285) se eluyó a un tiempo de retención de 11.11 min y se aisló como un aceite transparente (63 mg, rendimiento 73%). CLEM: T.R. = 2.19 min [M+H] 616.1 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.31 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.36 ppm, 2 H, s; 7.21 ppm, 3 H, m; 7.09 ppm, 2 H, m; 7.01 ppm, 2 H, t, $J$=8.57 Hz; 6.91 ppm, 3 H, m; 6.64 ppm, 2 H, d, $J$=7.03 Hz; 6.43 ppm, 1 H, s; 3.94 ppm, 1 H, d, $J$=13.18 Hz; 3.78 ppm, 1 H, d, $J$=13.18 Hz; 2.13 ppm, 2 H, s.

**EJEMPLO 286**



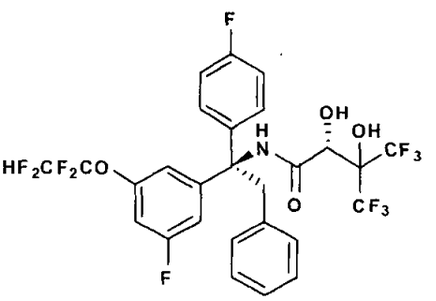
**(4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida**

**EJEMPLO 287A**



**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida**

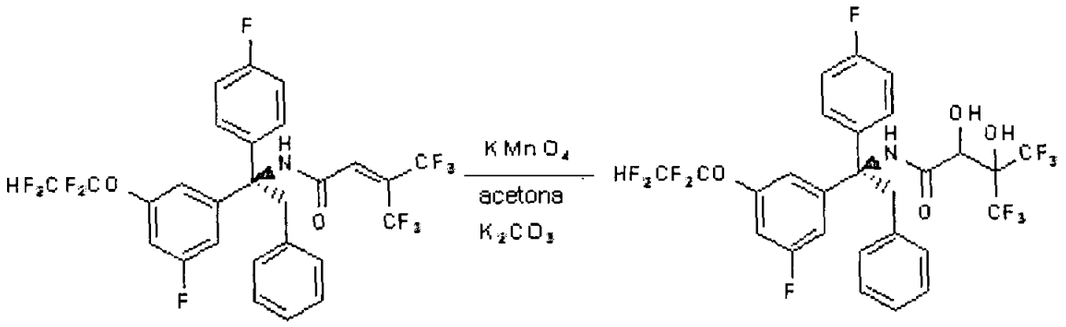
**EJEMPLO 287B**



**(R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida**

(289)

**Procedimiento 85**




A -78°C una mezcla de (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)but-2-enamida (Ejemplo 285, 36 mg, 0.06 mmoles) y $K_2CO_3$ (28 mg, 0.2 mmoles) en acetona (0.5 ml) se agregó $KMnO_4$ (9 mg, 0.06 mmoles). La mezcla de reacción morada resultante se agitó a -78°C durante 1 h, luego a 0°C durante 30 min. La mezcla de reacción se diluyó con EtOAc (25 ml) y la capa orgánica se lavó a través de HCl 1N (2 × 25 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo resultante se purificó por columna CLAR preparativa Shimadzu-YMC Sunfire 5µ, 30 × 100 mm eluyendo con 60-100% MeOH (90% en $H_2O$, 0.1% de TFA) gradiente durante 14 min con relación de flujo 40 ml/min y detección UV a 220 nm. La 4,4,4-Trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 286) se eluyó a un tiempo de retención de 12.86 min y se aisló como un aceite transparente (15 mg, rendimiento 39%). CLEM: T.R. = 2.12 min [M+H] 650.92 (columna Phenomenex Luna C18, 4.6 × 30

mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.36 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400 MHz $^1H$ ($CDCl_3$) 7.92 ppm, 1 H, d, *J*=6.15 Hz; 7.19 ppm, 5 H, m; 7.06 ppm, 1 H, t, *J*=8.57 Hz; 6.97 ppm, 5 H, m; 6.71 ppm, 1 H, m; 6.62 ppm, 2 H, t, *J*=6.37 Hz; 5.88 ppm, 1H, m; 4.51 ppm, 1 H, s; 4.11 ppm, 1 H, m; 3.56 ppm, 1 H, m; 3.25 ppm, 1H, m.

La mezcla de diaestereómeros de la 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 286, 189 mg, 0.3 mmoles) se separó por una columna CLAR quiral preparativa Chiralpak AD 20, 5 × 50 cm, eluyendo con 5% IPA/Heptano con relación de flujo 50 ml/min. La (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287A) se eluyó a un tiempo de retención de 52 min y la (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287B) se eluyó a un tiempo de retención de 70 min. La estereoquímica de la (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-

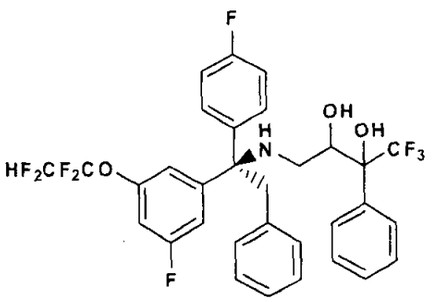
dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287A) y (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287B) se asignó arbitrariamente.

La (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287A) se purificó además por cromatografía ISCO (40 g columna, relación de flujo 20 ml/min) al usar hexanos/EtOAc (0-30% durante 30 min) para dar (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287A) como un sólido blanco a un tiempo de retención de 28 min (95 mg, 50% rendimiento). CLEM: T.R. = 2.12 min [M+H] 650.00 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.241 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400 MHz $^1H$ ($CDCl_3$) 7.95ppm, 1 H, s; 7.22 ppm, 2 H, m; 7.16 ppm, 2 H, t, $J$=7.25 Hz; 6.99 ppm, 8 H, m; 6.62 ppm, 2 H, d, $J$=7.47 Hz; 5.89 ppm, 1H, t, $J$=52.95 Hz; 4.52 ppm, 1 H, d, $J$=6.15 Hz; 4.08 ppm, 1 H, d, $J$=3.95 Hz;

3.53 ppm, 2 H, d, *J*=13.18 Hz.

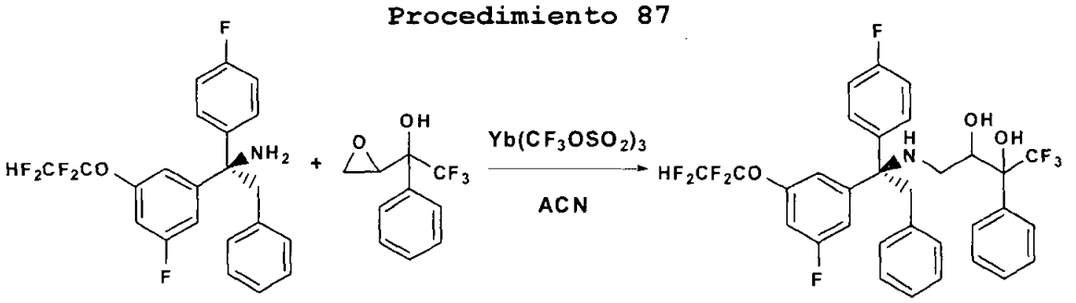
La (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287B) se purificó además por cromatografía ISCO (40 g columna, relación de flujo 20 ml/min) al usar hexanos/EtOAc (0-30% durante 30 min) para dar (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 287B) como un aceite transparente a un tiempo de retención de 28 min (57 mg, 30% rendimiento). CLEM: T.R. = 2.12 min [M+H] 650.00 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.285 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 1H RMN (400 MHz, Solvente) δ ppm 7.95 ppm, 1 H, s; 7.20 ppm, 6 H, m; 7.05 ppm, 2 H, t, *J*=8.57 Hz; 6.93 ppm, 1 H, d, *J*=8.79 Hz; 6.71 ppm, 2 H, m; 6.63 ppm, 2 H, d, *J*=7.03 Hz; 5.85 ppm, 1 H, tt, *J*=52.95, 2.64 Hz; 4.49 ppm, 1 H, d, *J*=6.15 Hz; 4.02 ppm, 1 H, d, *J*=13.62 Hz; 3.79 ppm, 1 H, d, *J*=6.15 Hz; 3.59 ppm, 1 H, d, *J*=13.18 Hz.

**EJEMPLO 288**



**1,1,1-trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-2-fenilbutano-2,3-diol**

**Procedimiento 87**

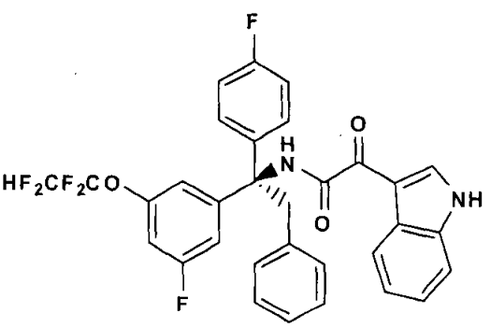


Una mezcla de la (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina, preparada como se describe en el Procedimiento 3, 4, 5 y 6, (20 mg, 0.047 mmoles), 2,2,2-trifluoro-1-(oxiran-2-il)-1-feniletanol (63 mg, 0.28 mmoles), y $Yb(CF_3OSO_2)_3$ (10 mg) en dicloroetano (0.5 ml) en donde se calentó a 45°C durante 72 h. La mezcla de reacción se concentró y el residuo se purificó por una columna CLAR preparativa Shimadzu-YMC Sunfire 5µ, 30 × 100 mm eluyendo con 40-100% MeOH (90% en $H_2O$, 0.1% de TFA) gradiente durante 10 min con relación de

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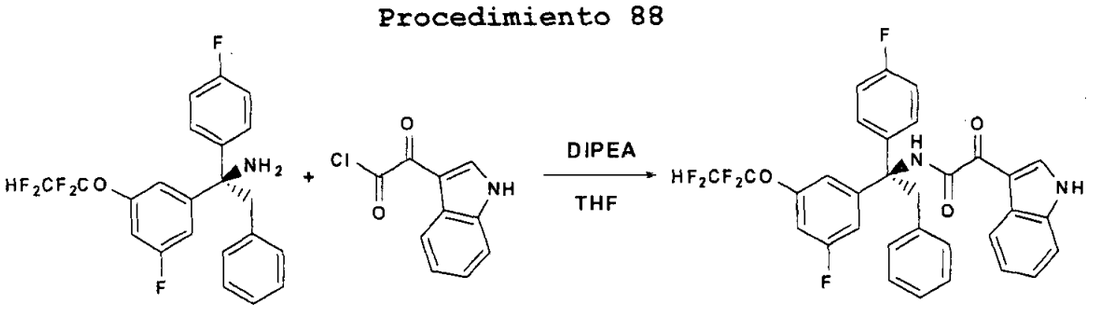
flujo 40 ml/min y detección UV a 220 nm. El 1,1,1-Trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-2-fenilbutano-2,3-diol (Ejemplo 288) se eluyó a un tiempo de retención de 9.11 min y se aisló como un aceite transparente (11 mg, rendimiento 37%). CLEM: T.R. = 1.85 min [M+H] 643.95 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.20 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.34 ppm, 5 H, m; 7.17 ppm, 1 H, t, *J*=7.47 Hz; 7.07 ppm, 4 H, m; 6.95 ppm, 2 H, m; 6.84 ppm, 1 H, m; 6.73 ppm, 2 H, m; 6.44 ppm, 2 H, d, *J*=7.47 Hz; 5.86 ppm, 1H, m; 4.02 ppm, 2 H, dd, *J*=6.59, 3.95 Hz; 3.33 ppm, 2 H, m; 2.32 ppm, 1 H, dt, *J*=12.74, 4.61 Hz; 2.18 ppm, 1 H, ddd, *J*=14.72, 12.52, 7.03 Hz.

**EJEMPLO 289**




**(R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-(1H-indol-3-il)-2-oxoacetamida**

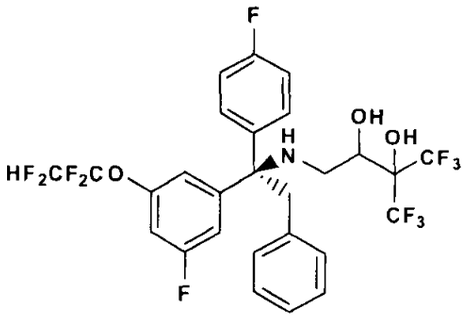
**Procedimiento 88**




A 0°C, una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina, preparada como se describe en el Procedimiento 3, 4, 5 y 6, (20 mg, 0.045 mmoles) y cloruro de 2-(1H-indol-3-il)-2-oxoacetilo (10 mg, 0.05 mmoles) en THF (0.5 ml) se agregó gota a gota diisopropiletilamina (10 µl, 0.06 mmoles). La mezcla de reacción se agitó a 0°C durante 3 h. La mezcla de reacción se concentró y el residuo se purificó por una columna CLAR preparativa Shimadzu-YMC Sunfire 5µ, 30 × 100 mm eluyendo con 40-100% MeOH (90% en $H_2O$, 0.1% de TFA) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm. La (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-(1H-indol-3-il)-2-oxoacetamida (Ejemplo 289) se eluyó a un tiempo de retención de 11.65 min y se aisló como un aceite transparente (13 mg, rendimiento 48%). CLEM: T.R. = 2.20 min [M+H] 596.96 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.45 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50

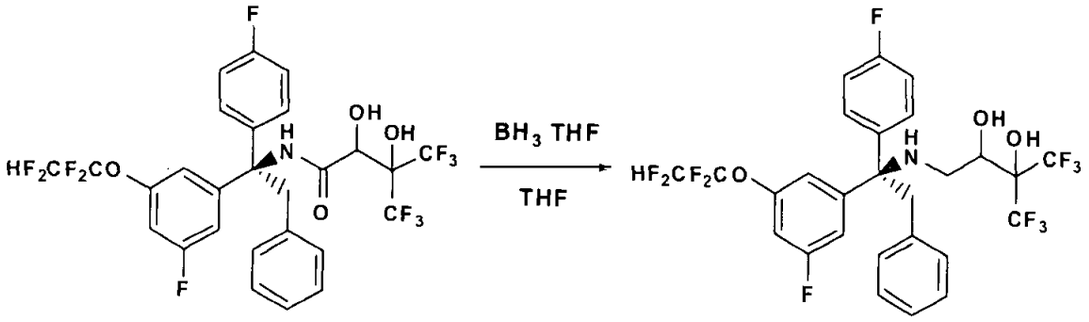
mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm). RMN: 400 MHz $^1H$ ($CDCl_3$) 8.98 ppm, 1 H, d, *J*=3.52 Hz; 8.83 ppm, 1 H, s; 8.43 ppm, 1 H, s; 8.40 ppm, 1 H, d, *J*=7.03 Hz; 7.42 ppm, 1 H, m; 7.34 ppm, 2 H, m; 7.14 ppm, 5 H, m; 7.01 ppm, 2 H, t, *J*=8.57 Hz; 6.93 ppm, 3 H, m; 6.68 ppm, 2 H, d, *J*=7.03 Hz; 5.86 ppm, 1 H, tt, *J*=53.06, 2.86, 2.64 Hz; 3.96 ppm, 1 H, d, *J*=12.74 Hz; 3.82 ppm, 1 H, m.

**EJEMPLO 290**




**1,1,1-trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-2-(trifluorometil)butano-2,3-diol**

**Procedimiento 89**



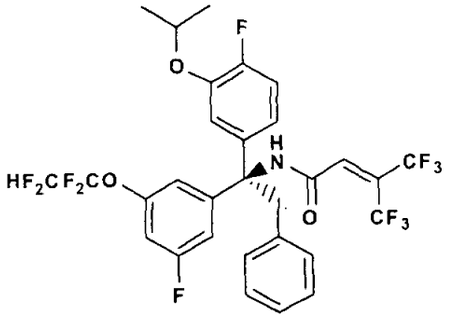

Una mezcla de la 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-

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2-feniletil)-2,3-dihidroxi-3-(trifluorometil)butanamida (Ejemplo 286, 20 mg, 0.031 mmoles) y $BH_3$/THF (248 µl, solución 1.0 M en THF, 0.248 mmoles) en THF (0.5 ml) se calentó a 100°C bajo radiación por microondas durante 30 min. La mezcla de reacción se concentró, se diluyó con EtOAc (25 ml) y la capa orgánica se lavó con $Na_2CO_3$ saturado (25 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo resultante se purificó por una columna CLAR preparativa Shimadzu-YMC Sunfire 5, 30 × 100 mm eluyendo con 40-100% MeOH (90% en $H_2O$, 0.1%TFA) gradiente durante 12 min con relación de flujo 40 ml/min y detección UV a 220 nm. El 1,1,1-Trifluoro-4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-2-(trifluorometil)butano-2,3-diol (Ejemplo 290) se eluyó a un tiempo de retención de 11.09 min y se aisló como un aceite transparente (12 mg, rendimiento 62%). CLEM: T.R. = 1.95 min [M+H] 636.38 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.01 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.21 ppm, 4 H, dd, *J*=8.57, 5.49 Hz; 7.15 ppm, 2 H, t, *J*=7.25 Hz; 7.06 ppm, 2 H, t, *J*=8.57 Hz; 6.90 ppm, 1 H, d, *J*=8.35 Hz; 6.80 ppm, 1 H, dd, *J*=9.67, 2.20 Hz; 6.77 ppm, 1

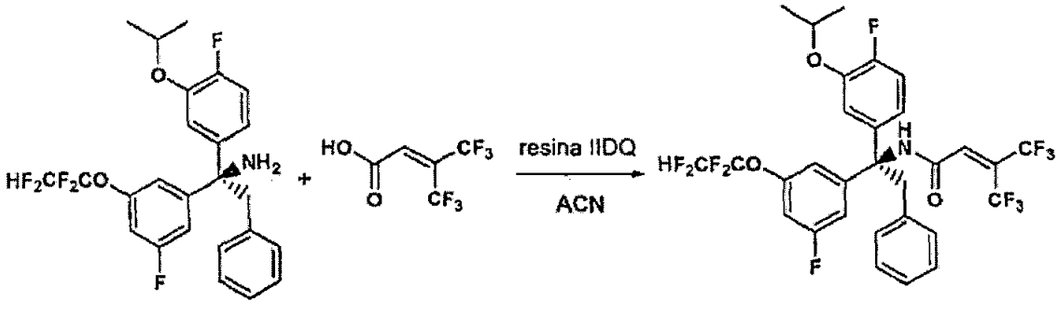
H, s; 6.60 ppm, 2 H, d, *J*=6.59 Hz; 5.87 ppm, 1 H, tt, *J*=52.95, 2.86 Hz; 3.84 ppm, 1 H, t, *J*=5.71 Hz; 3.59 ppm, 1 H, m; 3.46 ppm, 1 H, m; 3.07 ppm, 1 H, dd, *J*=12.74, 6.15 Hz; 2.86 ppm, 1 H, dd, *J*=12.96, 5.49 Hz.

**EJEMPLO 291**



**(R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)but-2-enamida**

**Procedimiento 90**



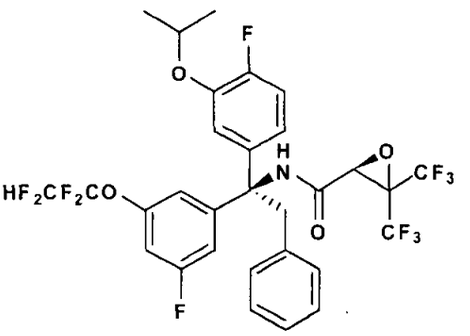

Un matraz de fondo redondo se cargó con Resina de poliestireno IIDQ (493 mg, 1.5 mmoles/g, 0.74 mmoles) y acetonitrilo (5 ml) y se selló con un septo de hule. La suspensión se vació y se volvió a mojar con argón tres veces. A la mezcla espesa resultante se agregó una solución de (R)-

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1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina, preparada como se describe en el Procedimientos 109, 110, 111, 112, 113, 114, (180 mg, 0.37 mmoles) y ácido 4,4,4-trifluoro-3-(trifluorometil)crotónico (93 mg, 0.45 mmoles) en acetonitrilo (5 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se filtró y el producto filtrado se concentró bajo presión reducida y se purificó cromatografía ISCO (40 g columna) al usar hexano/EtOAc (0-15% durante 30 min) para dar la (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)but-2-enamida (Ejemplo 291) como un sólido blanco a un tiempo de retención de 20 min (199 mg, 74% rendimiento). CLEM: T.R. = 2.18 min [M+H] 674.33 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.25 min, Pureza 98% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.19 ppm, 3 H, m; 7.02 ppm, 1 H, dd, $J$=10.55, 8.79 Hz; 6.95 ppm, 3 H, m; 6.85 ppm, 1 H, s; 6.67 ppm, 3 H, d, $J$=7.03 Hz; 6.62 ppm, 1 H,

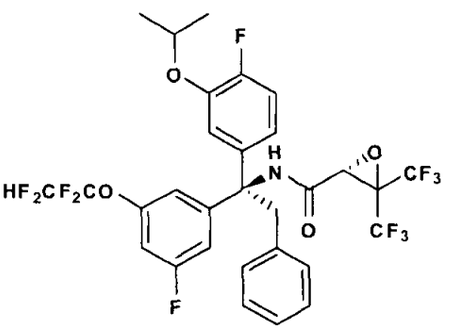
m; 6.13 ppm, 1 H, s; 5.88 ppm, 1 H, tt, *J*=53.00, 2.86, 2.75 Hz; 4.36 ppm, 1 H, ddd, *J*=11.97, 6.15, 6.04 Hz; 3.99 ppm, 1 H, d, *J*=13.18 Hz; 3.71 ppm, 1 H, d, *J*=13.18 Hz; 1.26 ppm, 6 H, m.

**EJEMPLO 292A**



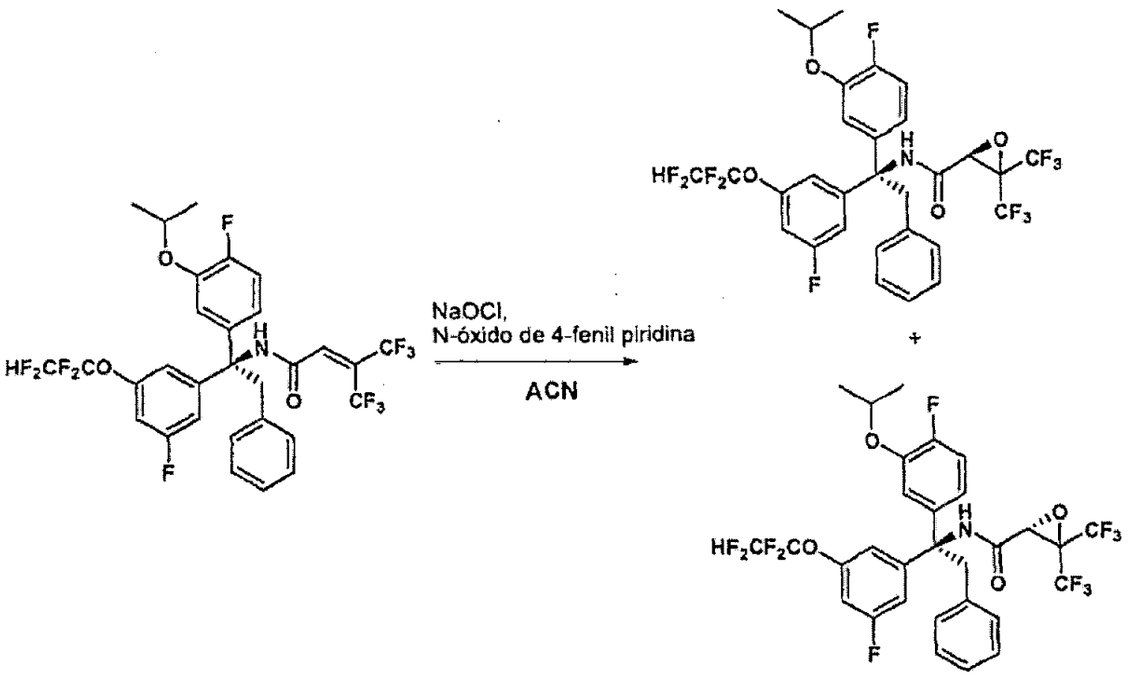
**(S)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida**

**EJEMPLO 292B**



**(R)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida**

**Procedimiento 91**




A 0°C una solución de (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)but-2-enamida (Ejemplo 291, 130 mg, 0.19 mmoles) y N-óxido de 4-fenil piridina (26 mg, 0.15 mmoles) en acetonitrilo (5 ml) se agregó Una solución NaOCl (206 µl, cloro % en peso 10-3%, 0.58 mmoles). La mezcla de reacción se agitó a 0°C durante 10 min, luego a temperatura ambiente durante 1 h. Los solventes se retiraron bajo presión reducida y el residuo se diluyó con EtOAc (30 ml), se lavó con $Na_2SO_3$ saturado (30 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo resultante se dejó purificar por cromatografía ISCO (columna 40 g, relación de flujo 25 ml/min) al usar hexanos/EtOAc (0-10%

durante 30 min) para dar la N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida como una mezcla diaestereomérica a un tiempo de retención de 26 min (97 mg, 74% rendimiento). La mezcla de diaestereómeros se separó por una columna CLAR quiral preparativa Chiralpak AD 20, 5 × 50 cm, eluyendo con 5% IPA/Heptano con relación de flujo 50 ml/min.

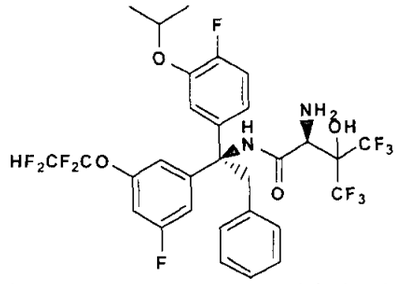
La (S)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (Ejemplo 292A) se eluyó a un tiempo de retención de 30 min y se aisló como un aceite transparente (50 mg, rendimiento 51%). CLEM: T.R. = 2.25 min [M+H] 690.30 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.225 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.20 ppm, 3 H, ddd, *J*=14.72, 7.25, 7.03 Hz; 6.98 ppm, 3 H, m; 6.90 ppm, 1 H, s; 6.60 ppm, 5 H, m; 5.87 ppm, 1H, t; 4.31 ppm, 1 H, ddd, *J*=12.19, 6.04, 5.93 Hz; 4.10 ppm, 1 H, d, *J*=13.18 Hz; 3.95 ppm, 1 H, s; 3.51 ppm, 1 H, d, *J*=13.18 Hz; 1.28 ppm, 3 H, d, *J*=5.71 Hz; 1.21p pm, 3 H, d,

*J*=5.71 Hz.

La (R)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (Ejemplo 292B) se eluyó a un tiempo de retención de 40 min y se aisló como un aceite transparente (38 mg, rendimiento 39%). CLEM: T.R. = 2.27 min [M+H] 690.30 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.20 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.20 ppm, 3 H, m; 7.05 ppm, 1 H, m; 6.95 ppm, 1 H, d, *J*=7.91 Hz; 6.85 ppm, 2 H, m; 6.72 ppm, 2 H, m; 6.64 ppm, 2 H, d, *J*=7.47 Hz; 6.59 ppm, 1 H, s; 5.87 ppm, 1H, m; 4.36 ppm, 1 H, m; 3.92 ppm, 1 H, m; 3.88 ppm, 1 H, m; 3.70 ppm, 1 H, m; 1.26 ppm, 6 H,9 m.

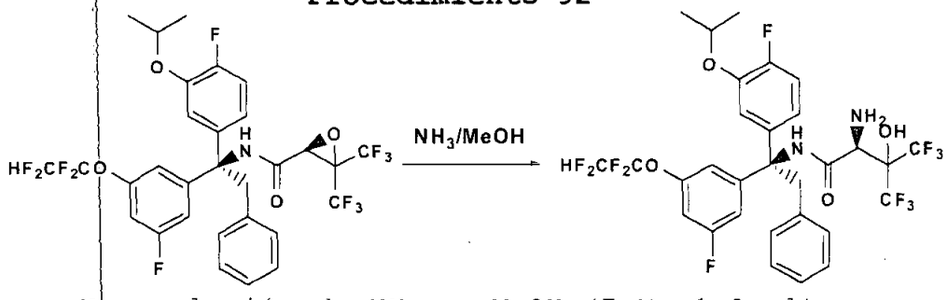
La estereoquímica relativa de (S)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (Ejemplo 292A) y (R)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (Ejemplo 292B) se asignó arbitrariamente.

**EJEMPLO 293**



**(S)-2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil)butanamida**

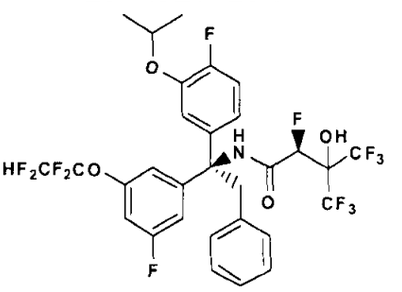
**Procedimiento 92**



Una solución de $NH_3$ en MeOH (7 M, 1.0 ml) se agregó a (S)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (Ejemplo 292A, 28 mg, 0.04 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró y se purificó por CLAR preparativa (columna Shimadzu-Phenomenex Luna AXIA 5µ, 21.2 × 100 mm eluyendo con 30-100% ACN (90% en $H_2O$, 0.1%TFA) gradiente durante 14 min con relación de flujo 20 ml/min y detección UV a 220 nm). La (S)-2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-

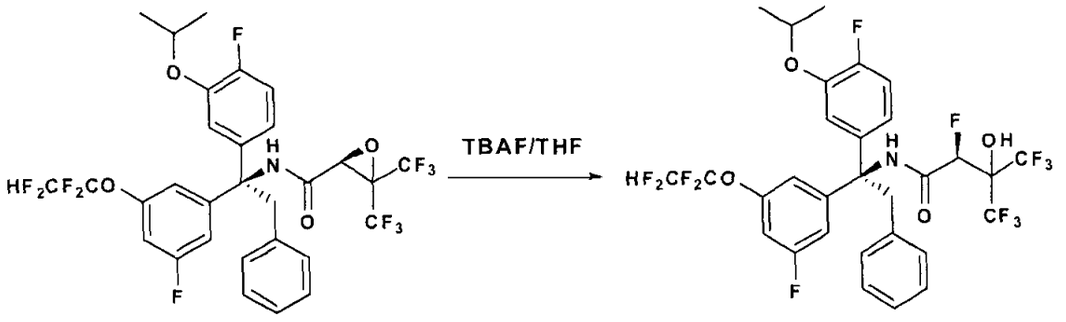
isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil)butanamida (Ejemplo 293) se eluyó a un tiempo de retención de 12.83 min y se aisló como un aceite transparente (20 mg, rendimiento 70%). CLEM: T.R. = 2.11 min [M+H] 707.41 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 3.99 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400 MHz $^1H$ ($CDCl_3$) 9.00 ppm, 1 H, s; 7.19 ppm, 3 H, m; 7.04 ppm, 1 H, m; 6.93 ppm, 1 H, d, $J$=8.79 Hz; 6.76 ppm, 4 H, m; 6.64 ppm, 2 H, d, $J$=7.03 Hz; 5.8 ppm, 1H, m; 4.38 ppm, 1 H, dq, $J$=6.15, 6.01 Hz; 3.87 ppm, 1 H, m; 3.70 ppm, 2 H, m; 1.89 ppm, 2 H, s; 1.28 ppm, 6 H, m.

**EJEMPLO 294**




**(S)-2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil)butanamida**

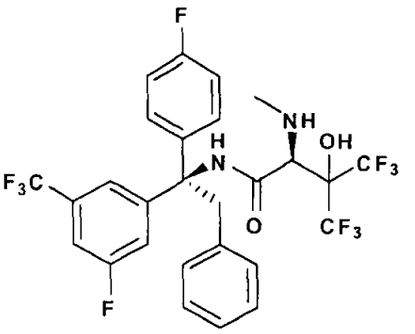
**Procedimiento 93**




A una solución de (S)-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (Ejemplo 292A, 25 mg, 0.036 mmoles) en THF (0.5 ml) se agregó TBAF (72 µl, 1.0 M solución en THF, 0.072 mmoles). La mezcla de reacción se calentó a 60°C bajo radiación por microondas durante 10 min. El solvente se retiró bajo presión reducida y el residuo se purificó por CLAR preparativa (columna Shimadzu-YMC ODS 5µ, 20 × 100 mm eluyendo con 30-100% ACN (90% en $H_2O$, 0.1%TFA) gradiente durante 18 min con relación de flujo 20 ml/min y detección UV a 220 nm). La (S)-2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil)butanamida (Ejemplo 294) se eluyó a un tiempo de retención de 17.28 min y se aisló como un aceite transparente (14 mg, rendimiento 55%). La estereoquímica de (S)-2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-

tetrafluoroetoxi)fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil)butanamida (Ejemplo 294) se asignó arbitrariamente. CLEM: T.R. = 2.22 min [M+H] 710.39 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.18 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.26 ppm, 1 H, m; 7.21 ppm, 3 H, m; 7.07 ppm, 1 H, m; 6.96 ppm, 1 H, d, *J*=8.79 Hz; 6.78 ppm, 4 H, m; 6.64 ppm, 2 H, d, *J*=7.15 Hz; 6.50 ppm, 1 H, s; 5.87 ppm, 1 H, tt, *J*=52.97, 2.61, 2.47 Hz; 5.10 ppm, 1H, d, *J*=46.17Hz; 4.41 ppm, 1 H, dt, *J*=12.09, 6.05 Hz; 3.97 ppm, 1 H, d, *J*=13.19 Hz; 3.58 ppm, 1 H, d, *J*=13.19 Hz; 1.30 ppm, 6 H, t, *J*=6.32 Hz.

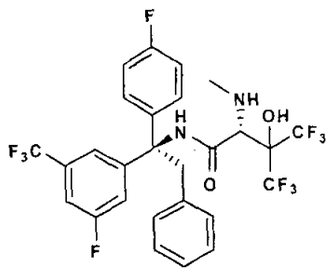
**EJEMPLO 295A**




**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(metilamino)-3-(trifluorometil)butanamida**

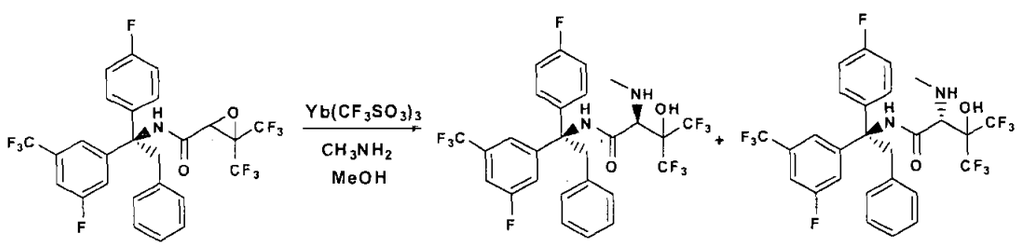
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**EJEMPLO 295B**



**(R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(metilamino)-3-(trifluorometil)butanamida**

**Procedimiento 94**




A una mezcla de diaestereómeros de N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (40 mg, 0.069 mmoles), preparada como se describe en el Procedimiento 90 y 91, se agregó $Yb(CF_3SO_3)_3$ (10 mg) y metilamina en MeOH (0.2 ml, solución 2M en MeOH). La reacción se calentó a 60°C bajo radiación por microondas durante 10 min y luego se concentró bajo presión reducida. El residuo se diluyó con EtOAc (25 ml) y se lavó con $Na_2CO_3$ saturado, se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó por una columna CLAR preparativa Shimadzu-YMC-ODS-A 5µ, 20 × 100 mm eluyendo

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con 30-100% MeOH (90% en $H_2O$, 0.1%TFA) gradiente durante 30 min con relación de flujo 20 ml/min y detección UV a 220 nm.

La (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(metilamino)-3-(trifluorometil)butanamida (Ejemplo 295A) se eluyó a un tiempo de retención de 22.96 min y se aisló como un aceite transparente (4 mg, rendimiento 9%). CLEM: T.R. = 4.17 min [M+H] 615.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 10 mM $NH_4OAc$; 4 ml/min, observando a 220 nm); CLAR: T.R. = 3.87 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 9.24 ppm, 1 H, s; 7.54 ppm, 1 H, s; 7.30 ppm, 3 H, m; 7.20 ppm, 3 H, m; 7.01 ppm, 2 H, t, $J$=8.35 Hz; 6.85 ppm, 2 H, m; 6.60 ppm, 2 H, d, $J$=7.03 Hz; 4.29 ppm, 1 H, d, $J$=12.74 Hz; 3.47 ppm, 1 H, d, $J$=12.74 Hz; 3.32 ppm, 1 H, s; 2.32 ppm, 3 H, s.

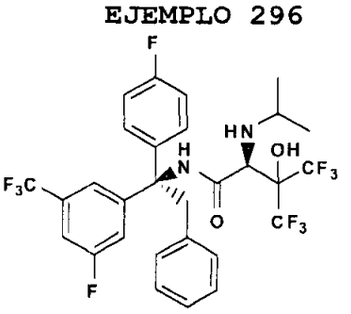
La (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(metilamino)-3-(trifluorometil)butanamida (Ejemplo 295B) se eluyó a un tiempo de retención de 23.45 min y se aisló como un aceite transparente (5 mg, rendimiento 11%). CLEM: 4.16 min [M+H] 615.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que

1402

contiene 10 mM $NH_4OAc$; 4 ml/min, observando a 220 nm); CLAR: T.R. = 3.93 min, Pureza 92% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 9.06 ppm, 1 H, s; 7.30 ppm, 2 H, m; 7.23 ppm, 3 H, d, *J*=5.71 Hz; 7.17 ppm, 2 H, t, *J*=7.25 Hz; 7.08 ppm, 2 H, t, *J*=8.57 Hz; 7.00 ppm, 1 H, m; 6.91 ppm, 1 H, d, *J*=10.11 Hz; 6.60 ppm, 2 H, d, *J*=7.03 Hz; 4.14 ppm, 1 H, m; 3.98 ppm, 1 H, s; 3.52 ppm, 2 H, m; 3.39 ppm, 2 H, m; 2.37 ppm, 3 H, s.

La estereoquímica de (S)-4,4,4-Trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(metilamino)-3-(trifluorometil)butanamida (Ejemplo 295A) y (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(metilamino)-3-(trifluorometil)butanamida isómero B (Ejemplo 295B) se asignó arbitrariamente.

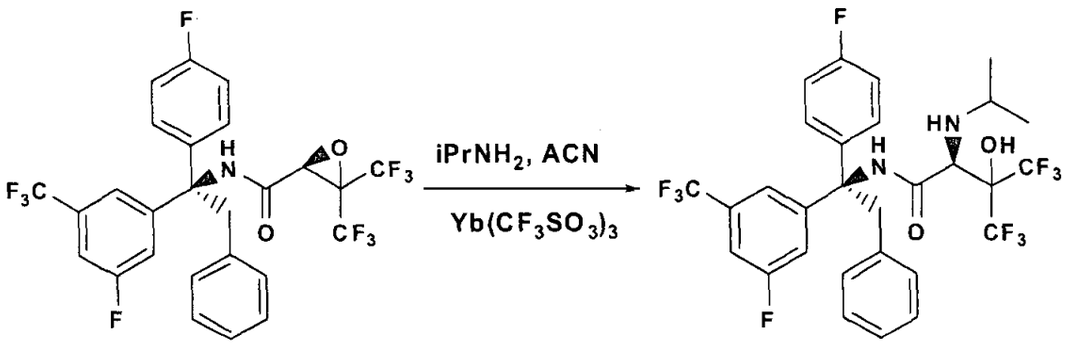
**EJEMPLO 296**




**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(isopropilamino)-3-(trifluorometil)butanamida**

1403

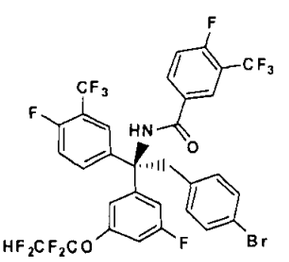
**Procedimiento 95**




A una solución de (S)-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3,3-bis(trifluorometil)oxirano-2-carboxamida (20 mg, 0.034 mmoles), preparada como se describe en el Procedimiento 90 y 91, en ACN (0.5 ml) se agregó $Yb(CF_3SO_3)_3$ (10 mg) y isopropilamina (10 µl, 0.1 mmoles). La mezcla de reacción se calentó a 60°C bajo radiación por microondas durante 10 min y luego se concentró bajo presión reducida. El residuo se diluyó con EtOAc (25 ml) y la capa orgánica se lavó por $Na_2CO_3$ saturado, se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó por una columna CLAR preparativa Shimadzu-YMC-ODS-A 5µ, 20 × 100 mm eluyendo con 30-100% MeOH (90% en $H_2O$, 0.1%TFA) gradiente durante 30 min con relación de flujo 20 ml/min y detección UV a 220 nm. La (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(isopropilamino)-3-(trifluorometil)butanamida (Ejemplo 296) se eluyó a un tiempo de retención de 27.36 min y se aisló como un aceite transparente (12 mg, rendimiento

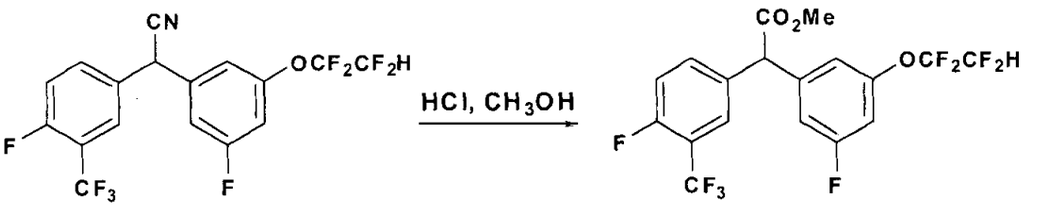
54%). CLEM: T.R. = 2.15 min [M+H] 643.4 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA, 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.293 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm). RMN: 400 MHz $^1H$ ($CDCl_3$) 9.23 ppm, 1 H, s; 7.77 ppm, 1 H, s; 7.30 ppm, 3 H, m; 7.20 ppm, 1 H, m; 7.14 ppm, 2 H, t, *J*=7.25 Hz; 7.02 ppm, 2 H, t, *J*=8.35 Hz; 6.93 ppm, 1 H, d, *J*=4.83 Hz; 6.60 ppm, 2 H, d, *J*=7.03 Hz; 4.29 ppm, 1 H, d, *J*=13.18 Hz; 3.51 ppm, 1 H, d, *J*=5.27 Hz; 3.47 ppm, 1 H, d, *J*=12.74 Hz; 2.74 ppm, 1 H, m; 1.87 ppm, 1 H, s; 1.04 ppm, 3 H, d, *J*=6.15 Hz; 0.71 ppm, 3 H, d, *J*=6.15 Hz. La estereoquímica de (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(isopropilamino)-3-(trifluorometil)butanamida (Ejemplo 296) se asignó arbitrariamente.

**EJEMPLO 297**




**(R)-N-(2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 96**

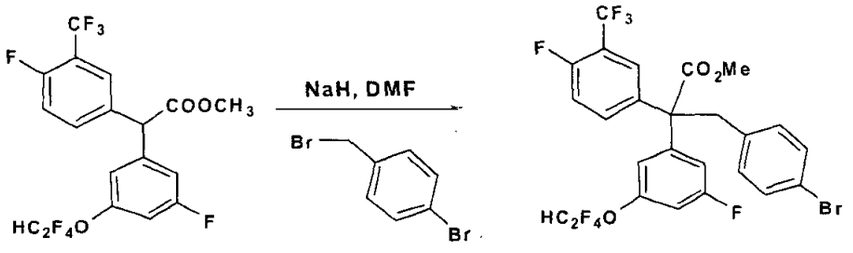



Una solución de 2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)acetonitrilo preparado como se describe en el Procedimiento 3, 4 y 73 (72% rendimiento, 453 mg, 1.1 mmoles) en MeOH (18 ml) se enfrió a 0°C y con gas HCl saturado. La solución resultante se calentó a reflujo durante la noche. La mezcla de reacción se concentró bajo presión reducida y el residuo se dividió entre EtOAc y NaCl saturado. La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó por ISCO (40 g columna de gel de sílice, 0-40 % EtOAc/hexano durante 50 min) para producir 2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)acetato de metilo como un aceite incoloro (394 mg, 80% rendimiento). CLEM: T.R. = 2.05 min [M+H] 446.97 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.%TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.22 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm); 1H RMN

1406

(400 MHz, $CDCl_3$) δ ppm 7.53 (1 H, d, *J*=6.59 Hz), 7.47 - 7.51 (1 H, m), 7.19 (1 H, t, *J*=9.23 Hz), 6.9-6.97 (3 H, m), 5.76-6.03 (1 H, m), 3.78 (3 H, s).

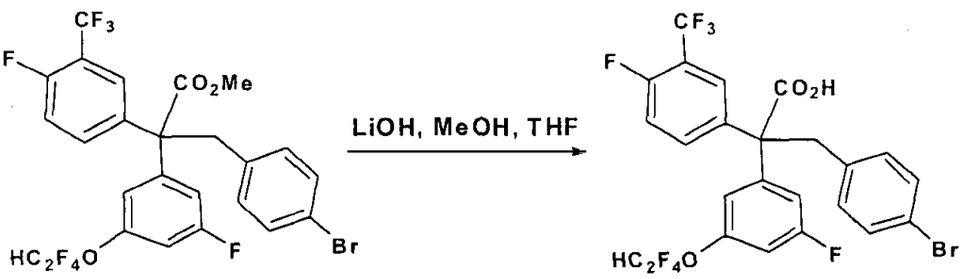
**Procedimiento 97**




A una suspensión de NaH (60% en aceite, 66 mg, 1.65 mmoles) en DMF (3 ml) a 0°C se agregó una solución de 2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)acetato de metilo (600 mg, 1.34 mmoles) en una porción. La mezcla de reacción se agitó a 0°C durante 10 min seguido por la adición de una solución de 4-bromobromuro de bencilo (343 mg, 1.37 mmoles) en DMF (2 ml). La reacción se agitó a 0°C durante 5 min y se apagó por la adición de $NH_4Cl$ saturado. La mezcla se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar 3-(4-bromofenil)-2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)propanoato de metilo como un aceite incoloro (865 mg, 100% rendimiento). CLEM: T.R. = 2.26 min, sin ionización (columna Phenomenex Luna C18 4.6x30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de

1407

onda 220 nm); CLAR: T.R. = 4.48 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm); 1H RMN (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.33 (1 H, m), 7.21-7.27 (4 H, m), 7.11 (1 H, t, *J*=9.23 Hz), 6.94 (1 H, d, *J*=8.79 Hz), 6.82 (1 H, d, *J*=9.67 Hz), 6.80 (1 H, s), 6.52 (2 H, d, *J*=8.35 Hz), 5.87 (1 H, t, *J*=53.2 Hz), 3.75 (3 H, s), 3.56 - 3.66 (2 H, m).

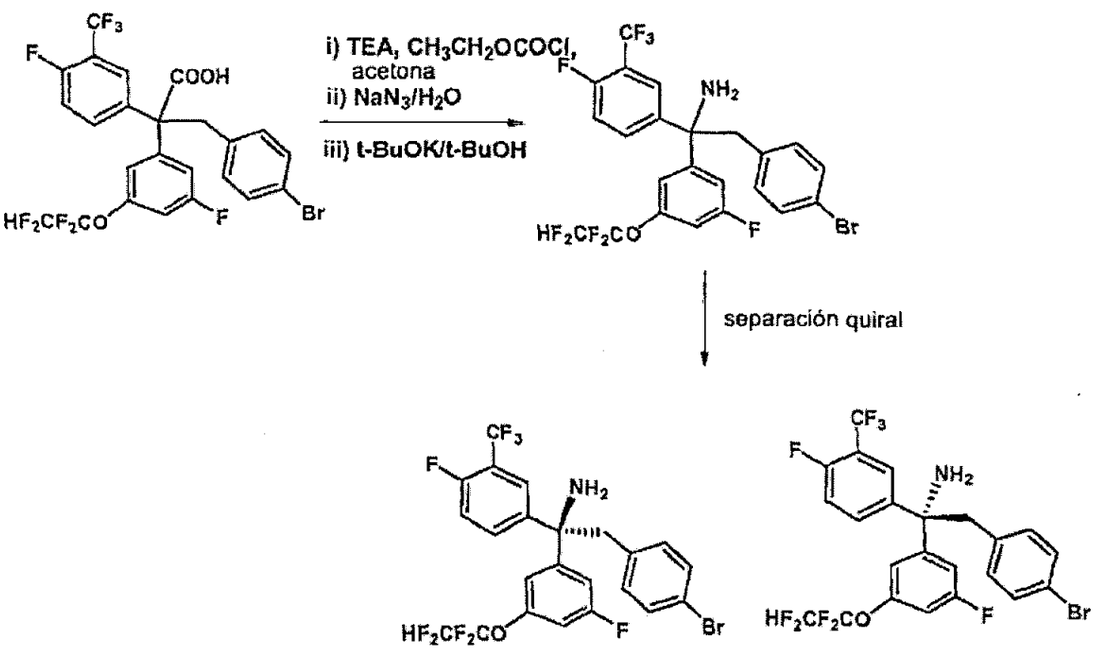



Una mezcla de 3-(4-bromofenil)-2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)propanoato de metilo (865 mg, 1.34 mmoles) en MeOH (10 ml)/THF (20 ml) y LiOH (2 N, 10 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se hizo ácida por la adición de HCl 1N a un pH = 1~2 y se concentró. El residuo resultante se dividió entre EtOAc y NaCl saturado. La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó por ISCO (40 g columna de gel de sílice, 0-10% MeOH/DCM durante 30 min) para producir el ácido 3-(4-bromofenil)-2-(4-fluoro-3-

1408

(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)propanoico como un aceite incoloro (650 mg, 81% rendimiento). CLEM: T.R. = 2.17 min [M+H] 600.88 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.%TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.45 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm).

**Procedimiento 98**



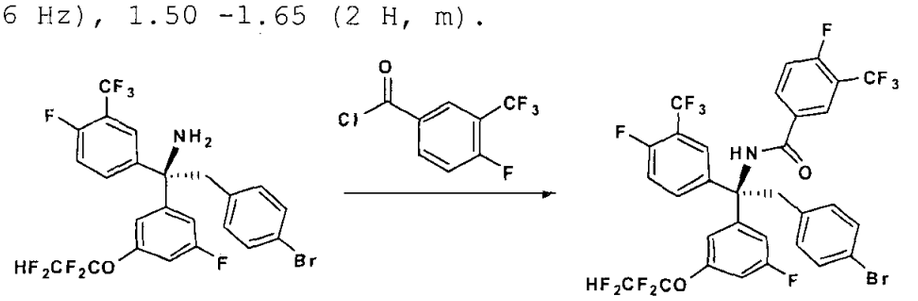

A 0°C una solución de ácido 3-(4-bromofenil)-2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)propanoico (1.59 g, 2.64 mmoles) en acetona (30 ml) se agregó TEA (442 µL, 3.17 mmoles) seguido

por cloroformiato de etilo (303 µL, 3.17 mmoles). La mezcla de reacción se agitó a 0°C durante 45 min y $NaN_3$ (343 mg, 5.28 mmoles) se agregó. La reacción se agitó a 0°C durante 1 h, se apagó por la adición de agua y la capa acuosa se extrajo con tolueno (3 x 30 ml). Las capas orgánicas combinadas se lavaron con NaCl saturado, se secaron sobre sulfato de magnesio, se filtraron y se concentraron bajo presión reducida. El residuo resultante se diluyó con tolueno (10 ml) y se calentó a 90°C durante 6 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se disolvió en t-BuOH/THF (1:1, 20 ml) y se trató con t-BuOK/t-BuOH (1 N, 13.2 ml, 13.2 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se calentó a 85°C durante 3 h. La mezcla de reacción se apagó por la adición de agua y la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con NaCl saturado, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó por ISCO (40 g columna de gel de sílice, 0-40% EtOAc/hexano durante 40 min para producir 2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etanamina como un aceite incoloro (1.2 g, 82% rendimiento). CLEM: T.R. = 1.82 min [M+H] 556.8 (columna *Phenomenex Luna* C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación

de flujo 5 ml/min, longitud de onda 220 nm). 1H RMN (400 MHz, $CDCl_3$) δ ppm 7.61 (1 H, d, *J*=6.15 Hz), 7.48 - 7.53 (1 H, m), 7.30 (1 H, d, *J*=7.91 Hz), 7.15 (1 H, t, *J*=9.23 Hz), 6.96 - 7.00 (2 H, m), 6.89 (1 H, d, *J*=8.79 Hz), 6.61 (2 H, d, *J*=7.91 Hz), 5.89 (1 H, t, *J*=53 Hz), 3.49 (1 H, d, *J*=13.6 Hz), 3.43 (1 H, d, *J*=13.6 Hz), 1.50 -1.65 (2 H, m).

La 2-(4-Bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etanamina (racémico, 510 mg) se sometió a separación CLAR preparativa quiral (columna quiral OD 10 micras 4.6 x 250 mm, eluyendo con 20% de iPA/heptano/0.1% DEA) para dar (R)-2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etanamina (211 mg) como un aceite incoloro y (S)-2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etanamina (195 mg) como un aceite incoloro. Para la (R)-2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etanamina: CLAR analítica quiral: T.R. = 6.0 min, 100% ee (columna quiral OD 10 micras 4.6x250 mm, eluyendo con 20%IPA/heptano/0.1%DEA, relación de flujo 1 ml/min, longitud de onda 220 nm); CLEM: T.R. = 1.82 min [M+H] 556.8 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente,

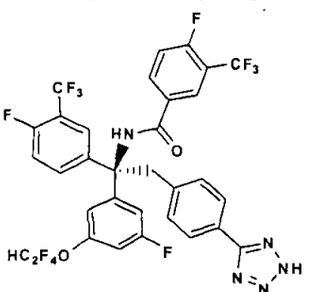
relación de flujo 5 ml/min, longitud de onda 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.61 (1 H, d, *J*=6.15 Hz), 7.48 - 7.53 (1 H, m), 7.30 (1 H, d, *J*=7.91 Hz), 7.15 (1 H, t, *J*=9.23 Hz), 6.96 - 7.00 (2 H, m), 6.89 (1 H, d, *J*=8.79 Hz), 6.61 (2 H, d, *J*=7.91 Hz), 5.89 (1 H, t, *J*=53 Hz), 3.49 (1 H, d, *J*=13.6 Hz), 3.43 (1 H, d, *J*=13.6 Hz), 1.50 -1.65 (2 H, m). Para la (S)-2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etanamina isómero B: CLAR analítica quiral: T.R. = 7.5 min, 100% ee (columna quiral OD 10 micras 4.6 x 250 mm, eluyendo con 20% IPA/heptano/0.1% DEA, relación de flujo 1 ml/min, longitud de onda 220 nm); CLEM: T.R. = 1.82 min [M+H] 556.8 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.61 (1 H, d, *J*=6.15 Hz), 7.48 - 7.53 (1 H, m), 7.30 (1 H, d, *J*=7.91 Hz), 7.15 (1 H, t, *J*=9.23 Hz), 6.96 - 7.00 (2 H, m), 6.89 (1 H, d, *J*=8.79 Hz), 6.61 (2 H, d, *J*=7.91 Hz), 5.89 (1 H, t, *J*=53 Hz), 3.49 (1 H, d, *J*=13.6 Hz), 3.43 (1 H, d, *J*=13.6 Hz), 1.50 -1.65 (2 H, m).




Siguiendo el procedimiento 7, la (R)-N-(2-(4-

bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 297) se preparó como una espuma blanca (471 mg, 88% rendimiento). CLEM: T.R. = 2.25 min [M+H] 761.8 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.52 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm); 1H RMN (400 MHz, $CDCl_3$) δ ppm 7.96 (1 H, dd, *J*=6.59, 2.20 Hz), 7.81 - 7.85 (1 H, m), 7.39 - 7.44 (2 H, m), 7.30 - 7.34 (2 H, m), 7.21 (1 H, t, *J*=9.45 Hz), 6.99 (1 H, d, *J*=8.79 Hz), 6.79 - 6.84 (2 H, m), 6.57 (1 H, s), 6.55 (2 H, d, *J*=8.35 Hz), 5.89 (1 H, t, *J*=54 Hz), 3.95 (1 H, d, *J*=13.2 Hz), 3.86 (1 H, d, *J*=13.2 Hz).

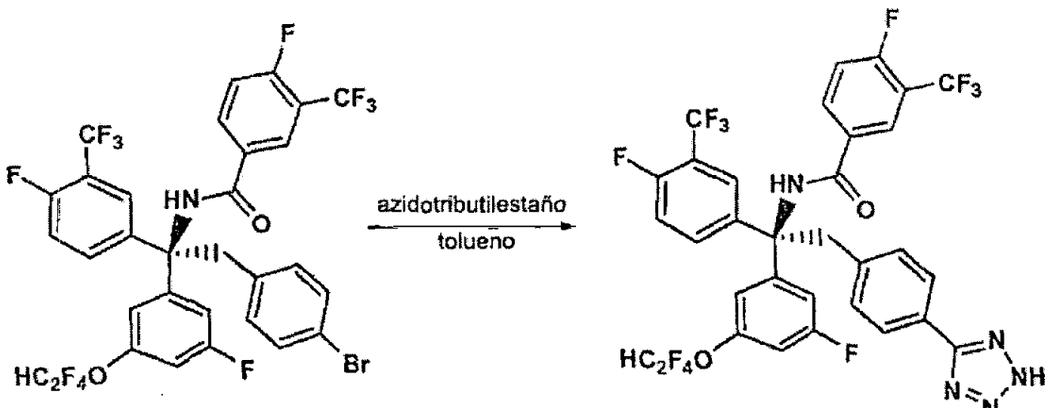
**EJEMPLO 298**




**(R)-N-(2-(4-(2H-tetrazol-5-il)fenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetil)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida**

1413

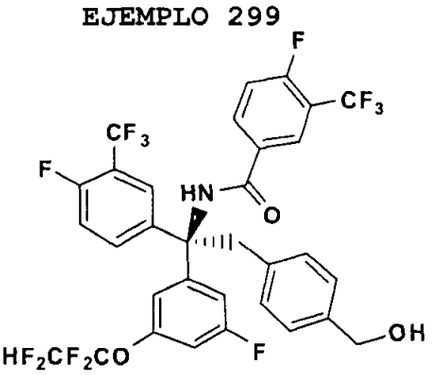
**Procedimiento 99**




Una mezcla de (R)-N-(2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 297, 20 mg, 0.028 mmoles) y azidotributilestaño (38 µL, 0.14 mmoles) en tolueno se calentó a 100°C durante la noche. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por ISCO (columna de gel de sílice 4 g, 0-10% MeOH/DCM) para dar (R)-N-(2-(4-(2H-tetrazol-5-il)fenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetil)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 298) como un sólido blanco (11 mg, 52% rendimiento). CLEM: T.R. = 2.07 min [M+H] 752.3 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.26 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo

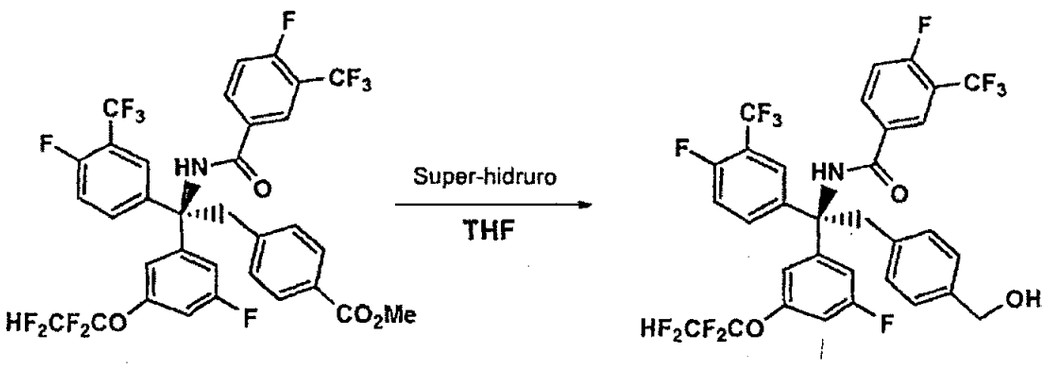
4 ml/min, longitud de onda 220 nm). 1H RMN (400 MHz, $CD_3OD$) δ ppm 8.98 (1 H, s), 7.95 - 7.98 (2 H, m), 7.71 (2 H, d, *J*=8.35 Hz), 7.49 (1 H, dd, *J*=7.47, 3.95 Hz), 7.34 - 7.42 (2 H, m), 7.22 (1 H, t, *J*=9.45 Hz), 7.04 (1 H, d, *J*=10.11 Hz), 6.94 - 6.98 (2 H, m), 6.84 (2 H, d, *J*=8.35 Hz), 6.18 (1 H, t, *J*=52.3 Hz), 4.11 (1H, d, *J*=12.7), 4.11 (1H, d, *J*=12.7).

**EJEMPLO 299**




**(R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(hidroximatil)fenil)etil)-3-(trifluorometil)benzamida**

**Procedimiento 100**



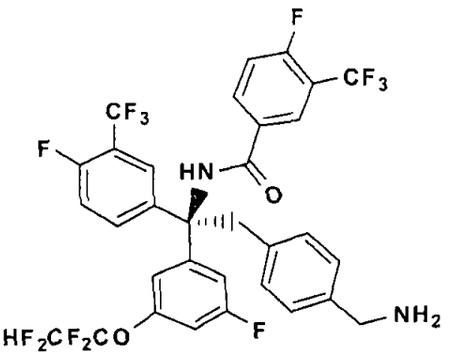

A una solución de 4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2-(4-fluoro-3-

(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)benzoato de (R)-metilo preparada como se describe en el Procedimiento 96, 97, 98, 56 y 57 (29 mg, 0.039 mmoles) en THF a -78°C se agregó una solución de trietilborohidruro de litio (1.0 M en THF, 0.5 ml, 0.5 mmoles). La mezcla resultante se agitó a -78°C durante 1.5 h. La reacción se apagó por la adición de 1 N NaOH (1 ml) y la capa acuosa se extrajo con EtOAc (15 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó por ISCO (12 g columna de gel de sílice, 0-50% EtOAc/hexano durante 30 min) para producir (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(hidroximatil)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 299) como una película incolora (22 mg, 79% rendimiento). CLEM: T.R. = 2.10 min [M+H] 714.31 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.0 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm); 1H RMN (400 MHz,$CDCl_3$) $\delta$ ppm 7.98 - 7.80 (1 H, m), 7.85 - 7.89 (1 H, m), 7.39 - 7.43 (3 H, m), 7.31 (1 H, t, *J*=9.23 Hz), 7.19 - 7.27 (1 H, m), 6.99 (1 H, d, *J*=8.79 Hz), 6.76 - 6.83 (5 H,

1416

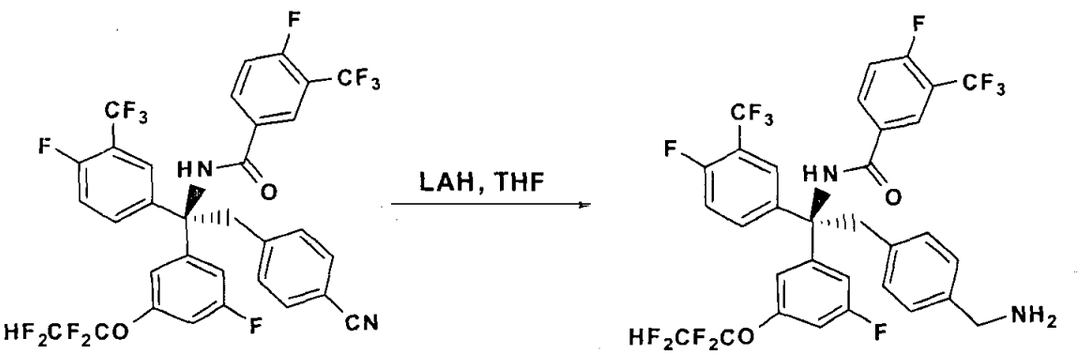
m), 5.89 (1 H, t, *J*=53.0 Hz), 4.16 (1 H, d, *J*=13.18 Hz), 4.02 (1 H, d, *J*=13.18 Hz).

**EJEMPLO 300**



**(R)-N-(2-(4-(aminometil)fenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 101**

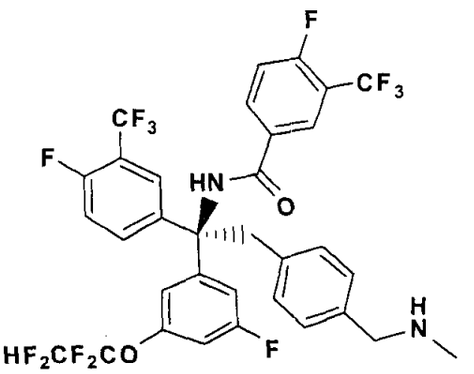



A una solución de (R)-N-(2-(4-cianofenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida, preparada como se describe en el Procedimiento 56, (77% rendimiento, 20 mg, 0.02 mmoles) en

THF (1.5 ml) a temperatura ambiente se agregó LAH (1.0 M en THF). La mezcla de reacción se agitó a temperatura ambiente durante 5 h, luego se apagó por la adición de 2 N LiOH. El sólido se retiró por filtración y el producto filtrado se concentró. El residuo resultante se purificó por CLAR preparativa (columna YMC Sunfire 5µ C18 30 x 100 mm, eluyendo con 20-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 10 min gradiente, relación de flujo 40 ml/min, longitud de onda 220 nm) para proporcionar (R)-N-(2-(4-(aminometil)fenil)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 300) como una película incolora (5 mg, 36% rendimiento). CLEM: RT = 1.8 min [M+H] 713.26 (columna Phenomenex Luna C18 4.6 x 30 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.31 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm). 1H RMN (400 MHz, $CD_3OD$) $\delta$ ppm 7.95 (1 H, d, $J$=6.59 Hz), 7.46 -7.48 (1 H, m), 7.36 7.41 (2 H, m), 7.22 (1 H, t, $J$=9.45 Hz), 7.16 (2 H, d, $J$=7.91 Hz), 6.99 (2 H, dd, $J$=16.48, 9.45 Hz), 6.93 (1 H, s), 6.73 (2 H, d,

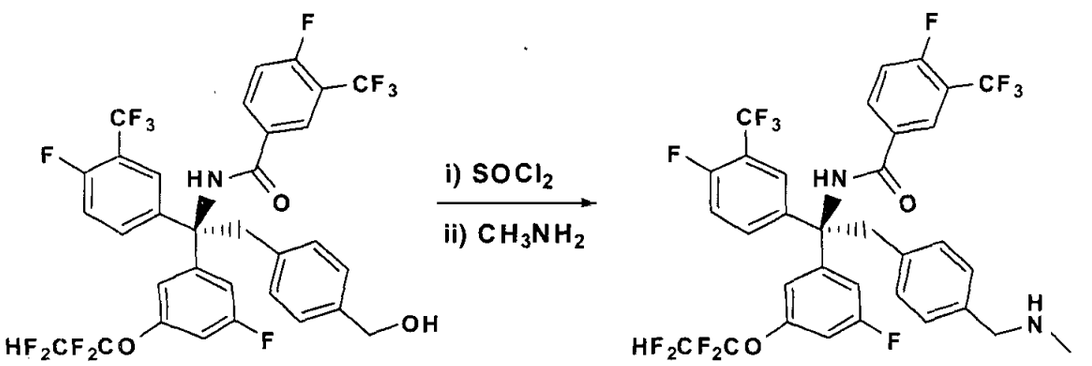
*J*=7.91 Hz), 6.21 H, t, *J* = 49.7 Hz), 4.01 - 4.06 (1 H, m), 3.93 - 3.99 (3 H, m).

**EJEMPLO 301**



**(R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-((metilamino)metil)fenil)etil)-3-(trifluorometil)benzamida**

**Procedimiento 102**

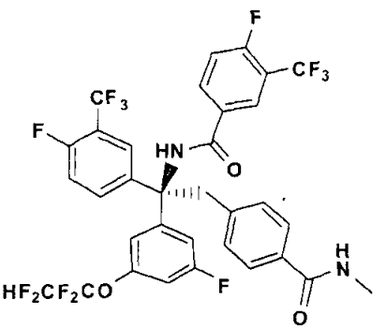



Una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(hidroximatil)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 299, 20 mg, 0.028 mmoles) en $SOCl_2$ se agitó a temperatura ambiente durante la noche. La mezcla de

reacción se concentró y el residuo se trató con una solución de metil amina en metanol (1.0 M, 2.0 ml, 2.0 mmoles) a temperatura ambiente durante la noche. El solvente se retiró y el residuo se purificó por CLAR preparativa (columna YMC Sunfire 5µ C18 30 x 100mm, eluyendo con 20-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 10 min gradiente, relación de flujo 40 ml/min, longitud de onda 220 nm) para proporcionar (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-((metilamino)metil)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 301) como un sólido blanco (13 mg, 65% rendimiento). CLEM: T.R. = 2.02 min [M+H] = 727.48 (columna Phenomenex Luna C18 4.6 x 30 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 3.11 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm). 1H RMN (400 MHz, $CD_3OD$) δ ppm 7.57 - 8.06 (2 H, m), 7.48 - 7.57 (1 H, m), 7.43 - 7.49 (2 H, m), 7.30 (1 H, t, *J*=9.45 Hz), 7.25 (2 H, d, *J*=7.91 Hz), 7.00 - 7.10 (3 H, m), 6.82 (2 H, d, *J*=8.35 Hz), 6.29 (1 H, t, *J*=46.6 Hz), 4.03 - 4.15 (4 H, m), 2.65 (3 H, s).

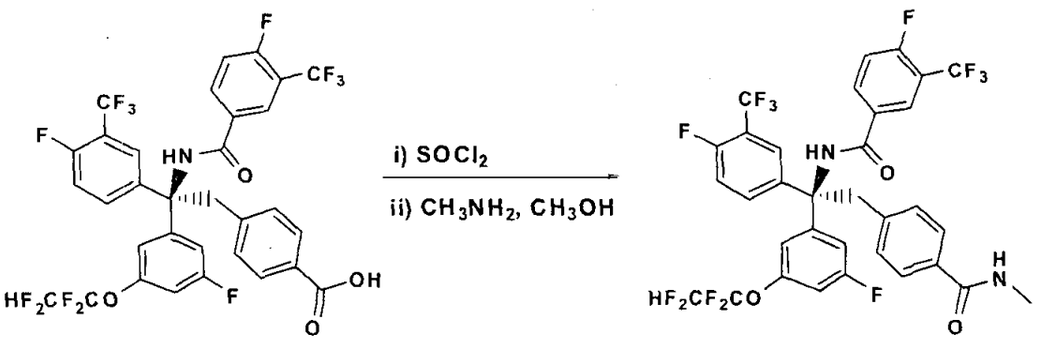
9420

**EJEMPLO 302**



**(R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(metilcarbamaceite)fenil)etil)-3-(trifluorometil)benzamida**

**Procedimiento 103**



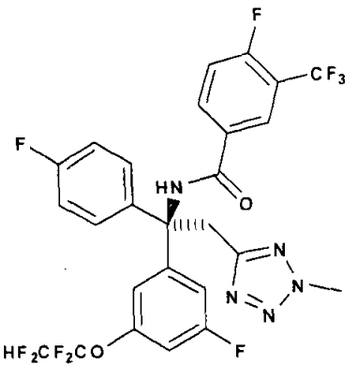

Una solución del ácido (R)-4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2-(4-fluoro-3-(trifluorometil)fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)benzoico, preparada como se describe en el Procedimiento 97, 98, 99 y 100, (65 mg, 0.09 mmoles) en $SOCl_2$ se calentó a 60°C durante la noche. La mezcla de reacción se concentró y 25 mg del residuo resultante se trató con una solución de metil amina en metanol (1.0 M, 2.0 ml, 2.0 mmoles) a

1421

temperatura ambiente durante la noche. El solvente se retiró y el residuo se purificó por ISCO (columna 12 g, 0-20% EtOAc/hexano) para producir (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(metilcarbamaceite)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 302) como un sólido blanco (14 mg, 85% rendimiento). CLEM: T.R. = 2.16 min [M+H] 741.55 (columna Phenomenex Luna C18 4.6 x 30 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: T.R. = 4.0 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) $\delta$ ppm 7.97 (1 H, d, $J$=5.71 Hz), 7.81 - 7.86 (1 H, m), 7.50 (2 H, d, $J$=7.91 Hz), 7.43 (2 H, d, $J$=5.27 Hz), 7.25 - 7.31 (1 H, m), 7.19 (1 H, t, $J$=9.45 Hz), 6.97 (1 H, d, $J$=8.35 Hz), 6.82 (2 H, d, $J$=4.83 Hz), 6.74 (2 H, d, $J$=7.91 Hz), 6.05 (1 H, d, $J$=4.83 Hz), 5.88 (1 H, t, $J$=52.1), 4.04 (1 H, d, $J$=13.2), 3.95 (1 H, d, $J$=13.2), 2.94 (3 H, d, $J$=4.83 Hz).

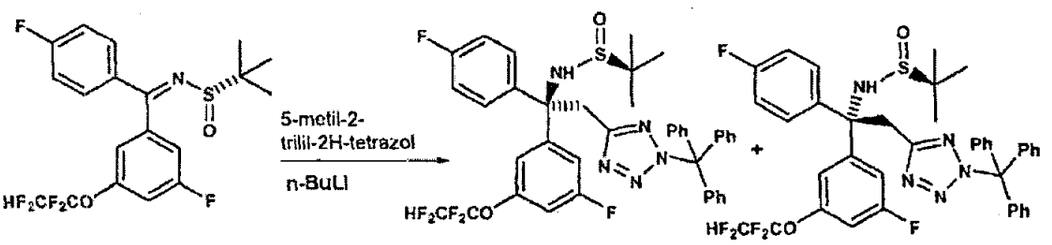
1422

**EJEMPLO 303**



**(*R*)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2-metil-2H-tetrazol-5-il)etil)-3-(trifluorometil)benzamida**

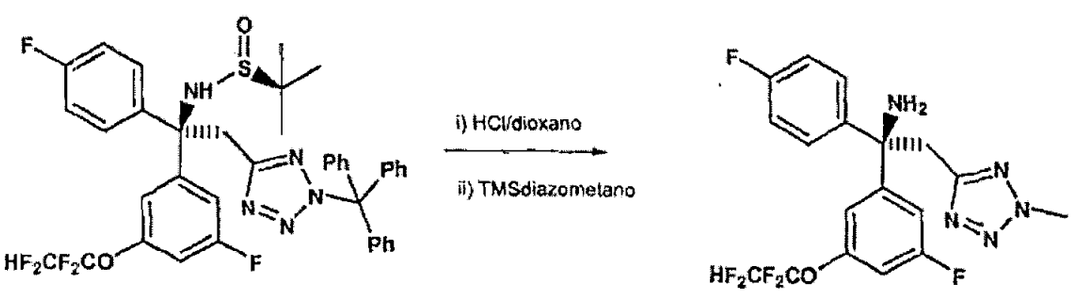
**Procedimiento 104**




A una solución de 5-metil-2-tritil-2H-tetrazol (0.90 g, 2.76 mmoles) en THF seco (20 ml) a -78°C bajo argón se agregó gota a gota n-BuLi (2.5 M en hexano, 1.2 ml, 3 mmoles). La solución resultante se agitó a -78°C durante 1 h, seguido por la adición gota a gota de una solución de (*R*)-N-((3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(4-fluorofenil)metileno)-2-metilpropano-2-sulfinamida, preparada como se describe en el Procedimiento 3, 4 y 5, (0.40 g, 0.91 mmoles) en THF (5 ml). La mezcla de reacción se agitó a -78°C hasta -70°C durante la noche. La mezcla de reacción se apagó

1423

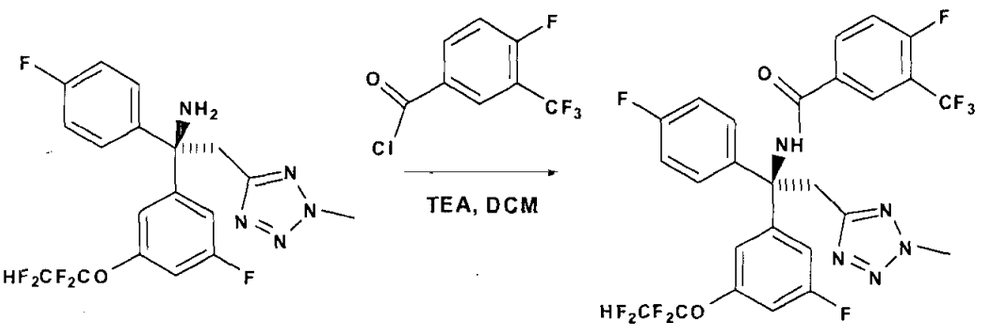
por la adición de $NH_4Cl$ saturado y la capa acuosa se extrajo con $Et_2O$ (2 x) y las capas orgánicas combinadas se lavaron con $H_2O$, NaCl saturado, se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El residuo se purificó por Cromatografía de vaporización instantánea ISCO (gel de sílice, hexanos/EtOAc) para dar (R)-N-((S)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2-tritil-2H-tetrazol-5-il)etil)-2-metilpropano-2-sulfinamida como el diaestereómero de rápida elución (90 mg, 13% rendimiento) y (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2-tritil-2H-tetrazol-5-il)etil)-2-metilpropano-2-sulfinamida como el diaestereómero de elución lenta (85 mg, 12% rendimiento).




A una solución de (R)-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2-tritil-2H-tetrazol-5-il)etil)-2-metilpropano-2-sulfinamida (60 mg, 0.079 mmoles) en MeOH (3 ml) se agregó 4 N HCl en dioxano (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 20 min, luego se concentró para producir (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-

1424

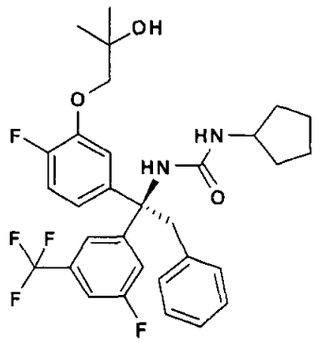
fluorofenil)-2-(2H-tetrazol-5-il)etanamina. CLEM: T.R. = 2.66 min [M+H] 418.55 (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.1% de TFA, 4 min gradiente, relación de flujo 4 ml/min, longitud de onda 220 nm). A una solución de ((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2H-tetrazol-5-il)etanamina en THF (3 ml) y MeOH (0.5 ml) se agregó (diazometil)trimetilsilano (2.0 M en hexanos, 0.05 ml). Después de agitar a temperatura ambiente durante 20 min, la mezcla de reacción se concentró y se purificó Por cromatografía de columna instantánea ISCO (gel de sílice, EtOAc) para dar ((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2-metil-2H-tetrazol-5-il)etanamina (10 mg, rendimiento: 30%). CLEM: T.R. = 2.83 min [M+H] 432.57 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).




Siguiendo el procedimiento 7, la ((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-(2-

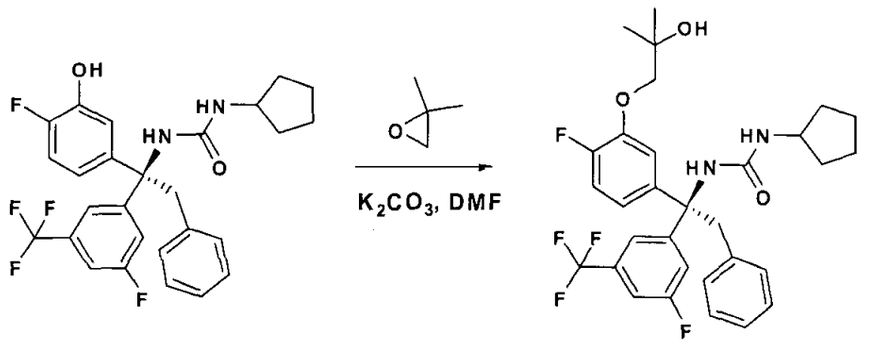
metil-2H-tetrazol-5-il)etanamina (Ejemplo 303) se obtuvo (10 mg, rendimiento 67%). CLEM: T.R. = 3.86 min [M+H] 622.01 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) ppm 8.30 (m, 2 H), 8.19 (m, 1 H), 7.37(m, 3 H), 7.05 (m, 4 H), 6.92 (d, *J*=8.6 Hz, 1 H), 5.89 (tt, J=53.05, 3.03 Hz, 1 H), 4.26 (s, 3 H), 4.09 (AB, *J*=15.2 Hz, 2 H).

**EJEMPLO 304**




**(R)-1-ciclopentil-3-(1-(4-fluoro-3-(2-hidroxi-2-metilpropoxi)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea**

**Procedimiento 105**




A una solución de (R)-1-ciclopentil-3-(1-(4-fluoro-

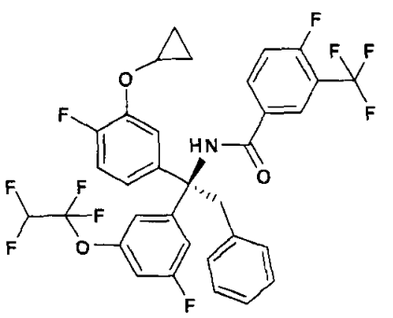
1426

3-hidroxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea, preparada como se describe en el Procedimiento 59, (20 mg, 0.039 mmoles) en DMF (0.1 ml) se agregó $K_2CO_3$ (12 mg, 0.086 mmoles), seguido por 2,2-dimetiloxirano (28 mg, 0.39 mmoles). La mezcla resultante se agitó a 60°C durante 16 h. La mezcla de reacción se filtró y el sólido se lavó con EtOAc. El producto filtrado se lavó con $H_2O$, NaCl saturado y se secó sobre $Na_2SO_4$ y se filtró. El solvente orgánico se evaporó bajo presión reducida y el residuo se purificó por CLAR preparativa (columna phenomenex AXIA Luna 75 X 30 mm, 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para resultar (R)-1-ciclopentil-3-(1-(4-fluoro-3-(2-hidroxi-2-metilpropoxi)fenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea (Ejemplo 304) como liofilato blanco (11 mg, 56% rendimiento). CLEM: T.R. = 4.066 min [M+H] 577.3 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm (tiempo de retención, tipo de columna, tamaño, solvente, relación de flujo, gradiente). RMN: 400MHz $^1H$ ($CD_3OD$) ppm 1.27 (d, *J*=2.20 Hz, 6 H), 1.32 - 1.49 (m, 2 H), 1.54 - 1.76 (m, 4 H), 1.81 - 1.98 (m, 2 H), 3.53 (d, *J*=9.23 Hz, 1 H), 3.69 (d, *J*=9.23 Hz, 1 H), 3.78 (d, *J*=12.74 Hz, 1 H), 3.91 (t, *J*=6.15 Hz, 1 H), 4.02 (d, *J*=12.74 Hz, 1 H), 6.63 - 6.70 (m, 1 H), 6.72 - 6.79

1427

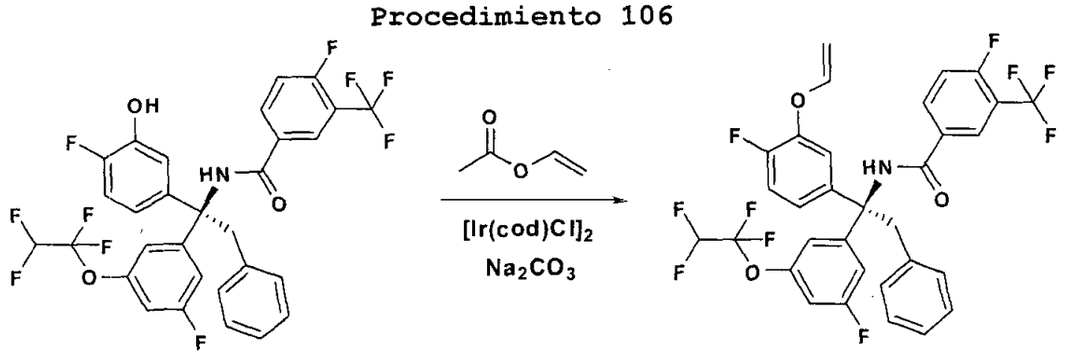
(m, 3 H), 7.01 (dd, *J*=10.99, 8.79 Hz, 1 H), 7.09 - 7.20 (m, 3 H), 7.27 - 7.42 (m, 3 H).

**EJEMPLO 305**



**(R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 106**

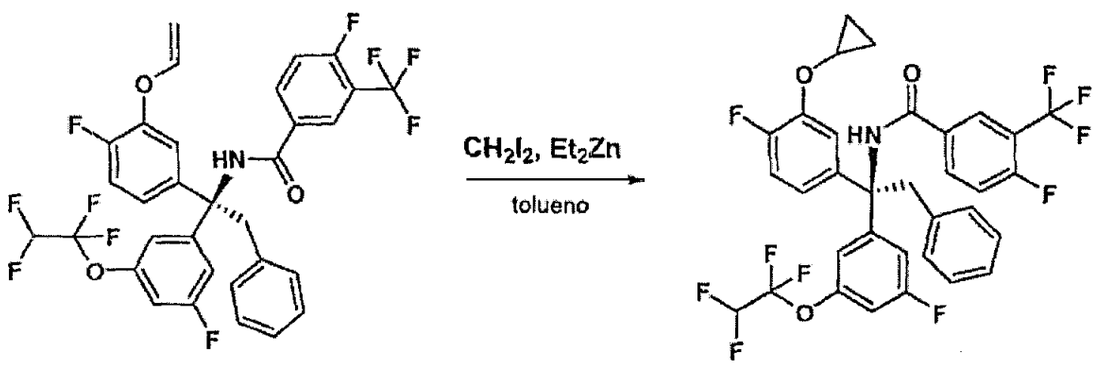



A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264, 100 mg, 0.158 mmoles) en tolueno (0.2 ml) se agregó $Na_2CO_3$ (25 mg, 0.235 mmoles) y una cantidad catalítica de $[Ir(cod)Cl]_2$ (2 mg), seguido por acetato de vinilo (68 mg, 0.79 mmoles). La mezcla de reacción se agitó a 100°C durante 16 h. La mezcla resultante se filtró y el sólido se lavó con $CH_2Cl_2$. La capa

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$CH_2Cl_2$ se lavó con 1 N NaOH, $H_2O$ y se secó sobre $Na_2SO_4$ y se filtró. El solvente se evaporó bajo presión reducida y el residuo se purificó por columna de gel de sílice al usar 0 hasta 60% EtOAc en hexano para resultar (R)-4-fluoro-N-(1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida eluyendo con 20% EtOAc en hexano como un aceite incoloro (80 mg, 77%). CLEM: T.R. = 2.237 min [M+H] 658.3 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm. RMN: 400MHz $^1H$ ($CD_3OD$) ppm 3.87 (d, *J*=12.74 Hz, 1 H), 4.05 - 4.15 (m, 1 H), 4.35 (dd, *J*=5.93, 1.98 Hz, 1 H), 4.55 (dd, *J*=13.84, 1.98 Hz, 1 H), 6.12 - 6.41 (m, 1 H), 6.48 (dd, *J*=13.62, 6.15 Hz, 1 H), 6.72 (d, *J*=7.03 Hz, 2 H), 6.87 - 7.24 (m, 9 H), 7.37 - 7.51 (m, 1 H), 7.88 - 8.04 (m, 2 H).

**Procedimiento 107**

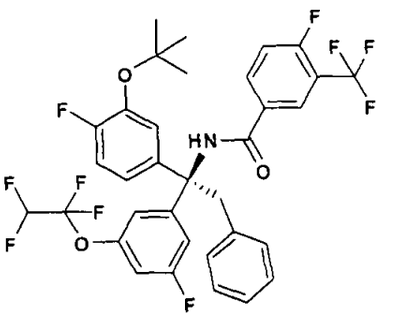



A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-

tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (66 mg, 0.10 mmoles) en 0.5 ml tolueno se agregó $Et_2Zn$ (1 N, 0.2 ml, 0.2 mmoles), seguido por $CH_2I_2$ (16 ml, 0.2 mmoles). La mezcla de reacción se agitó a 120°C durante 3 h. La mezcla de reacción se apagó por la adición de HCl 1N y la capa acuosa se extrajo con $CH_2Cl_2$. La capa orgánica se lavó con $NaHCO_3$ saturado y se concentró bajo presión reducida. El residuo resultante se purificó por Columna de gel de sílice ISCO al usar 0 hasta 50% hasta EtOAc en hexano como solventes de elución y CLAR preparativa (columna phenomenex AXIA Luna 75X30 mm, 5µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para resultar (R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 305) como liofilato blanco (36 mg, 52% rendimiento). CLEM: T.R. = 4.268 min [M+H] 672.3 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm. RMN: 400MHz $^1H$ ($CDCl_3$) ppm 0.45 - 0.73 (m, 4 H), 3.51 - 3.59 (m, 1 H), 3.76 (d, J=13.18 Hz, 1 H), 4.22 (d, J=12.74 Hz, 1 H), 6.13 - 6.44 (m, 1 H), 6.66 - 6.76 (m, 3 H), 6.97 - 7.08 (m, 3 H), 7.10 - 7.23 (m, 5 H), 7.42 - 7.50 (m, 1 H), 7.95 - 8.03 (m, 2 H).

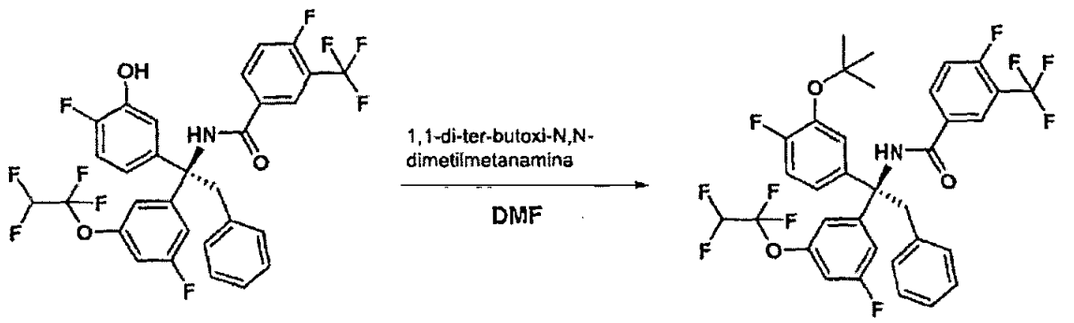
1430

**EJEMPLO 306**



**(R)-N-(1-(3-ter-butoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 108**

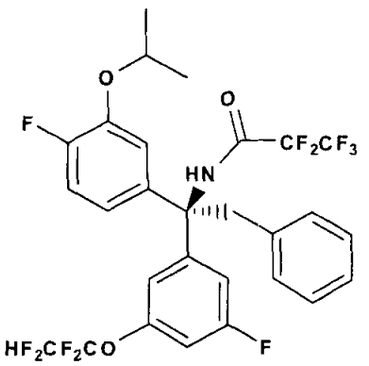



A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264, 50 mg, 0.079 mmoles) en DMF (0.2 ml) se agregó 1,1-di-ter-butoxi-N,N-dimetilmetanamina (100 µl, 0.49 mmoles). La mezcla de reacción se agitó a 110°C durante 5 h. La mezcla de reacción se concentró y se purificó por CLAR preparativa (columna phenomenex AXIA Luna 75 X 30 mm, 5 µ eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm) para resultar (R)-N-(1-(3-ter-

1431

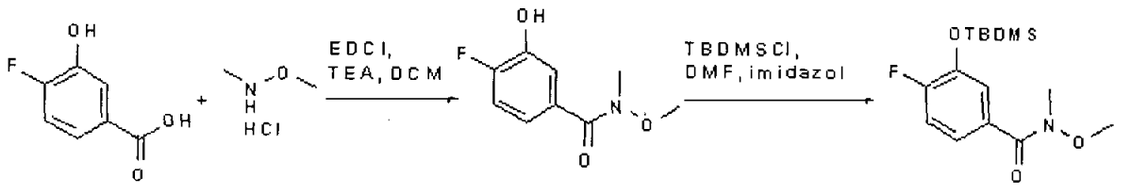
butoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 306) como liofilato blanco (46 mg, 81% rendimiento). CLEM: T.R. = 4.341 min [M+H] 688.2 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm. RMN: 400MHz $^1H$ ($CDCl_3$) ppm 1.22 (s, 9 H), 3.89 (s, 1 H), 4.06 (d, J=13.19 Hz, 1 H), 6.08 - 6.42 (m, 1 H), 6.73 (d, J=7.15 Hz, 2 H), 6.91 - 7.21 (m, 9 H), 7.39 - 7.44 (m, 1 H), 7.94 - 8.00 (m, 2 H).

**EJEMPLO 307**




**(R)-2,2,3,3,3-pentafluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)**

**Procedimiento 109**




A una solución del ácido 4-fluoro-3-hidroxibenzoico (1.49 g, 9.55 mmoles) en DCM (40 ml) se agregó TEA (1.2 ml,

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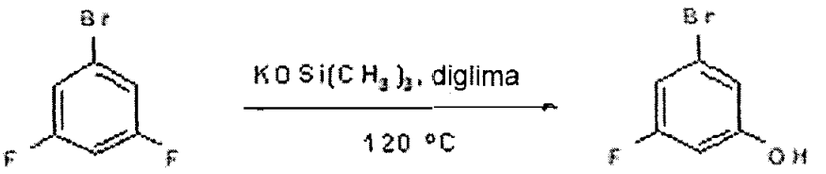
8.61 mmoles) seguido por clorohidrato de N,O-dimetilhidroxilamina (1.12 g, 11.5 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se diluyó con DCM, se lavó con agua dos veces, se secó sobre $Na_2SO_4$, se filtró y se concentró para producir 4-fluoro-3-hidroxi-N-metoxi-N-metilbenzamida como un aceite incoloro (1.90 g, 100% rendimiento). CLEM: T.R. = 0.89 min [M+H] 200.10 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

A una solución de 4-fluoro-3-hidroxi-N-metoxi-N-metilbenzamida (1.90 g, 9.55 mmoles) en DMF (8 ml) se agregó imidazol (740 mg, 10.8 mmoles) y TBDMSCl (1.62 g, 10.8 mmoles) a temperatura ambiente. La mezcla de reacción se agitó durante 48 h y se apagó con $NaHCO_3$ saturado. La solución se extrajo con éter (3 x) y las porciones de éter combinadas se lavaron con LiCl (10%), se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El aceite incoloro resultante se purificó por cromatografía ISCO (120 g de columna) al usar hexanos/EtOAc (0-100% durante 30 min) para dar 3-(ter-butildimetilsililoxi)-4-fluoro-N-metoxi-N-metilbenzamida (T.R. = 10-12 minutos) como un aceite incoloro (2.00 g, 67% rendimiento). CLEM: T.R. = 2.06 min [M+H] 314.22 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min,

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observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) 7.26 ppm, 2 H, m; 7.02 ppm, 1 H, m; 3.50 ppm, 3 H, s; 3.31 ppm, 3 H, s; 0.97 ppm, 9 H, s, 0.16 ppm, 6H, s.

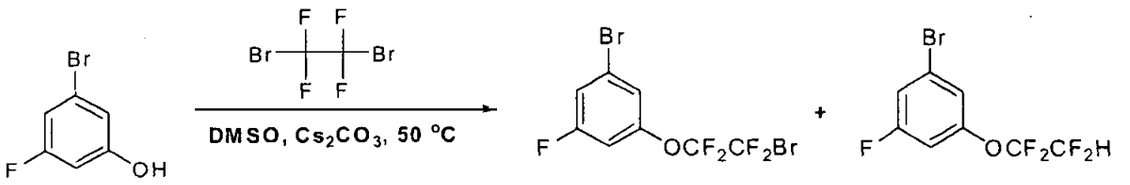
**Procedimiento 110**




A un matraz de fondo redondo de 2 L enjuagado con $N_2$ equipado con un agitador mecánico, un condensador, controlador de temperatura y una entrada $N_2$, se agregó trimetilsilanolato de potasio (225.0 g, 1.75 mol, técnica de purificación 90%), 1-bromo-3,5-difluorobenceno (96.5 g, 0.5 mol) y diglima (300 ml). La mezcla de reacción se calentó a 120°C bajo $N_2$ durante 5 h. Después del enfriamiento hasta temperatura ambiente, la capa caliente se reemplazó con un baño con hielo. La mezcla de reacción se acidificó con una solución HCl 3N (600 ml) de bajo de 30°C. El TBME (1 L) se agregó y la mezcla resultante se agitó de bajo de 20°C durante 30 min luego se transfirió a un embudo de separación de 5 L. La capa orgánica se separó y se lavó con agua (3 X 500 ml), NaCl saturado (500 ml), se secó sobre $MgSO_4$, se filtró y se concentró in vacuo para dar el producto crudo rojizo (145.0 g). El material crudo luego se destiló a 52-55°C/0.1 mm Hg para producir 3-bromo-5-fluorofenol como un aceite ligeramente amarillo (88.0 g, 92% rendimiento). $^1H$ RMN

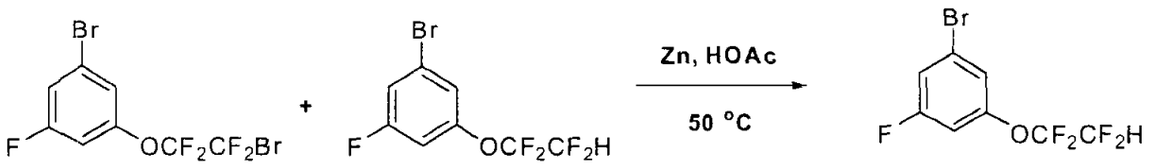
1934

(300 MHz, $CDCl_3$) δ 5.34 (s, H), 6.47-6.52 (m, 1H), 6.77-6.83 (m, 2 H).




A matraz de fondo redondo de tres cuellos de 1 L secado a la flama (1 L) equipado con un controlador de temperatura, un agitador mecánico, un condensador y una entrada $N_2$ se cargó 3-bromo-5-fluorofenol (57.3 g, 300 mmoles), 1,2-dibromotetrafluoroetano (156.0 g, 600 mmoles), DMSO seco (300 ml) y $Cs_2CO_3$ (146.6 g, 450 mmoles) bajo $N_2$. La mezcla de reacción se calentó a 50°C durante 5 h. Después del enfriamiento hasta temperatura ambiente, agua (300 ml) y hexano (300 ml) se agregaron. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La fase orgánica se separó y la capa acuosa se extrajo con hexano (300 ml). Los extractos orgánicos combinados se lavaron con agua (500 ml), NaCl saturado (500 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron in vacuo para dar 1-bromo-3-(2-bromo-1,1,2,2-tetrafluoroetoxi)-5-fluorobenceno (104.2 g, 94% rendimiento) que contiene 5% de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (5.2 g). El 1-Bromo-3-(2-bromo-1,1,2,2-tetrafluoroetoxi)-5-fluorobenceno: $^1H$ RMN (300 MHz, $CDCl_3$) δ 6.91-6.94 (m, 1H), 7.18-7.23 (m, 2 H).

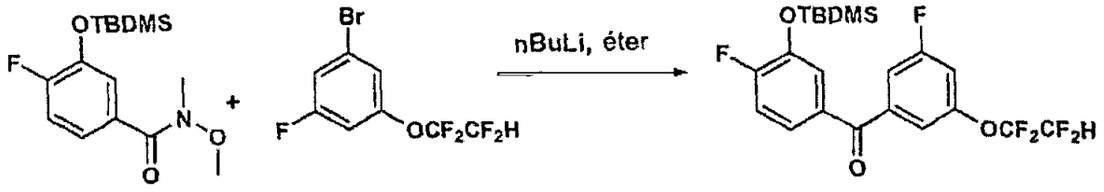
1435




A un matraz de fondo redondo de 1L equipado con un controlador de temperatura, un agitador mecánico, y una entrada $N_2$, se agregó 1-bromo-3-(2-bromo-1,1,2,2,-tetrafluoro-etoxi)-5-fluorobenceno (104.0 g, 281 mmoles) y 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (5.2 g, 18 mmoles), ácido acético (300 ml). La mezcla de reacción luego se calentó a 50°C. El polvo de zinc (91.9 g, 1.405 mol) se agregó en porciones. La mezcla de reacción se agitó a 50°C durante 1 h y se dejó enfriar hasta temperatura ambiente. El agua (300 ml) y hexano (300 ml) se agregaron. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La fase orgánica se separó y la capa acuosa se extrajo con hexano (2 x 300 ml). Los extractos orgánicos combinados se lavaron con agua (500 ml), NaCl saturado (500 ml), se secaron sobre MgSO4, se filtraron y se concentraron in vacuo para producir 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno como un líquido ligeramente amarillo (71 g, 87% rendimiento). $^1H$ RMN (300 MHz, $CDCl_3$) $\delta$ ppm 5.87 (tt, J = 52.7 y 2.9 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 7.16-7.18 (m, 2 H).

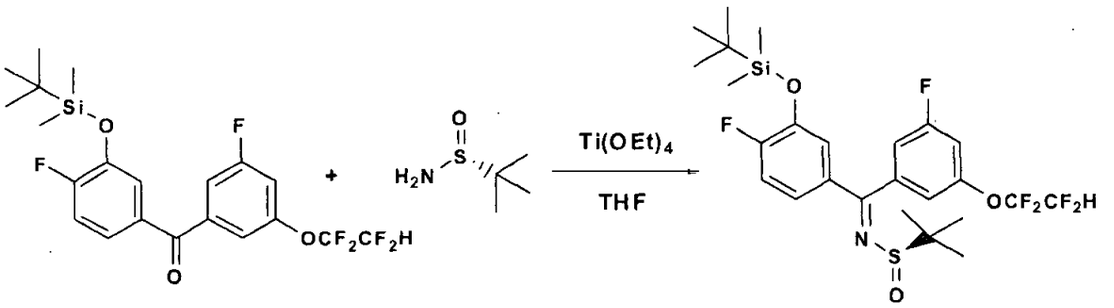
1436

**Procedimiento 111**




A -78°C bajo argón, una solución de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (2.04 g, 7.01 mmoles) en éter anhidro (20 ml) se agregó nBuLi (3.5 ml, 2.0 M en ciclohexano, 7.0 mmoles) gota a gota y la mezcla de reacción se agitó durante 1 h. La 3-(Ter-butildimetilsililoxi)-4-fluoro-N-metoxi-N-metilbenzamida (2.00 g, 6.38 mmoles) se agregó en una porción y la mezcla de reacción se agitó a -78°C durante 1.5 h. La solución amarilla pálida se vació dentro de la solución acuosa 1N HCl (30 ml) y éter (30 ml) se usó para enjuagar el matraz de reacción. La fase acuosa se separó y se extrajo con éter (20 ml). Las porciones de éter combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El aceite resultante se purificó por cromatografía ISCO (120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min) para dar (3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona a un tiempo de retención de 7 min (2.11 g, 71% rendimiento). CLEM: T.R. = 2.41 min [M+H] 465.19 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) 7.33 ppm,

3 H, m; 7.28 ppm, 1 H, m; 7.11 ppm, 2 H, m; 5.86 ppm, 1 H, t, J=53.39 Hz; 0.95 ppm, 9 H, s; 0.15 ppm, 6 H, s.

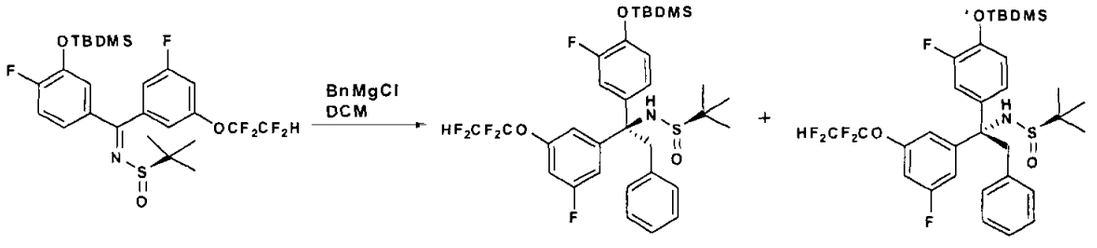



Un matraz de fondo redondo se cargó con (3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (2.09 g, 4.50 mmoles), (R)-2-metilpropano-2-sulfinamida (653 mg, 5.4 mmoles), $Ti(OEt)_4$ (1.54 g, 6.76 mmoles) y THF anhidro (40 ml). La solución resultante se calentó a 75°C bajo argón durante 14 h. Los solventes se retiraron y el residuo se diluyó con éter (50 ml) y NaCl saturado (20 ml). La mezcla resultante se filtró a través una frita de vidrio y el producto filtrado se transfirió a un embudo de separación. La porción orgánica se separó y el acuoso se extrajo con éter (2 x 20 ml). Las porciones orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El residuo se disolvió en hexano:EtOAc y se purificó cromatografía ISCO (2 × 120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min) para producir (R)-N-((3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida

1438

a un tiempo de retención de 14 min (2.05 g, 80% rendimiento) CLEM: T.R. = 2.37 min [M+H] 568.24 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). RMN: 400MHz $^1H$ ($CDCl_3$) 7.36 ppm, 1 H, m; 7.11 ppm, 5 H, m; 5.90 ppm, 1 H, t, J=52.73 Hz; 0.97 ppm, 9 H, s; 0.18 ppm, 6 H, s.

**Procedimiento 112**

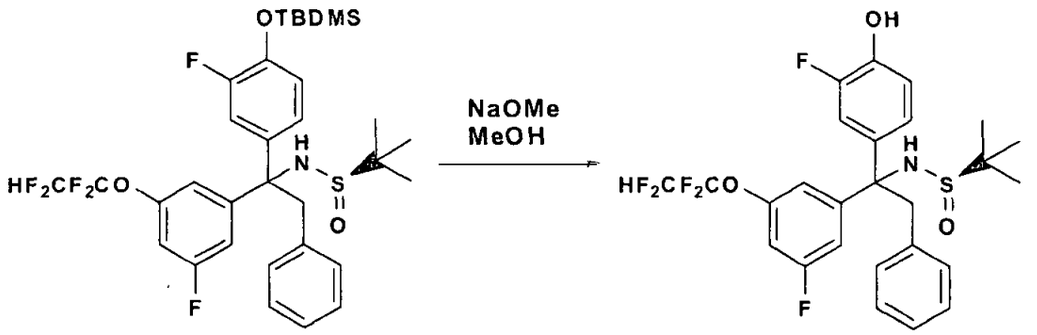



A -78°C una solución de (R)-N-((3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida (1.0 g, 1.76 mmoles) en DCM (50 ml) se agregó $BF_3 \cdot Et_2O$ (0.77 ml, 3.52 mmoles) por medio de jeringa. Después de 5 min, la solución BnMgCl (3.5 ml, solución 1.0 M en éter, 3.5 mmoles) se agregó gota a gota y la mezcla de reacción se agitó a -78°C durante 1 h. Una porción adicional de BnMgCl (3.5 ml, 1.0 M solución en éter, 3.5 mmoles) se agregó gota a gota y la reacción se agitó durante 1 h adicional a -78°C. La mezcla de reacción se vació dentro de NaCl saturado (50 ml) y la capa orgánica se separó. La capa acuosa se extrajo con DCM (2 × 20 ml) y las capas orgánicas combinadas se secaron sobre

$Na_2SO_4$, se filtraron y se concentraron. El aceite resultante se purificó por cromatografía ISCO (120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min) para dar una mezcla 4:1 aproximada de (R)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida y (S)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida a un tiempo de retención de 12 min (824 mg, 71% rendimiento) CLEM: T.R. = 2.43 min [M+H] 660.39 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). La relación diaestereomérica del producto se determinó que es 4:1 por análisis CLAR quiral (Chiralcel® AD, 90:10 heptano :i-PrOH, 1 ml / min, 254 nm, TR (menor)= 4.43 min, PA=17%; TR (mayor) = 19.28 min, PA=71%) y la mezcla diaestereomérica se tomó directamente en la siguiente etapa, Procedimiento 112, o los diaestereómeros se prepararon como se describe en el Procedimiento 114. RMN: 400MHz $^1H$ ($CDCl_3$) 7.30 ppm, 2 H, m; 7.06 ppm, 5 H, m; 6.85 ppm, 2 H, m; 6.76 ppm, 1 H, m; 6.62 ppm, 2 H, m; 5.79 ppm, 1 H, m; 4.13 ppm, 1H, s; 3.84 ppm, 1 H, m; 3.47 ppm, 1 H, m; 1.12 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6 H, d, $J$=4.39 Hz.

1440

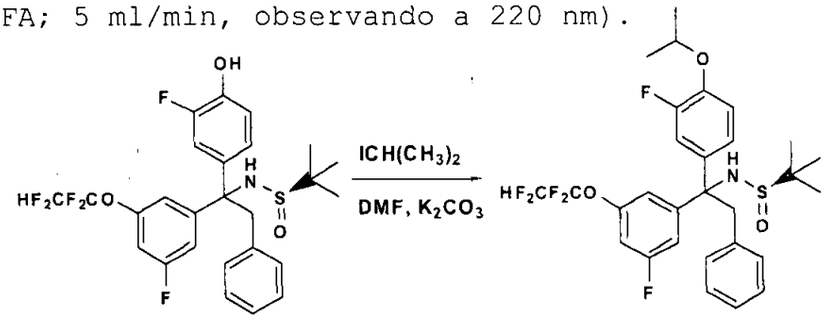
**Procedimiento 113**



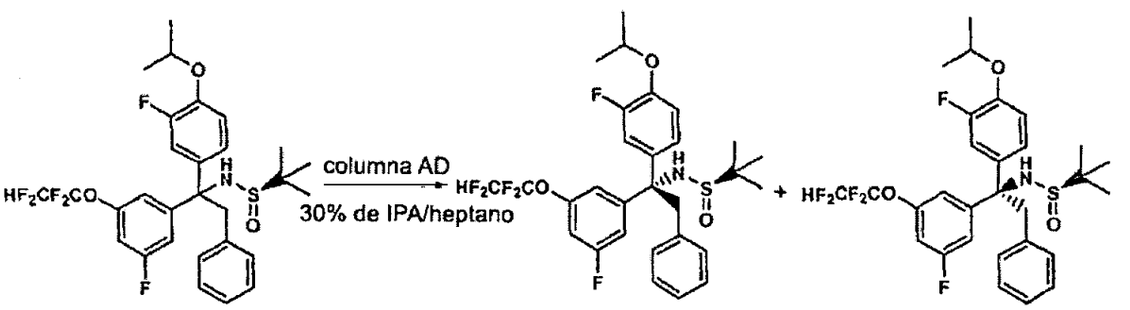

A temperatura ambiente una solución de NaOMe (5 ml, solución 0.5 M en MeOH) se agregó a la mezcla 4:1 diaestereomérica de (R)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (801 mg, 1.22 mmoles). La mezcla de reacción se agitó durante 15 minutos, MeOH se retiró luego el residuo se disolvió en EtOAc (50 ml) y se transfirió a un embudo de separación. El HCl (20 ml, solución 1.0 N) se agregó y la capa EtOAc se separó. La capa acuosa se extrajo con EtOAc (2 × 10 ml) y las capas orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron para producir (R)-N-(1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma blanca (578 mg, 87% de rendimiento). CLEM: T.R. = 1.987 min [M+H] 546.35 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene

1441

0.1% de TFA; 5 ml/min, observando a 220 nm).




A temperatura ambiente una solución de (R)-N-(1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (578 mg, 1.06 mmoles) en DMF (10 ml) se agregó $K_2CO_3$ (800 mg, 5.80 mmoles) y la solución espesa se agitó vigorosamente. El 2-Iodopropano (220 mg, 1.27 mmoles) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con éter (50 ml), se lavó sucesivamente con 10% LiCl (2 × 20 ml) y agua (20 ml). La porción orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró para producir (R)-N-(1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma anaranjada pálida (780 mg, 100% rendimiento).



1442

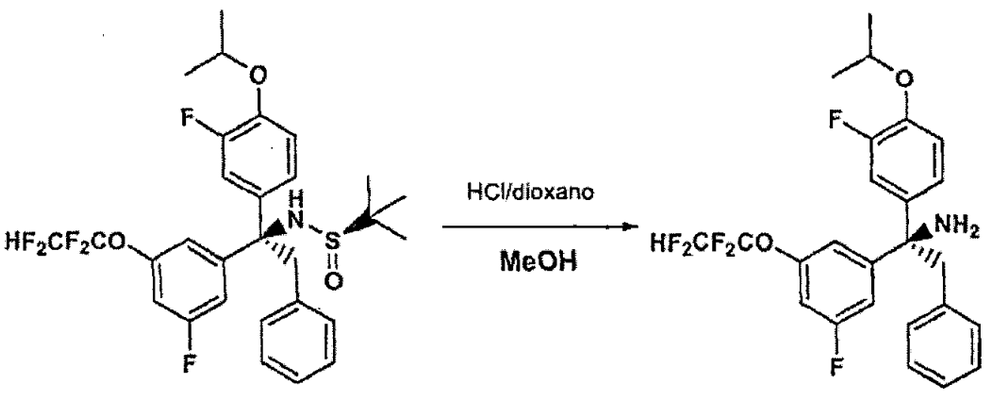
La mezcla diaestereomérica de (R)-N-(1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (780 mg, 1.06 mmoles crudo) se separó por una columna CLAR quiral preparativa chiralpak AD 20, 5 × 50 cm, eluyendo con 30% IPA/Heptano con relación de flujo 50 ml/min.

La (R)-N-((S)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 17 min y se aisló como un aceite incoloro (101 mg, rendimiento 16%). CLEM: T.R. = 2.128 min [M+H] 588.38 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR quiral: T.R. = 4.35 min, ee 100% (columna Diacel Chiralpak AD 10μ, 4.6 × 250 mm elución isocrática con IPA (20%) y heptano; 1 ml/min, observando a 254 nm).

La (R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 39 min y se aisló y se aisló como un aceite incoloro (398 mg, rendimiento 64%). CLEM: T.R. = 2.138 min [M+H] 588.38 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR quiral: T.R. = 9.98 min,

1943

ee 100% (columna Diacel Chiralpak AD 10μ, 4.6 × 250 mm elución isocrática con IPA (20%) y heptano; 1 ml/min, observando a 254 nm) RMN: 400MHz $^1$H ($CDCl_3$) 7.08 ppm, 5 H, m; 6.84 ppm, 2 H, d, *J*=7.47 Hz; 6.77 ppm, 2 H, d, *J*=7.47 Hz; 6.63 ppm, 2 H, m; 5.79 ppm, 1 H, t, *J*=52.95 Hz; 4.33 ppm, 1 H, m; 4.15 ppm, 1 H, s; 3.92 ppm, 1 H, d, *J*=12.30 Hz; 3.48 ppm, 1 H, d, *J*=12.30 Hz; 1.22 ppm, 3 H, d, *J*=6.15 Hz; 1.18 ppm, 3 H, d, *J*=5.71 Hz; 1.14 ppm, 9 H, s.

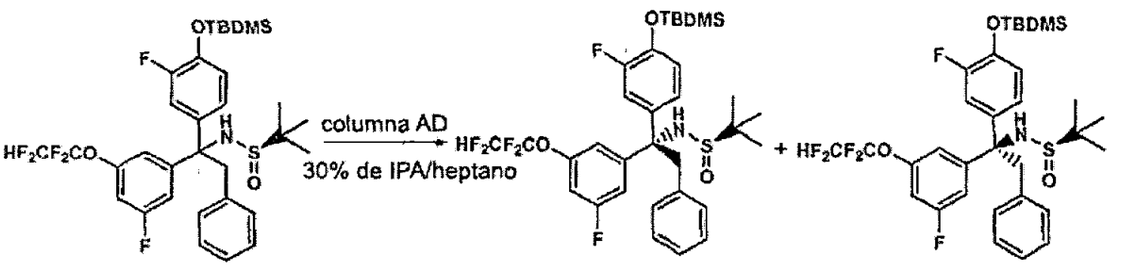



A una solución de (R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (398 mg, 0.678 mmoles) en MeOH (1.5 ml) se agregó HCl (1.5 ml, 4 M solución en dioxano) y la mezcla de reacción se agitó durante 30 min. La mezcla de reacción se diluyó con éter (50 ml) y la capa orgánica se lavó con $NaHCO_3$ saturado (20 ml), se secó sobre $Na_2SO_4$, se filtró y se concentró para dar (R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina como un aceite incoloro (334 mg, 100% rendimiento). CLEM: T.R. = 1.76

min [M-$NH_2$] 467.24 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 3.04 min, Pureza 95% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.15 ppm, 3 H, m; 6.99 ppm, 4 H, m; 6.89 ppm, 1 H, m; 6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=6.15 Hz; 5.87 ppm, 1 H, m; 4.42 ppm, 1 H, m; 3.47 ppm, 2 H, s; 1.27 ppm, 6 H, dd, *J*=7.91,6.15 Hz.

Una ruta alternativa se usó para preparar la (R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina como sigue:

**Procedimiento 114**

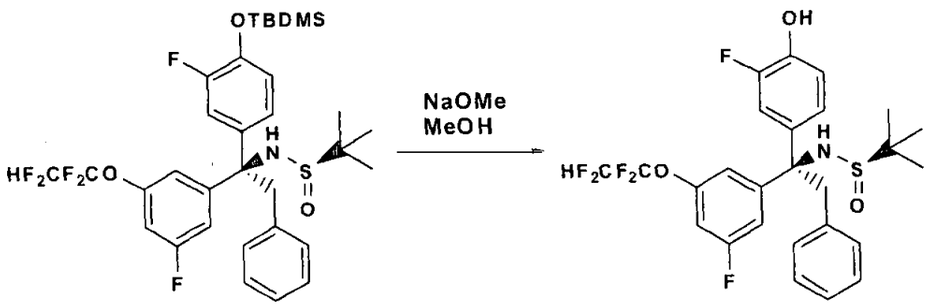



La mezcla de diaestereómeros de (R)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (1.14 g, 1.73 mmoles) se separó por una columna CLAR quiral preparativa Chiralpak AD 20, 5 × 50 cm, eluyendo con 30% IPA/Heptano con relación de flujo 50 ml/min.

La (R)-N-((S)-1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 19 min (114 mg, rendimiento 10%). CLEM: T.R. = 2.45 min [M+H] 660.41 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm).

La (R)-N-((R)-1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 36 min (634 mg, rendimiento 56%). CLEM: T.R. = 2.41 min [M+H] 660.39 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR quiral: T.R. = 8.54 min, ee 100% (columna Diacel Chiralpak AD 10μ, 4.6 × 250 mm elución isocrática con IPA (20%) y heptano; 1 ml/min, observando a 254 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.03 ppm, 5 H, m; 6.84 ppm, 2 H, m; 6.74 ppm, 1 H, d, *J*=8.79 Hz; 6.66 ppm, 1 H, dd, *J*=8.13, 1.98 Hz; 6.61 ppm, 2 H, m; 5.76 ppm, 1 H, m; 4.12 ppm, 1 H, s; 3.90 ppm, 1 H, d, *J*=12.74 Hz; 3.46 ppm, 1 H, d, *J*=12.30 Hz; 1.11 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6

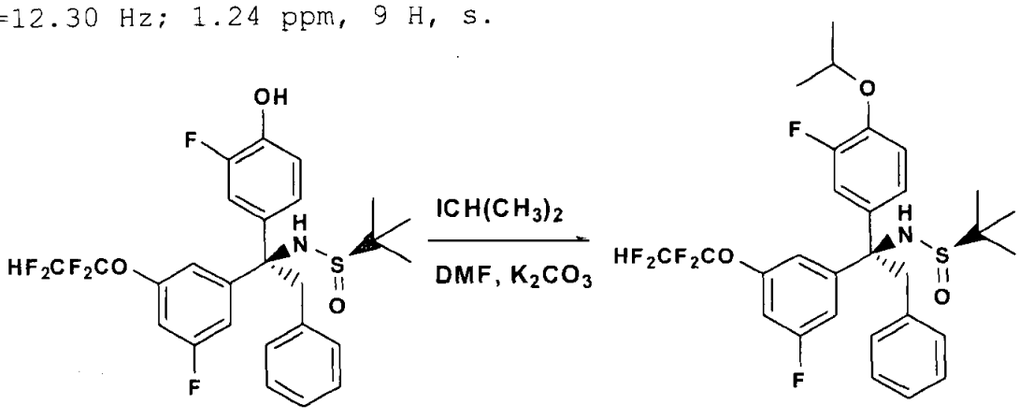
H, d, $J$=4.83 Hz.




La (R)-N-((R)-1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se preparó a partir de la (R)-N-((R)-1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como se describe en el Procedimiento 112 en rendimiento cuantitativo. CLEM: T.R. = 1.998 min [M+H] 546.28 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). CLAR: T.R. = 3.83 min, Pureza 98% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.61 ppm, 1 H, s; 7.40 ppm, 1 H, dd, $J$=8.13, 1.98 Hz; 7.13 ppm, 3 H, m; 6.99 ppm, 1 H, dd, $J$=10.33, 8.57 Hz; 6.84 ppm, 3 H, m; 6.68 ppm, 2 H, m; 6.61 ppm, 1 H, m; 5.85 ppm, 1 H, tt, $J$=52.95, 2.64 Hz; 4.30 ppm, 1

1447

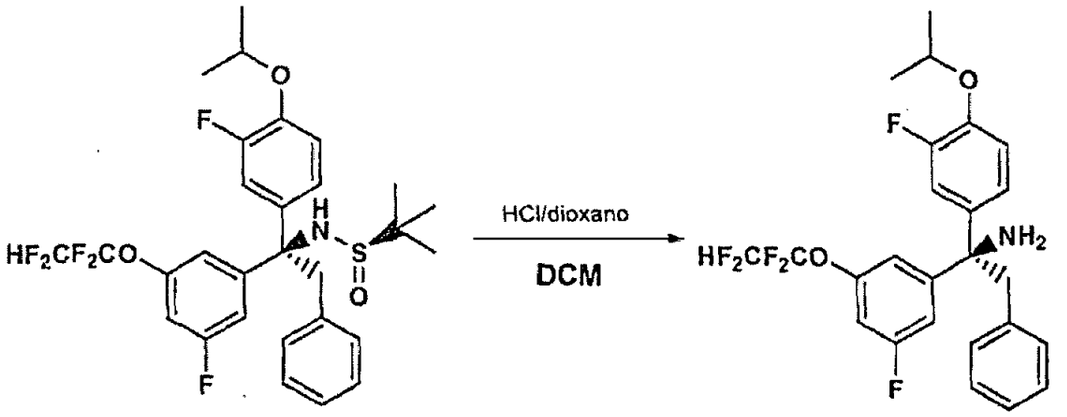
H, s; 4.02 ppm, 1 H, d, *J*=12.30 Hz; 3.50 ppm, 1 H, d, *J*=12.30 Hz; 1.24 ppm, 9 H, s.




La (R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se preparó a partir de la (R)-N-(1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como se describe en el Procedimiento 6 en 78% rendimiento. CLEM: T.R. = 2.17 min [M+H] 588.17 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm) CLAR: T.R. = 4.20 min, Pureza 95% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.10 ppm, 2 H, m; 6.87 ppm, 4 H, m; 6.70 ppm, 2 H, m; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 4.31 ppm, 1 H, s; 3.98 ppm, 1 H, d, *J*=12.74 Hz; 3.56 ppm, 1 H, d, *J*=12.74 Hz; 1.30 ppm, 3 H, d, *J*=5.71 Hz; 1.25 ppm, 3 H, d, *J*=6.15 Hz; 1.22 ppm, 9 H,

1498

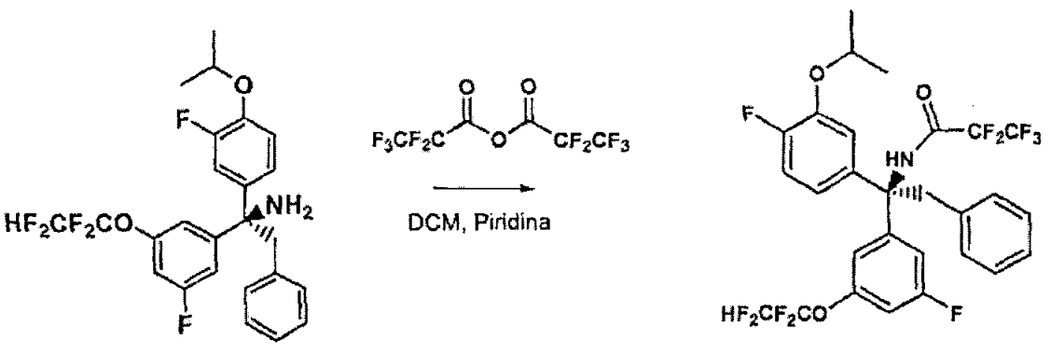
s.




La (R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina se preparó a partir de la (R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como se describe en el Procedimiento 6 en 97% rendimiento. CLEM: T.R. = 1.83 min [M-$NH_2$] 467.24 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 3.17 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.01 ppm, 3 H, m; 6.92 ppm, 2 H, m; 6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=7.03 Hz; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 3.49 ppm, 2 H, s; 1.25 ppm, 6 H, m.

1449

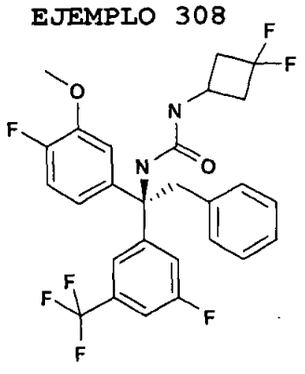
**Procedimiento 115**




A temperatura ambiente, una solución de (R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina (25 mg, 0.05 mmoles) en DCM anhidro (0.5 ml) se agregó piridina (1 gota) y anhídrido 2,2,3,3,3-pentafluoropropanoico (19 mg, 0.08 mmoles). La solución resultante se agitó durante 5 min, se diluyó con MeOH (0.5 ml) y se purificó por CLAR preparativa (columna YMC Sunfire 30 x 100 mm, eluyendo con 10-90% MeOH/$H_2O$ durante 10 minutos que contiene 0.1% de TFA; 40 ml/min, observando a 220 nm). La (R)-2,2,3,3,3-pentafluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)propanamida (Ejemplo 307) se aisló como un aceite incoloro (7 mg, 21% rendimiento) a un tiempo de retención de 11.84 min. CLEM: T.R. = 2.19 min [M+H] 630.32 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm); CLAR: T.R. = 4.21 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con

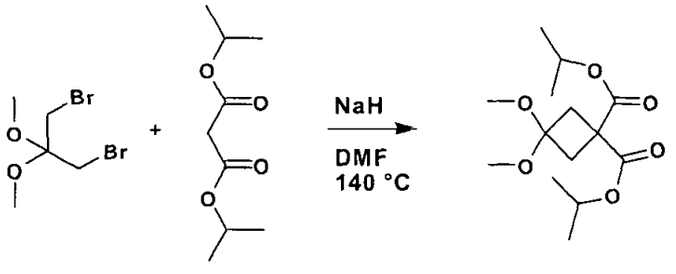
10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.25 ppm, 3 H, m; 7.03 ppm, 1 H, t, J=8.0 Hz; 6.86 - 6.97 ppm, 4 H, m; 6.66 ppm, 2 H, d, *J*=8.0 Hz; 6.58 ppm, 2 H, d, *J*=8.0 Hz; 5.87 ppm, 1 H, d, J=57.8 Hz; 4.32 ppm, 1 H, sept, *J*=8.0 Hz; 3.93 ppm, 1 H, d, *J*=12.0 Hz; 3.68 ppm, 1 H, d, *J*=12.0 Hz; 1.28 ppm, 3 H, d, *J*=8.0 Hz; 1.22 ppm, 3 H, d, *J*=8.0 Hz.

**EJEMPLO 308**



**(R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea**

**Procedimiento 116**

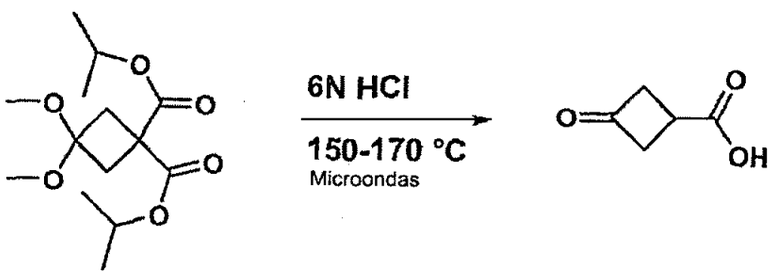



A una suspensión de hidruro de sodio (60% en mineral aceite, 3.7 g, 92 mmoles) en DMF seco (32 ml) bajo nitrógeno se agregó gota a gota malonato de diisopropilo (16 ml, 84 mmoles) y la temperatura se mantuvo debajo de 0°C. Al suspender la evolución del hidrógeno, 1,3-dibromo-2,2-

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dimetoxipropano (11.0 g, 42 mmoles) se agregó a temperatura ambiente y la mezcla de reacción se calentó a 140°C durante 24 h. La mezcla fría se vació dentro de cloruro de amonio saturado (100 ml) y se extrajo con hexano (3 x 75 ml). Los extractos orgánicos combinados se lavaron con agua (100 ml), $NaHCO_3$ saturado (50 ml), se secaron sobre sulfato de magnesio y el solvente se evaporó para dar 17.42 g del aceite amarillo pálido. La destilación del residuo a través la columna Vigreux con un condensador de aire y purificación adicional por una columna de sílice Analogix (12 g, 20% acetato de etilo en hexano) proporcionando 3,3-dimetoxiciclobutano-1,1-dicarboxilato de diisopropilo (6.2 g, 51 % rendimiento). CLEM: T.R. = 3.26 min, sin ión precursor (Phenominex, Luna C18, 4.6 X 50 mm, 4 min gradiente de 10% metanol, 90% agua, 0.1% de TFA hasta 90% metanol, 10% agua, 0.1% de TFA); $^1H$ RMN (500 MHz, $CDCl_3$) δ ppm 5.06 (2 H, dq), 3.15 (6 H, s), 2.69 (4 H, s), 1.24 (12 H, d, J=6.0 Hz); $^{13}C$ RMN (126 MHz, $CDCl_3$) δ ppm 170.34 (2 C, s), 98.50, 69.03 (2 C, s), 48.59 (2 C, s), 45.01, 39.63 (2 C, s), 21.47 (4 C, s).

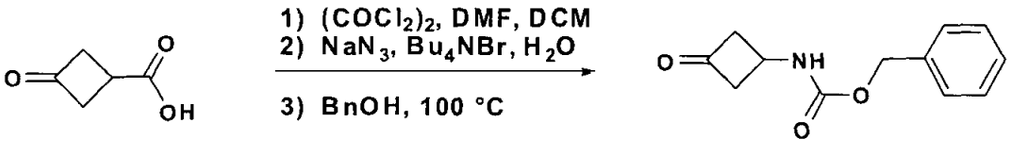
**Procedimiento 117**




Una solución de 3,3-dimetoxiciclobutano-1,1-

dicarboxilato de diisopropilo (2.2 g, 7.63 mmoles) en HCl (6 N, 6 ml) se calentó a 155-160°C bajo radiación por microondas durante 60 min. La mezcla de reacción se diluyó con éter (150 ml) y se agitó vigorosamente durante el fin de semana. La capa de éter se secó con $MgSO_4$, se filtró y se concentró para dar ácido 3-oxociclobutanocarboxílico (1.0 g, 118 % rendimiento) como un sólido café. $^1H$ RMN (500 MHz, $CDCl_3$) δ ppm 10.80 (1 H, br. s.), 3.43 - 3.51 (2 H, m), 3.26 - 3.40 (3 H, m); $^{13}C$ RMN (126 MHz, CDCl3) δ ppm 203.14, 180.17, 51.64 (2 C, s), 27.32 (1 C, s).

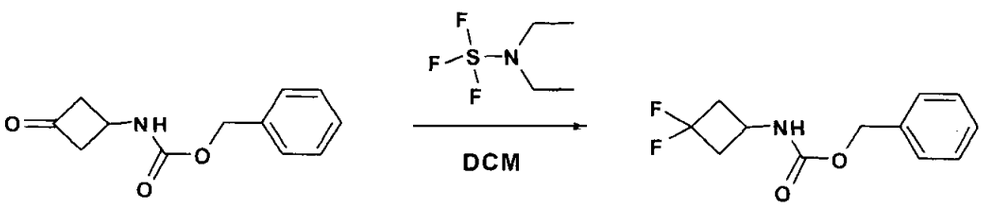
**Procedimiento 118**




A una solución de ácido 3-oxociclobutanocarboxílico (3.34 g, 29.2 mmoles) en diclorometano (29 ml) a 0°C se agregó cloruro de oxalilo (19.0 ml, 38.0 mmoles) seguido por DMF (0.057 ml, 0.731 mmoles). La mezcla de reacción se agitó durante 2 h a temperatura ambiente. La mezcla de reacción se concentró bajo presión reducida y el residuo se disolvió en diclorometano (15 ml). A 0°C, a la solución resultante se agregó azida de sodio (3.23 g, 49.7 mmoles) en agua (7 ml) seguido por bromuro de tetrabutilamonio. La mezcla de reacción se agitó vigorosamente durante 2 h. La fase acuosa se separó y se extrajo con diclorometano (2 x 40 ml). Las

porciones orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron rápidamente y alcohol bencílico (30.4 ml, 292 mmoles) se agregó y el volumen del solvente se redujo bajo presión reducida. La mezcla de reacción se calentó a 95°C durante 1 h. El alcohol bencílico se retiró bajo presión reducida y el residuo de aceite se purificó por Cromatografía de vaporización instantánea ISCO (columna 80 g, hexano/acetato de etilo) para dar 3-oxociclobutilcarbamato de bencilo como un sólido amarillo pálido (693 mg, 11% rendimiento). CLAR: T.R. = 1.16 min, 90% puro (Phenomenex, Onix C18, 4.6 X 100 mm, 2 min gradiente a partir de 10% MeCN, 90% agua, 0.1% de TFA hasta 90% MeCN, 10% agua, 0.1% de TFA); CLEM: T.R. = 2.37 min, 75% Pureza, [M+H] 220.1 (Phenomenex, Luna C18, 4.6 X 50 mm, 4 min gradiente a partir de 10% metanol, 90% agua, 0.1% de TFA a 90% metanol, 10% agua, 0.1% de TFA); $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 7.32 - 7.38 (5 H, m), 5.27 (1 H, d, J=3.3 Hz), 5.12 (2 H, s), 4.33 (1 H, d, J=5.5 Hz), 3.40 (2 H, dd, J=13.2, 6.6 Hz), 3.08 (2 H, d, J=14.3 Hz). $^{13}$C RMN (101 MHz, $CDCl_3$) δ ppm 204.50, 155.87, 136.06, 128.56 (2 C, s), 128.28, 128.13 (2 C, s), 66.97, 54.59 (2 C, s), 37.08.

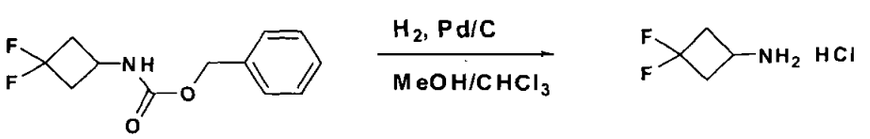
**Procedimiento 119**




A una solución de 3-ociclobutilcarbamato de bencilo

(2.58 g, 11.77 mmoles) en diclorometano (23.5 ml) a 0°C hasta -5°C se agregó gota a gota DAST (4.66 ml, 35.3 mmoles). La mezcla de reacción se agitó durante 4.5 h a temperatura ambiente, luego se diluyó con NaCl saturado a 0°C y las capas acuosas se extrajeron con diclorometano (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. El aceite resultante se purificó por Cromatografía de vaporización instantánea ISCO (columna 120 g, hexanos a acetato de etilo) para producir 3,3-difluorociclobutilcarbamato de bencilo (1.7 g, rendimiento 60%). CLEM: T.R. = 2.95 min [M+H] 242.1 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm); $^1H$ RMN (500 MHz, $CDCl_3$) δ ppm 7.30 - 7.41 (5 H, m), 5.10 (2 H, br. s.), 4.99 (1 H, br. s.), 4.04 - 4.16 (1 H, m), 2.90 - 3.04 (2 H, m), 2.42 - 2.56 (2 H, m); $^{13}C$ RMN (126 MHz, $CDCl_3$) δ ppm 155.52, 136.07, 128.58 (2 C, s), 128.30, 128.18 (2 C, s), 66.97, 42.72 - 43.57 (1 C, m), 35.71 - 36.66 (2 C, m), el triplete para la señal de difluorocarbono no se elevo arriba de la línea base; $^{19}F$ RMN (471 MHz, CDCl3) δ ppm -84.90 (1 F, d, J=195.8 Hz), -97.62 (1 F, d, J=201.5 Hz).

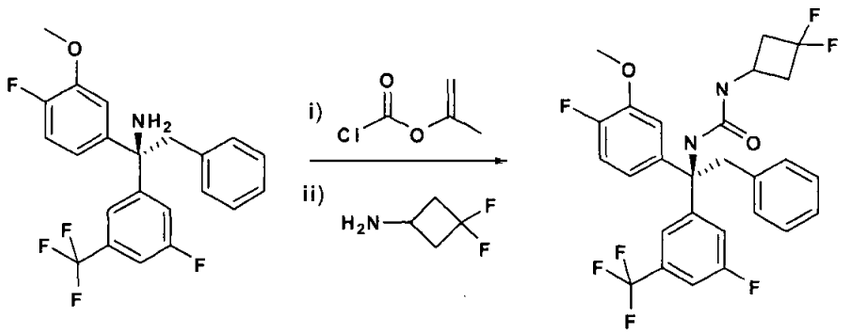
**Procedimiento 120**




A una solución de 3,3-difluorociclobutilcarbamato

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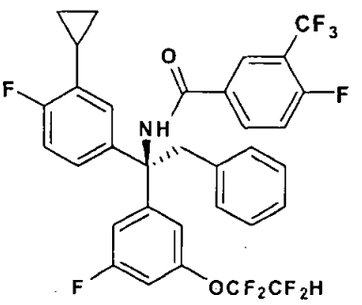
de bencilo (1.86 g, 7.71 mmoles) en metanol (49 ml) y cloroformo (2 ml) se agregó 10% paladio en carbono (0.41 g, 0.39 mmoles) y la solución espesa se sometió a hidrogenación en globo durante la noche. La mezcla de reacción se filtró, se lavó con metanol y HCl (1.0 M) en éter (1 ml) y el producto filtrado se concentró. El residuo se trituró con éter, se filtró, se lavó con éter y se secó para dar clorohidrato de 3,3-difluorociclobutanamina como un sólido amarillo pálido (1.01 g, 92 % rendimiento). $^{1}$H RMN (400 MHz, DMSO-D6) δ ppm 8.48 (m, 3 H), 3.60 - 3.69 (m, 1 H), 2.72 - 3.02 (m, 4 H); $^{19}$F RMN (376 MHz, DMSO-D6) δ ppm -81.57 (1 F, d, *J*=189.6 Hz), -97.13 (1 F, ddd, *J*=198.8 Hz, 18.5 Hz).




La (R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea (Ejemplo 308) fue preparada como se describe en el Procedimiento 10. CLEM: T.R. = 2.003 min [M+H] 639 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene 0.1% de TFA; 5 ml/min, observando a 220 nm). CLAR: T.R. = 4.10 min, 100 % Pureza (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con

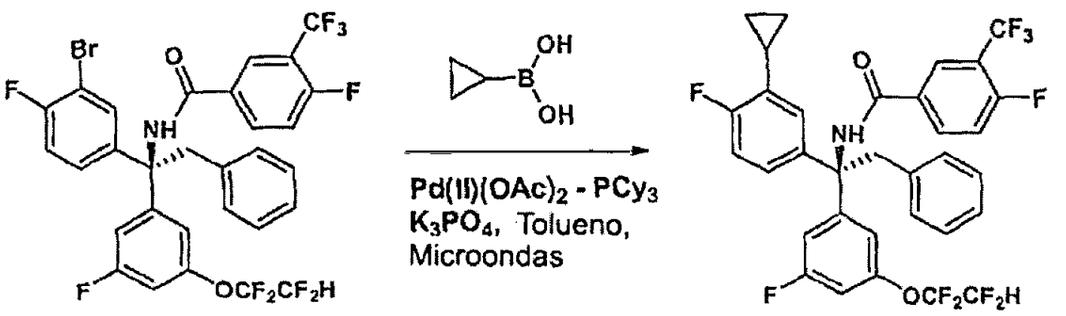
10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, Solvente) δ ppm 2.33 - 2.44 (m, 2 H), 2.86 - 2.97 (m, *J*=15.25, 7.83, 7.70, 3.30 Hz, 2 H), 3.63 - 3.72 (m, 3 H), 3.74 - 3.85 (m, 1 H), 3.93 - 4.03 (m, 1 H), 4.09 (d, *J*=7.15 Hz, 1 H), 6.62 - 6.69 (m, 1 H), 6.70 - 6.78 (m, 3 H), 7.00 (ddd, *J*=11.13, 8.11, 3.30 Hz, 1 H), 7.10 - 7.21 (m, 3 H), 7.29 - 7.40 (m, 3 H).

**EJEMPLO 309**




**(R)-N-(1-(3-ciclopropil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 121**

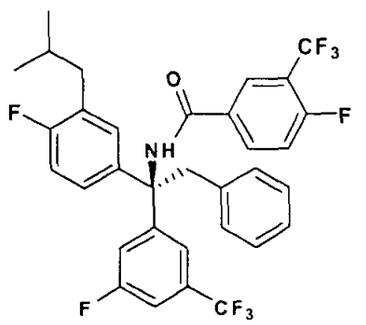



A una mezcla de (S)-N-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-

fluoro-3-(trifluorometil)benzamida, preparada como se describe en los Procedimientos 3, 62, 5, 6 y 7, (50 mg, 0.07 mmoles), (50 mg, 0.07 mmoles), ácido ciclopropilborónico (6 mg, 0.07 mmoles), acetato de paladio (II) (1 mg, 0.004 mmoles) y triciclohexilfosfina (2 mg, 0.007 mmoles) en tolueno (2 ml) se agregó $K_3PO_4$ (0.072 ml, 0.22 mmoles). La mezcla de reacción se calentó a 100°C bajo radiación por microondas durante 15 min. La mezcla de reacción se filtró, se concentró y el residuo resultante se purificó por CLAR preparativa (columna Sunfire-S5-C18 18 x 50mm, eluyendo con 10-90% MeOH/$H_2O$ gradiente durante 8 min, con relación de flujo 20 ml/min y detección UV a 220 nm) para producir (R)-N-(1-(3-ciclopropil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 309, 14 mg, 30 % rendimiento). CLEM: T.R. = 4.37 min [M+H] 656.38 (Waters Sunfire-S5-C18 4.6 x 50mm, eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 7.90 (1 H, dd, *J*=6.60, 1.92 Hz), 7.81 - 7.84 (1 H, m), 7.22 - 7.30 (5 H, m), 7.16 (2 H, t, *J*=7.56 Hz), 6.93 - 7.00 (4 H, m), 6.77 - 6.81 (1 H, m), 6.68 (2 H, d, *J*=7.42 Hz), 6.62 (1 H, s), 6.54 (1 H, dd, *J*=6.87, 2.47 Hz), 5.88 (1 H, t, *J*=52.73 Hz), 4.08 (1 H, d, *J*=13.20 Hz), 3.66 (1 H, d, *J*=13.20 Hz), 2.03 (1 H, ddd, *J*=13.75, 8.52, 5.22 Hz), 0.92 - 0.96 (2 H, m), 0.52 -

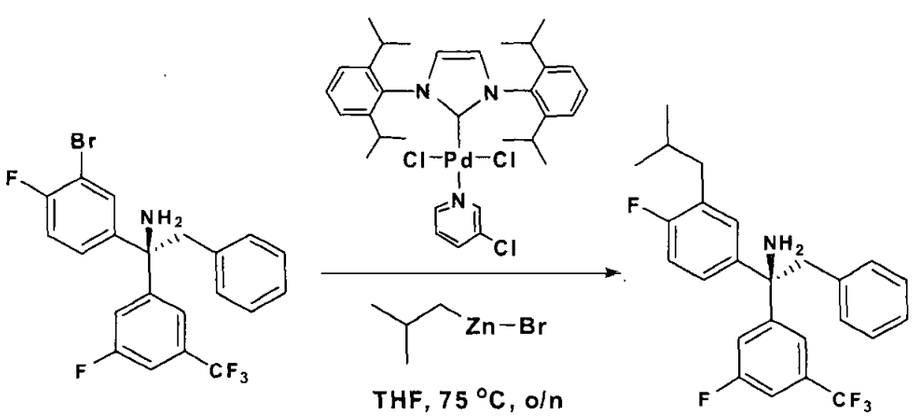
0.56 (1 H, m), 0.43 - 0.47 (1 H, m).

**EJEMPLO 310**



**(R)-4-fluoro-N-(1-(4-fluoro-3-isobutilfenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

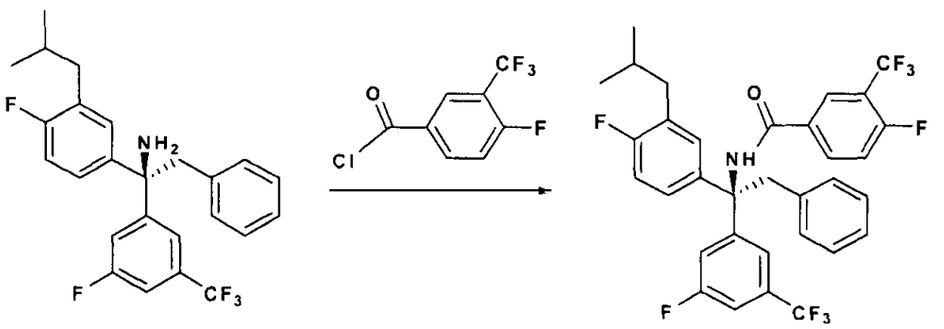
**Procedimiento 122**




A una solución de dicloruro de [1,3-bis(2,6-diisopropilfenil)imidazol-2-ilideno](3-cloropiridil)paladio(II) (8 mg, 0.01 mmoles) en NMP (0.5 ml) se agregó bromuro de isobutilzinc(II) en THF (0.5 M, 0.7 ml, 0.35 mmoles) seguido por (S)-1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletanamina, se preparó como se describe en los Procedimientos 62, 5 y 6, (50 mg,

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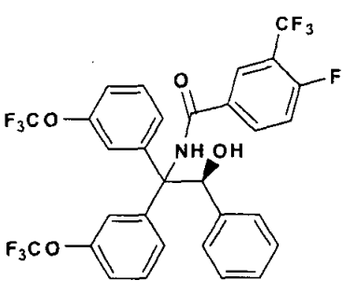
0.11 mmoles) en THF anhidro. La mezcla de reacción se calentó a 75°C durante la noche. La mezcla de reacción se diluyó con EtOAc y la capa orgánica se lavó con $NH_4Cl$ saturado, se secó sobre $Na_2SO_4$ y se concentró para producir (R)-1-(4-fluoro-3-isobutilfenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletanamina. CLEM: T.R. = 3.62 min [M-$NH_2$] 417 (Waters Sunfire-S5-C18 4.6 x 50mm, eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm).




Siguiendo el procedimiento 7, la (R)-4-fluoro-N-(1-(4-fluoro-3-isobutilfenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 310) se preparó (13 mg, 18% rendimiento). CLEM: T.R. = 4.68 min [M+H] 624.33 (Waters Sunfire-S5-C18 4.6 x 50mm, eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.1% de TFA; 4 ml/min, observando a 220 nm). $^1H$ RMN (500 MHz, $CDCl_3$) $\delta$ ppm 7.89 (1 H, dd, *J*=6.46, 2.06 Hz), 7.82 (1 H, ddd, *J*=8.45, 4.61, 2.34 Hz), 7.37 (1 H, s), 7.22 - 7.30 (6 H, m), 7.16 (2 H, t, *J*=7.56 Hz), 6.98 (1 H, t, *J*=8.80 Hz), 6.87 - 6.90 (1 H, m), 6.83 (1

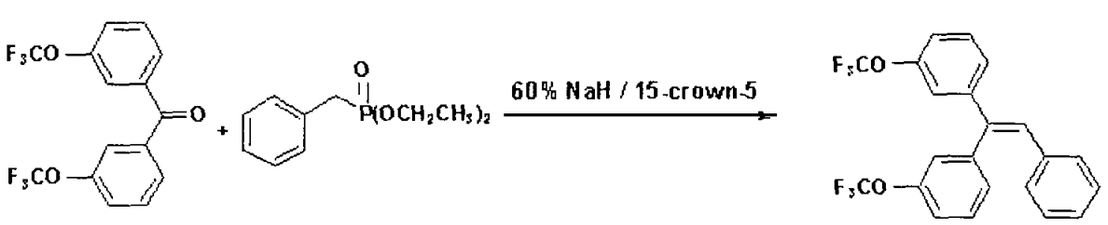
H, dd, *J*=6.74, 2.61 Hz), 6.71 (1 H, s), 6.69 (2 H, d, *J*=7.15 Hz), 4.07 (1 H, d, *J*=12.92 Hz), 3.78 (1 H, d, *J*=13.20 Hz), 2.47 - 2.52 (1 H, m), 2.40 - 2.45 (1 H, m), 1.80 (1 H, dt, *J*=13.54, 6.84 Hz), 0.85 (6 H, dd, *J*=9.62, 6.60 Hz).

**EJEMPLO 311**




**(S)-4-fluoro-N-(2-hidroxi-2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(trifluorometil)benzamida**

**Procedimiento 123**

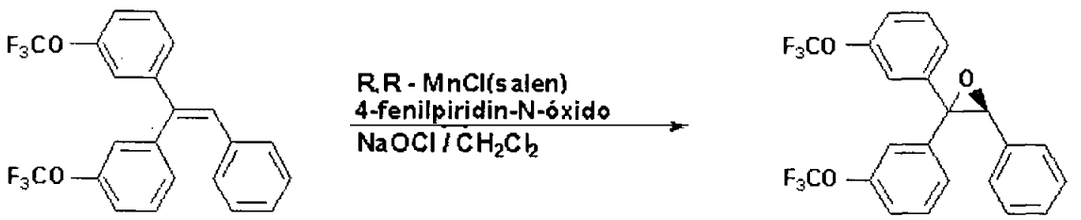



A una suspensión de NaH (60% en aceite, 0.24 g, 6 mmoles) en THF seco (25 ml) bajo nitrógeno se agregó 15-crown-5 (0.06 g). La suspensión se enfrió en un baño con hielo. Bis(3-(trifluorometoxi)fenil)metanona (2.10 g, 6 mmoles ) y bencilfosfonato de dietilo (1.37 g, 6 mmoles) se disolvieron en THF (12 ml) y se agregó a la suspensión. La mezcla de reacción se agitó a temperatura de baño con hielo durante 15 min, se permitió entibiar hasta temperatura

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ambiente y se agitó durante la noche. La mezcla de reacción se vació dentro de agua y se extrajo con éter (2 x). Las capas de éter combinadas se lavaron con $NaHSO_3$ 10%, NaCl saturado, se secaron sobre $K_2CO_3$, se filtraron y purificaron por ISCO al usar un gradiente de 0-4% EtOAc/hexanos como eluyente para dar 3,3'-(2-fenileteno-1,1-diil)bis((trifluorometoxi)benceno) como un aceite incoloro (1.34 g, 53% de rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.33 (m, 2 H), 7.2 - 7.1 (m, 8 H), 7.04 (s, 1 H), 7.0 - 6.97 (m, 3 H).

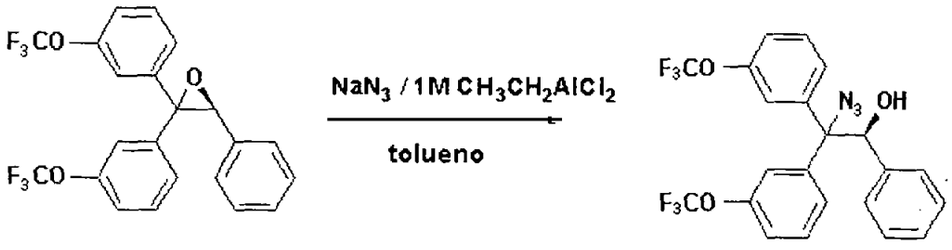
**Procedimiento 124**




Una mezcla de 3,3'-(2-fenileteno-1,1-diil)bis((trifluorometoxi)benceno) (1.30 g, 3.06 mmoles), R,R-MnCl (salen) (0.40 g, 0.64 mmoles), 4-fenilpiridina-N-óxido (0.22 g, 1.27 mmoles) en $CH_2Cl_2$ (30 ml) se enfrió en un baño con hielo. Un blanqueador frío (NaOCl 6.2% en agua, 11.54 g, 9.52 mmoles) se agregó y la mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 48 h. La mezcla de reacción café obscura se diluyó con $CH_2Cl_2$ y se filtró a través de celite. La capa orgánica se separó, se lavó con agua, NaCl saturado, se secó sobre $MgSO_4$, se filtró y se concentró para producir un aceite café

obscuro. El aceite resultante se purificó por ISCO al usar un gradiente de 0-7% EtOAc/hexanos para dar (S)-3-Fenil-2,2-bis(trifluorometoxi)fenil)oxirano como un aceite amarillo ligero (0.96 g, 71% de rendimiento). CLAR: T.R. = 4.68 min (columna Phenomenex Luna C18 5 u, eluyendo con 10-90% $MeOH/H_2O$ que contiene ácido fosfórico al 0.1% durante un gradiente de 4 minutos, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.4-7.0 (m, 13 H), 4.32 (s, 1 H).

**Procedimiento 125**

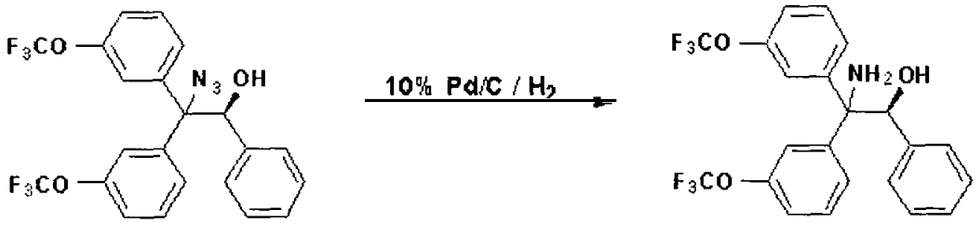



A una suspensión de sodio azida (65 mg, 1 mmoles) en tolueno (9.1 ml) se enfrió a -78°C se agregó dicloruro de etilaluminio 1 M (0.91 ml, 0.91 mmoles). La mezcla de reacción se agitó durante 4 h a -78°C. (S)-3-Fenil-2,2-bis(trifluorometoxi)fenil)oxirano (0.2 g, 0.45 mmoles) se disolvió en tolueno (0.5 ml) y se agregó gota a gota por medio de jeringa. La mezcla de reacción se agitó a -78°C durante 30 min y luego se permitió entibiar hasta temperatura ambiente y se agitó durante la noche. La mezcla de reacción se diluyó con EtOAc (5 ml) y $NaN_3$ (1 g) y agua (1 ml) se agregaron y se agitaron durante 1 h. La mezcla resultante se filtró a través de una almohadilla de sulfato de sodio y el

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producto filtrado se concentró a un aceite amarillo. El residuo se purificó por ISCO al usar un gradiente de 0-30% EtOAc/hexano como eluyente para dar (S)-2-azido-1-fenil-2,2-bis(3-(trifluorometoxi)fenil)etanol como un aceite amarillo ligero (69 mg, 31% de rendimiento). CLAR: TR = 4.438 min (columna Phenomenex Luna C18 5 u, eluyendo con 10-90% MeOH/$H_2O$ que contiene ácido fosfórico al 0.1% durante un gradiente de 4 minutos, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.5-7.0 (m, 13 H), 5.63 (d, 1 H), 2.35 (d, 1 H).

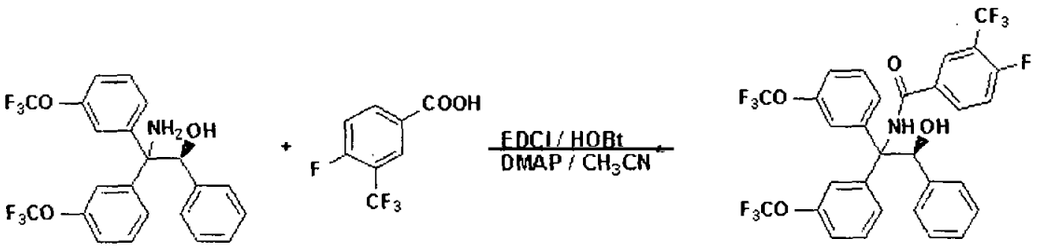
**Procedimiento 126**




Una mezcla espesa de (S)-2-azido-1-fenil-2,2-bis(3-(trifluorometoxi)fenil)etanol (64 mg, 0.132 mmoles) y Pd en C al 10% (40 mg) en metanol (2 ml) se sometió a hidrogenación en globo durante la noche a temperatura ambiente. La mezcla de reacción se filtró a través celite y el producto filtrado se concentró para dar (S)-2-amino-1-fenil-2,2-bis(3-(trifluorometoxi)fenil)etanol como un aceite amarillo ligero (53 mg, 87% de rendimiento). CLAR: TR = 3.40 min (columna Phenomenex Luna C18 5 u, eluyendo con 10-90% MeOH/$H_2O$ que contiene ácido fosfórico al 0.1% durante un gradiente de 4

minutos, observando a 220 nm). CLEM: [M+H] 458.1 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

**Procedimiento 127**

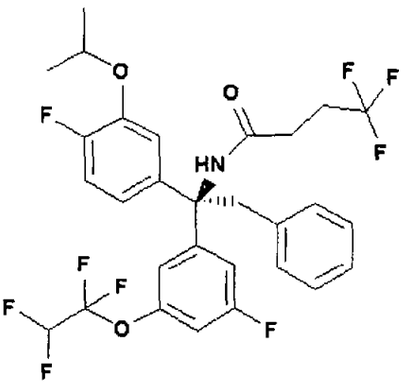



Una solución de (S)-2-amino-1-fenil-2,2-bis(3-(trifluorometoxi)fenil)etanol (44 mg, 0.096 mmoles), ácido 4-fluoro-3-(trifluorometil)benzoico (20 mg, 0.096 mmoles), EDCI (28 mg, 0.14 mmoles), HOBT (14 mg, 0.096 mmoles) y una cantidad catalítica de DMAP en acetonitrilo (3 ml) se agitó durante 24 h a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc y se lavó sucesivamente con HCl 1N, NaOH 1 N, NaCl saturado, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por CLAR preparativa de columna Shimadzu-YMC Sunfire 5 μ, 30 × 100 mm eluyendo con 50-100% MeOH (90% en $H_2O$, TFA 0.1%) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm. La (S)-4-Fluoro-N-(2-hidroxi-2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 311) se aisló como una película incolora (10 mg, 15% de rendimiento). CLAR: TR = 4.143 minutos (columna Phenomenex

1465

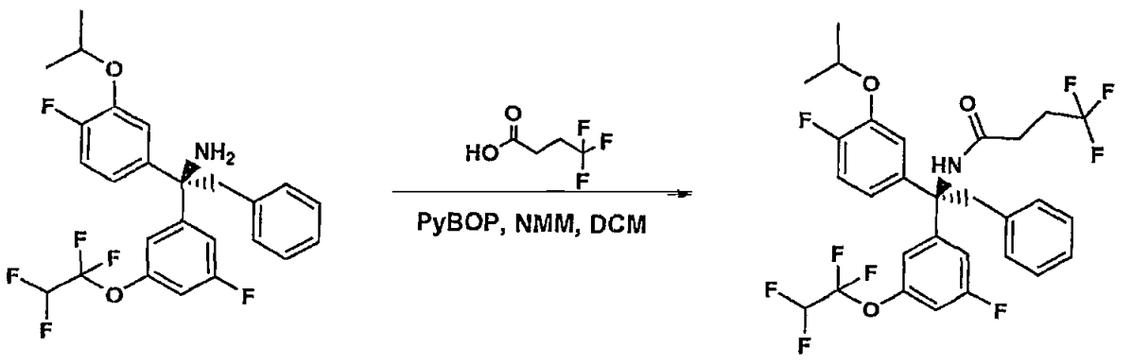
Luna C18 5 u eluyendo con 10-90% metanol acuoso que contiene ácido fosfórico al 0.1% durante un gradiente de 4 minutos observando a 220nm). CLEM: [M+H] 648.0 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 8.23 (m, 1 H), 7.37-6.9 (m, 15 H), 5.41 (s, 1 H).

**EJEMPLO 312**



**(R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)butanamida**

**Procedimiento 128**



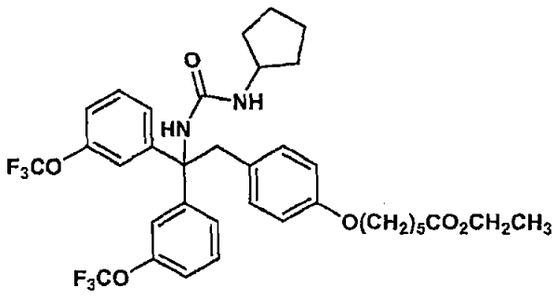

A una solución de ácido 4,4,4-trifluorobutírico (13

1466

mg, 0.09 mmoles) en DCM (0.8 ml) se le agregó hexafluorofosfato de (benzotriazol-1-iloxi)tripirrolidinfosfonio (52 mg, 0.1 mmoles), (R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina (40 mg, 0.08 mmoles), seguido por NMM (28 µl, 0.25 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 h, luego otras 16 h a 60°C. La mezcla de reacción se diluyó con EtOAc (10 ml) y la capa orgánica se lavó con $H_2O$, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por CLAR preparativa de Columna Phenomenex Luna C18, 30 X 50 mm eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene TFA 0.1%; 40 ml/min, observando a 220 nm; 40-100% ACN (90% en agua, TFA 0.1%) gradiente durante 10 min con relación de flujo 40 ml/min y detección UV a 220 nm. (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2,-tetrafluoroetoxi)fenil)-2-feniletil)butanamida (Ejemplo 312) se aisló como un liofilato (27 mg, 55% de rendimiento). CLEM: TR = 2.15 min [M+H] 608.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); CLAR: TR = 3.79 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% ACN/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 1.18 (d, $J$=6.05 Hz, 3 H), 1.24 (d,

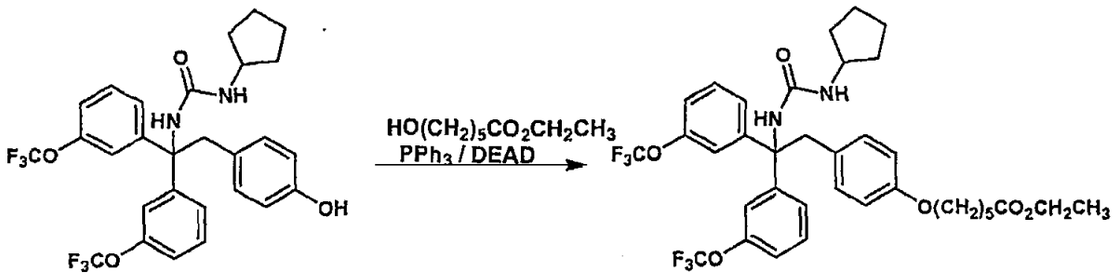
$J$=6.05 Hz, 3 H), 2.34 - 2.48 (m, 2 H), 2.51 - 2.61 (m, 2 H), 3.79 (d, $J$=13.19 Hz, 1 H), 3.98 (d, $J$=13.19 Hz, 1 H), 4.29 - 4.39 (m, 1 H), 6.12 - 6.44 (m, 1 H), 6.67 - 6.82 (m, 4 H), 6.91 - 7.07 (m, 4 H), 7.10 - 7.19 (m, 3 H), 8.29 (s, 1 H).

**EJEMPLO 313**




**6-(4-(2-(3-Ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)hexanoato de etilo**

**Procedimiento 129**

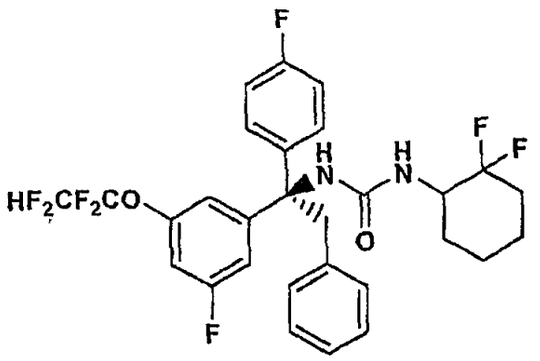



A un matraz de fondo redondo 10 ml de 3 cuellos secado al horno bajo nitrógeno se le agregó 1-ciclopentil-3-(2-(4-hidroxifenil)-1,1-bis(3-(trifluorometoxi)fenil)etil)urea, preparada como se describe en el Procedimiento 11, 6, 2 y 59, (50 mg, 0.1 mmoles), trifenilfosfina (34 mg, 0.1 mmoles), 6-hidroxihexanoato de etilo (17 mg, 0.1 mmoles) y THF seco (0.5 ml). La mezcla de

reacción se enfrió en un baño de metanol con hielo y dietilazodicarboxilato (23 mg, 0.13 mmoles) se agregó por medio de jeringa. La reacción se permitió entibiar hasta temperatura ambiente y se agitó durante la noche. La mezcla de reacción se concentró in vacuo y se purificó por cromatografía de gel de sílice ISCO al usar un gradiente de 5-25% EtOAc/hexanos como eluyente para producir 6-(4-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)hexanoato de etilo (Ejemplo 313) se aisló como un sólido blanco (43 mg, 61% de rendimiento). CLAR: TR = 4.69 minutos (columna Phenomenex Luna C18 5µ 4.6 x 50 mm eluyendo con 10-90% metanol acuoso que contiene ácido fosfórico al 0.1% durante un gradiente de 4 minutos observando a 220 nm). CL/EM [M+H] 711.3 (columna Phenomenex Luna C18 5µ 4.6 x 30 mm eluyendo con 10-90% metanol acuoso que contiene TFA 0.1% durante un gradiente de 4 minutos observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.33 (t, J= 7.9 Hz, 2 H), 7.20 (d, J= 7.9 Hz, 2 H), 7.12 (d, J= 7.9 Hz, 2 H), 7.07 (s, 2 H), 6.62 (d, J= 8.8 Hz, 2 H), 6.56 (d, J= 8.8 Hz, 2 H), 4.10 (q, J= 7.1 Hz, 2 H), 3.86 t, J = 6.1Hz, 2 H), 3.68 (s, 1 H), 3.62 (t, J= 6.6Hz, 1 H), 2.30-2.27 (m, 2 H), 1.82-1.14 (m, 17 H), 1.23 (t, J= 7.1Hz, 3 H).

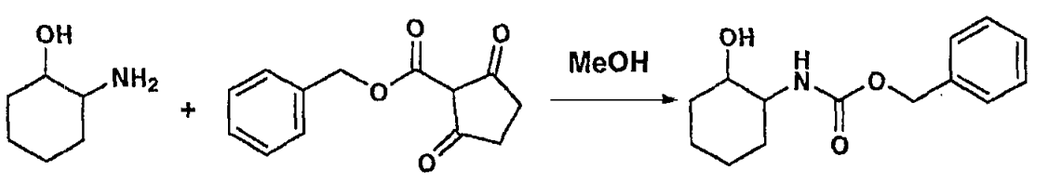
1469

**EJEMPLO 314**



**1-(2,2-difluorociclohexil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea**

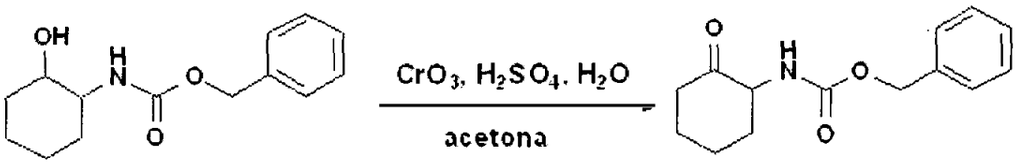
**Procedimiento 130**



A 0°C a una solución de 2,5-dioxociclopentanocarboxilato de bencilo (2.58 g, 10.35 mmoles) en MeOH (20 ml) se le agregó 2-aminociclohexanol (1.25 g, 10.87 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 18 h y se apagó con HCl 0.25 N (8 ml). El MeOH se retiró bajo vacío y la capa acuosa se extrajo con $CH_2Cl_2$ (4 × 10 ml). Las capas orgánicas combinadas se lavaron con NaCl saturado (20 ml), se secaron sobre $Na_2SO_4$, se filtraron y concentraron. El residuo se purificó por cromatografía ISCO (columna 40 g) al usar hexanos/EtOAc (0-5% durante 15 min, 5-10% durante 7 min) para dar 2-hidroxiciclohexilcarbamato de bencilo como un sólido amarillo

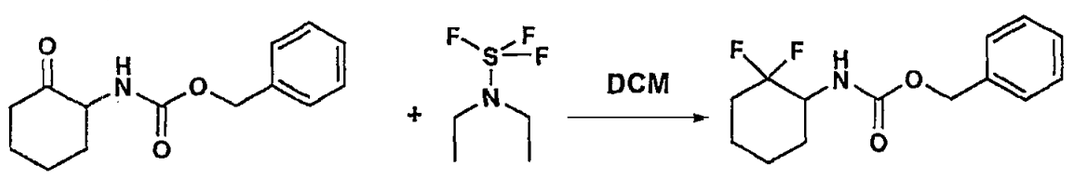
1470

ligero a un tiempo de retención de 11-13 min (2.15 g, 83% de rendimiento). CLAR: TR = 2.83 min, Pureza 95% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400 MHz $^1H$ ($CDCl_3$) 7.33 ppm, 5 H, m; 5.16 ppm, 1 H, m; 5.09 ppm, 2 H, s; 3.95 ppm, 1 H, s; 3.68 ppm, 1 H, m; 1.54 ppm, 8 H, m.



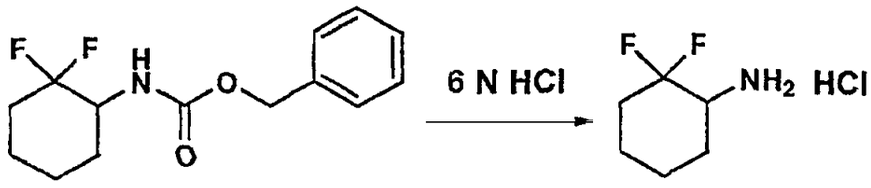

Una mezcla de $CrO_3$ (0.70 g) en $H_2SO_4$ concentrado (0.61 ml) se diluyó con $H_2O$ al volumen de 6 ml. A una solución de 2-hidroxiciclohexilcarbamato de bencilo (1.60 g, 6.43 mmoles) en acetona (5.4 ml) a 0°C se le agregó Reactivo Jones (5.51 ml, 1.17 M, 6.43 mmoles) gota a gota durante 5 min. La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, se apagó con $K_2CO_3$ acuoso al 20% a un pH = 8. La capa acuosa se extrajo con EtOAc (3 × 15 ml). Las capas orgánicas combinadas se lavaron con NaCl saturado (20 ml), se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El aceite amarillo crudo resultante se purificó por cromatografía ISCO (columna 40 g) al usar hexanos/EtOAc (0-30% durante 8 min, 30-45% durante 10 min) para dar 2-oxociclohexilcarbamato de bencilo como un aceite incoloro a un tiempo de retención de 8.5-11 min (1.26 g, 79% de

rendimiento). CLAR: TR = 2.69 min, Pureza 99% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm). RMN: 400MHz $^1H$ ($CDCl_3$) 7.33 ppm, 5 H, m; 5.76 ppm, 1 H, s; 5.11 ppm, 2 H, m; 4.27 ppm, 1 H, m; 2.65 ppm, 1 H, dd, *J*=6.60, 2.75 Hz; 2.52 ppm, 1 H, m; 2.38 ppm, 1 H, m; 2.13 ppm, 1 H, m; 1.89 ppm, 1 H, m; 1.77 ppm, 1 H, m; 1.64 ppm, 1 H, m; 1.42 ppm, 1 H, m.

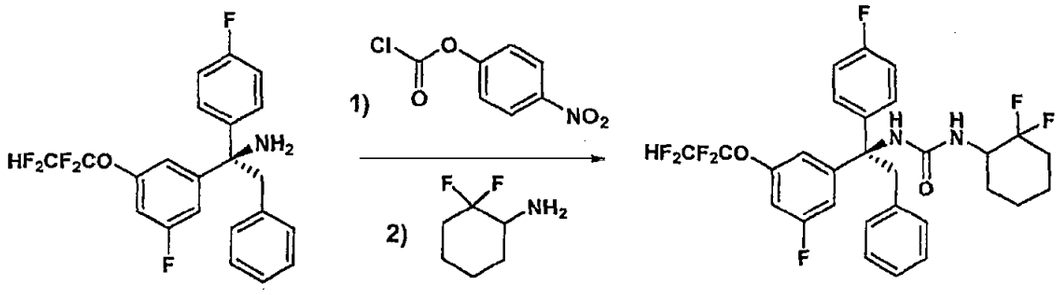



A temperatura ambiente, a una solución de 2-oxociclohexilcarbamato de bencilo (294 mg, 1.19 mmoles) en DCM (5 ml) se le agregó DAST (0.5 ml, 3.92 mmoles). La mezcla de reacción se agitó durante 18 h, se enfrió hasta 0°C y se apagó por la adición de NaCl saturado (1 ml). La fase acuosa se separó y se extrajo con DCM (3 × 8 ml). Las capas orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El residuo se purificó por cromatografía ISCO (12 g columna) al usar hexanos/EtOAc (0-30% durante 15 min, 30-45% durante 10 min) para dar 2,2-difluorociclohexilcarbamato de bencilo como un aceite café a un tiempo de retención de 7 - 10 min (272 mg, 85% de rendimiento). CLAR: TR = 3.03 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$

durante 4 minutos que contiene PPA 0.2%; 4 ml/min, observando a 220 nm). RMN: 400MHz $^1H$ ($CDCl_3$) 7.34 ppm, 5 H, m; 5.12 ppm, 2 H, m; 4.99 ppm, 1 H, d, $J$=8.35 Hz; 3.93 ppm, 1 H, m; 2.18 ppm, 1 H, m; 2.04 ppm, 1 H, m; 1.77 ppm, 2 H, m; 1.46 ppm, 4 H, m.



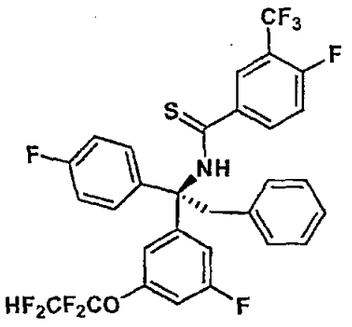

Una solución de 2,2-difluorociclohexilcarbamato de bencilo (38 mg, 0.14 mmoles) en HCl 6 N (2 ml) se calentó a 100°C durante 2 h. La mezcla de reacción fría se extrajo con éter (3 × 1 ml) y las capas orgánicas combinadas se concentraron para dar clorohidrato de 2,2-difluorociclohexanamina como un sólido café ligero (23 mg, 96% crudo).




La 1-(2,2-Difluorociclohexil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea (Ejemplo 314) fue preparada como se describe en el Procedimiento 12 (43 mg, 60% de rendimiento). CL/EM: TR

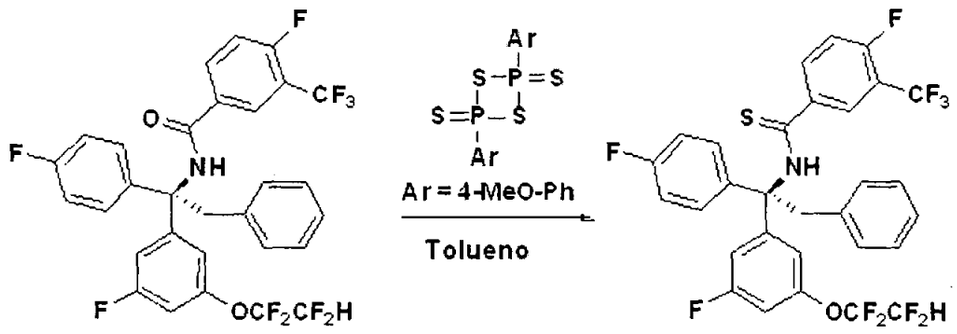
= 4.07 min [M+H] 587.3 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene 0.1% $NH_4OAc$; 4 ml/min, observando a 220 nm).

**EJEMPLO 315**



**(R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)benzotioamida**

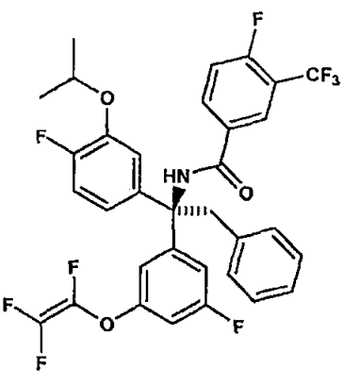
**Procedimiento 131**




A una solución agitada de (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)benzamida (105 mg, 0.17 mmoles), preparada como se describe en el Procedimiento 3, 4, 5, 6 y 7, en tolueno (5.2 ml) se agregó reactivo de Lawesson (83 mg, 0.20 mmoles). La mezcla de reacción se calentó a

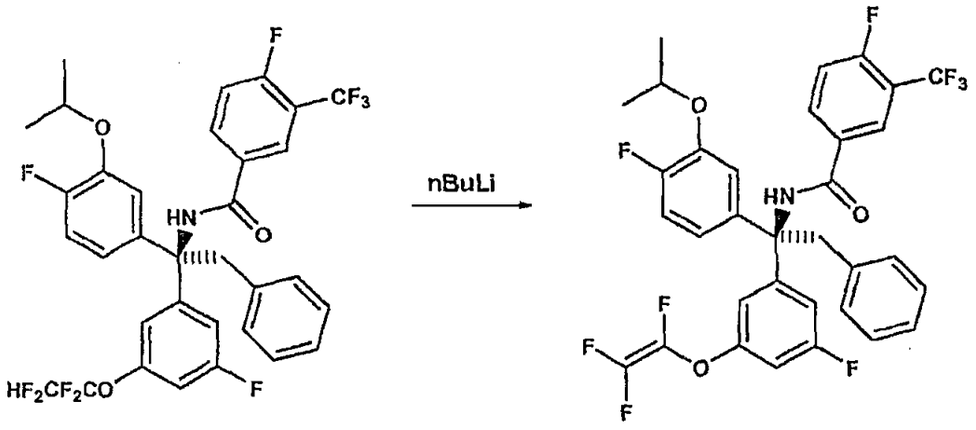
110°C. Después de 8 h, la mezcla de reacción se concentró y el residuo se purificó por cromatografía en columna ISCO (EtOAc/hexano 0-100%, $SiO_2$) para proporcionar (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil)benzotioamida (Ejemplo 315, 89 mg, 83% de rendimiento) como un aceite amarillo. $^1$H RMN (500 MHz, $CDCl_3$) δ ppm 7.92 (s, 1H), 7.74-7.72 (m, 1H), 7.68-7.66 (m, 1H), 7.22-6.86 (m, 11H), 6.72 (d, *J* = 5 Hz, 2H), 5.92-5.70 (m, 1H), 4.36 (d, *J* = 15 Hz, 1H), 3.82 (d, *J* = 10 Hz, 1H); $^{13}$C RMN (125 MHz, $CDCl_3$) δ ppm 195 (C=S); CL/EM: TR = 4.393 min [M+H] 632.4 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeCN/$H_2O$ durante 4 minutos que contiene $NH_4OAc$ 0.1%; 4 ml/min, observando a 220 nm).

**EJEMPLO 316**




**(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,2,2-trifluoroviniloxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

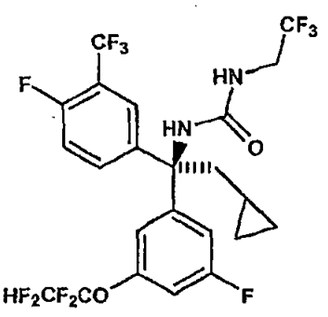
**Procedimiento 132**




A -78°C bajo argón, a una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (31 mg, 0.046 mmoles), preparada como se describe en el Procedimiento 3, 4, 5, 6, 7, 59 y 68, en THF seco (0.7 ml) se agregó nBuLi (2.5 M en hexano, 0.25 ml, 0.625 mmoles) gota a gota. La mezcla de reacción se permitió entibiar a -5°C durante un periodo de 1.5 h. Después de agitar durante un total de 2 h, la mezcla de reacción se apagó por la adición de $NH_4Cl$ saturado y la fase acuosa se extrajo con EtOAc y la capa orgánica se concentró. El residuo resultante se purificó por CLAR de fase inversa para dar el producto puro deseado (7 mg, 23% de rendimiento). CL-EM: TR = 4.19 min [M+H] 654.3 (columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% $MeOH/H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, Metanol-$d_4$) $\delta$ ppm 8.85 (m, 1 H), 8.00 (m, 2 H),

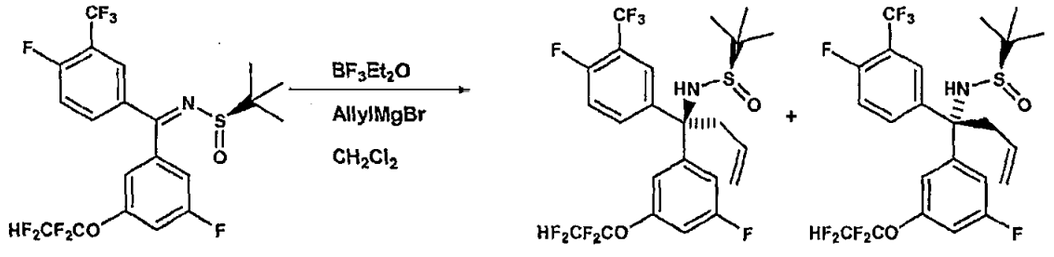
7.47 (t, *J*=8.8 Hz, 1 H), 7.22 (m, 1 H), 7.15 (t, *J*=7.7 Hz, 2 H), 7.07 (m, 1 H), 7.01-6.94 (m, 2 H), 6.90 (m, 1 H), 6.88-6.83 (m, 2 H), 6.75 (m, 1 H), 4.01 (AB, *J*=12.9 Hz, 2 H), 1.27, 1.21 (d, *J*=6.1 Hz, 6 H).

**EJEMPLO 317**



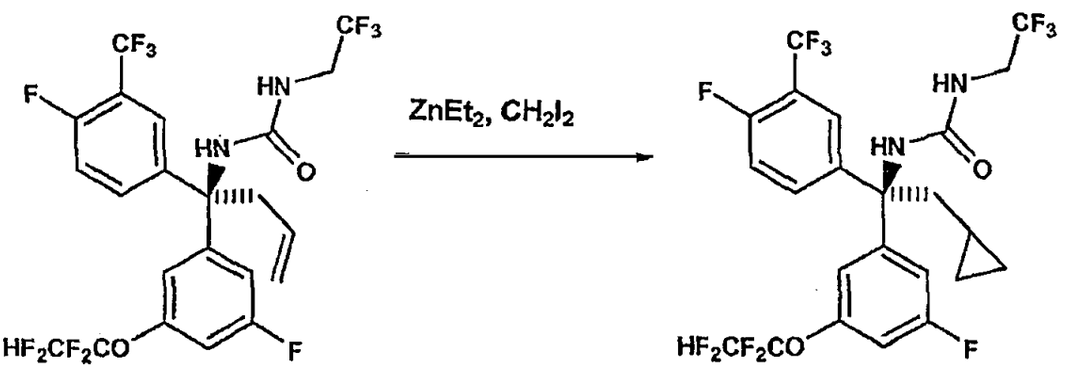
**(*R*)-1-(2-ciclopropil-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea**

**Procedimiento 133**




Siguiendo el procedimiento 14, (R)-N-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)but-3-enil)-2-metilpropano-2-sulfinamida se preparó (1.9 g, 92% de rendimiento). Los dos diaestereómeros se separaron por medio de columna quiral AD (20% isopropanol/heptanos/DEA 0.1%) para dar (R)-N-((S)-1-(4-

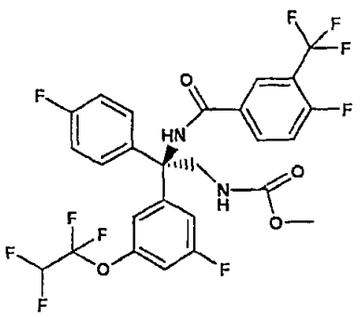
fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)but-3-enil)-2-metilpropano-2-sulfinamida (1.02 g) como el isómero de elución rápida y (R)-N-((R)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)but-3-enil)-2-metilpropano-2-sulfinamida (0.88 g) como el isómero de elución lenta. (R)-N-((R)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)but-3-enil)-2-metilpropano-2-sulfinamida: CLEM: TR = 4.08 min [M+H] 548.2 (columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).




A 0°C bajo argón, a una solución de (R)-1-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)but-3-enil)-3-(2,2,2-trifluoroetil)urea (40 mg, 0.070 mmoles), preparada

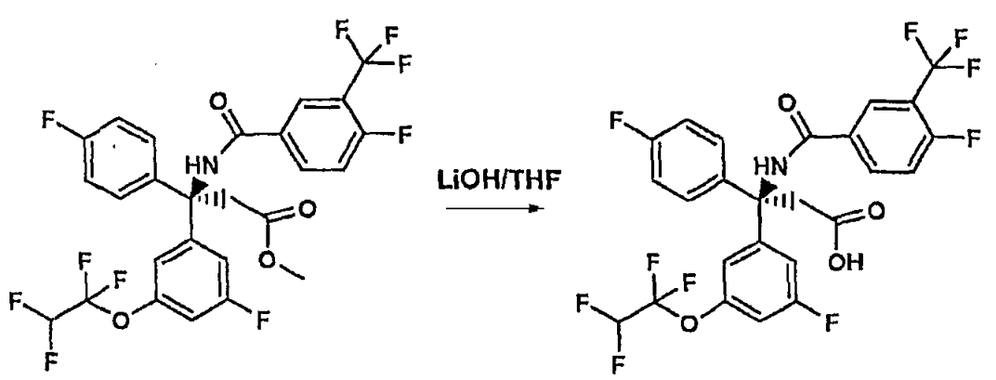
como se describe en el Procedimiento 6 y 10, en tolueno seco (1 ml) se agregó Zinc de dietilo (1.0 M en hexano, 1.2 ml, 1.2 mmoles), seguido por adición gota a gota de diyodometano (0.2 ml). La mezcla de reacción se entibió gradualmente a 110°C, y se calentó a 110°C durante 1 h. Después del enfriamiento, HCl 1N se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 5 min. La mezcla de reacción se extrajo con EtOAc y la capa orgánica se lavó con $H_2O$, $NaHCO_3$ saturado, NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se purificó por CLAR preparativa (columna phenomenex AXIA Luna 75 x 30 mm, 5 u eluyendo con 50-100% MeOH en $H_2O$ con TFA 0.1%, 40 ml/min, observando a 220 mn) para dar (R)-1-(2-ciclopropil-1-(4-fluoro-3-(trifluorometil)-fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 317) como un sólido blanco (13 mg, rendimiento 32%). CLEM: TR = 3.26 min [M+H] 583.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 50-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.55 (d, *J*=6.6 Hz, 1 H), 7.46 (m, 1 H), 7.12 (t, *J*=9.3 Hz, 1 H), 6.94-6.85 (m, 3 H), 5.84 (tt, *J*=52.8, 2.8 Hz, 1 H), 5.61 (br, s, 1 H), 4.78 (br, t, *J*=6.1 Hz, 1 H), 3.69 (m, 2 H), 2.31 (m, 2 H), 0.36 (m, 3 H), 0.00 (m, 2 H).

**EJEMPLO 318**



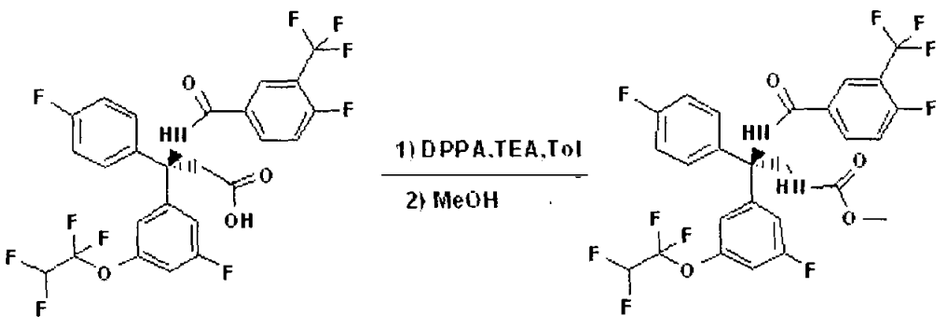
**3-(4-fluoro-3-(trifluorometil)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-3-(4-fluorofenil)propanoato de (R)-metilo**

**Procedimiento 134**




Acido (R)-3-(4-fluoro-3-(trifluorometil)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-3-(4-fluorofenil)propanoico fue preparado como se describe en el Procedimiento 3, 4, 5, 14, 6, 7 y 23 (32 mg, 79% de rendimiento). CLEM: 2.03 min [M+H] 584.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 3.70 (s, 2 H), 6.18 (t, *J*=53 Hz, 1 H), 6.97 (d, *J*=8.79 Hz, 1 H), 7.08 (t, *J*=8.79

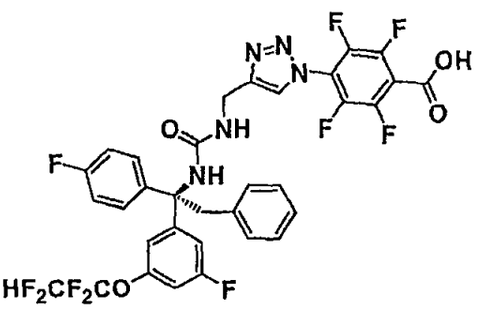
Hz, 2 H), 7.14 (s, 1 H), 7.19 (d, $J$=10.44 Hz, 1 H), 7.34 - 7.50 (m, 3 H), 8.05 - 8.18 (m, 3 H).




A una solución de ácido (R)-3-(4-fluoro-3-(trifluorometil)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-3-(4-fluorofenil)propanoico (32 mg, 0.055 mmoles) en tolueno (0.5 ml) se le agregó DPPA (18 mg, 0.066 mmoles) y TEA (7 mg, 0.066 mmoles). La mezcla de reacción se calentó a 100°C durante 1 h seguido por la adición de MeOH y TEA. La reacción se calentó a 65°C durante la noche. El $K_2CO_3$ en exceso se agregó y la reacción se calentó a reflujo durante 3 h. La mezcla de reacción se concentró y el residuo resultante se purificó por CLAR preparativa (columna phenominex 30 x 100 mm, 30-100% MeOH (90% en agua, TFA 0.1%) gradiente durante 12 min con relación de flujo 40 ml/min y detección UV a 220 nm) para producir 3-(4-fluoro-3-(trifluorometil)benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-3-(4-fluorofenil)propanoato de (R)-metilo (Ejemplo 318) como un sólido blanco (5 mg, 15% de rendimiento). CLEM: TR = 3.92 min [M+H] 613.3 (4 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90%

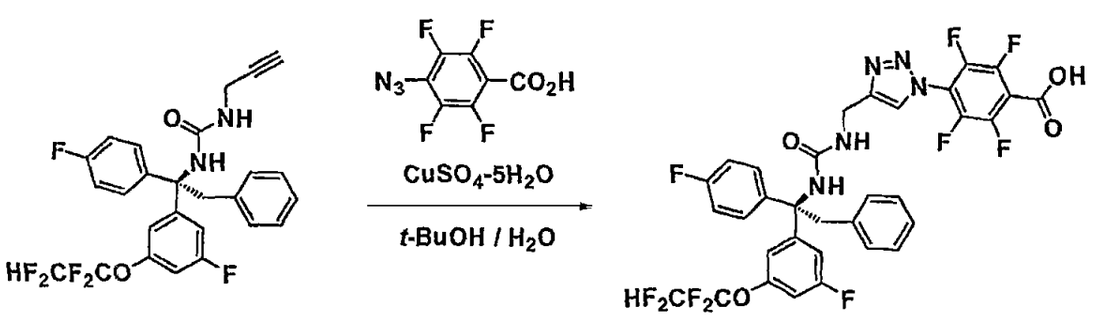
MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) ppm 3.74 (s, 3 H), 3.87 - 4.11 (m, 2 H), 4.89 (m, 1 H), 5.86 (t, 1 H), 6.95 (d, 1 H), 6.99 - 7.13 (m, 5 H), 7.28 - 7.40 (m, 3 H), 8.09 - 8.16 (m, 1 H), 8.26 (d, 1 H), 8.94 (s, 1 H).

**EJEMPLO 319**



**Acido (R)-2,3,5,6-tetrafluoro-4-(4-((3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)metil)-1H-1,2,3-triazol-1-il)benzoico**

**Procedimiento 135**

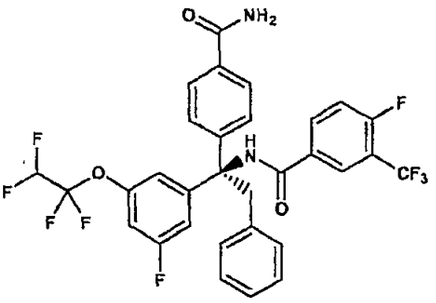



A una suspensión de (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(prop-2-inil)urea (5.0 mg, 0.01 mmoles), preparada como se

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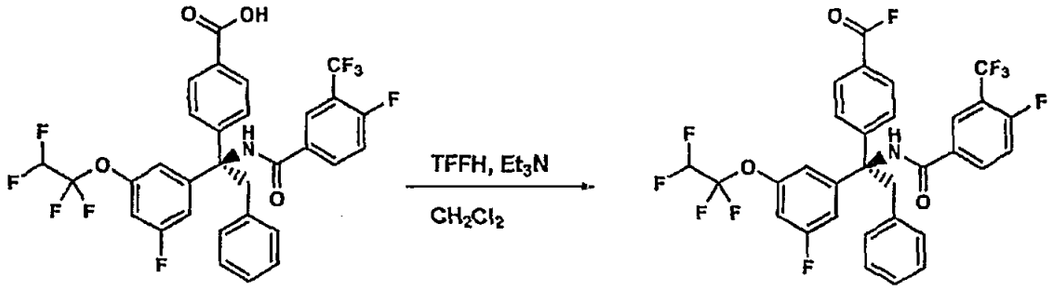
describe en el Procedimiento 3, 4, 5, 6 y 12, en una mezcla 1:1 de agua y alcohol ter-butílico (100 µl) se le agregó ácido 4-azido-2,3,5,6-tetrafluorobenzoico (2.3 mg, 0.01 mmoles), seguido por ascorbato de sodio (solución 1M en $H_2O$, 100 µl) y $CuSO_4 \cdot 5H_2O$ (1 mg). La mezcla de reacción se agitó vigorosamente durante la noche en un vial sellado. La mezcla de reacción se diluyó con $H_2O$ y se extrajo con EtOAc (3 x). Las porciones orgánicas combinadas se concentraron y el residuo se disolvió en MeOH y se purificó por CLAR preparativa (Phenoma Onyx Monolithic 10 x 100mm; eluyendo con 10%-90% MeCN/$H_2O$ con TFA 0.1%, observando a 220 nm) para proporcionar ácido (R)-2,3,5,6-tetrafluoro-4-(4-((3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)metil)-1H-1,2,3-triazol-1-il)benzoico (Ejemplo 319, 5.7 mg, 78% de rendimiento). CL/EM: TR = 3.610 min [M+H] 742.3 (columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene $NH_4OAc$ 0.1%; 4 ml/min, observando a 220 nm). $^1H$ RMN (500 MHz, MeOH-$d_4$) δ 8.02 (s, 1 H), 7.10-6.79 (m, 11 H), 6.53 (d, *J* = 5Hz, 2 H), 6.27-6.04 (m, 1 H), 4.38-4.31 (m, 2 H), 3.81 (d, *J* = 15Hz, 1 H), 3.73 (d, *J* = 10Hz, 1 H).

**EJEMPLO 320**



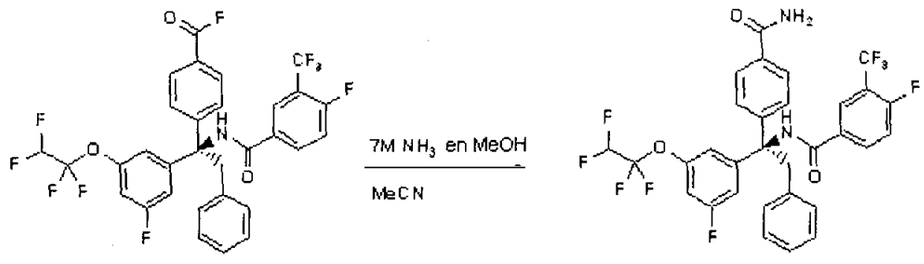
**(R)-N-(1-(4-carbamoilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 136**




A una suspensión de ácido (R)-4-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)benzoico (224 mg, 0.4 mmoles), preparada como se describe en el Procedimiento 3, 4, 5, 6, 7, 56, 57 y 23, en diclorometano (3 ml) se agregó trietil amina (97 µL, 0.70 mmoles) seguido por hexafluorofosfato de fluoro-N,N,N',N'-tetrametilformamidinio (TFFH) (138 mg, 0.5 mmoles). La mezcla de reacción se agitó durante 18 h. La mezcla de reacción se concentró y el residuo se purificó por Cromatografía de vaporización instantánea (40

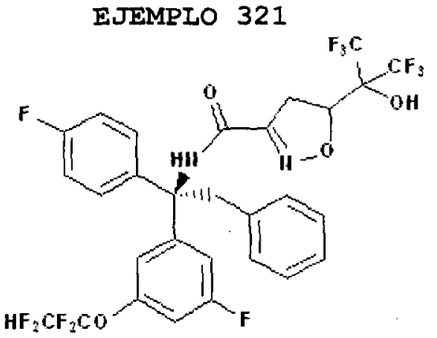
g gel de sílice; acetato de etilo 0-40%, gradiente de hexanos durante 14 min., 40 ml/min) para proporcionar fluoruro de (R)-4-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)benzoilo (127 mg, 56% de rendimiento). CLEM: TR = 2.39 min [M+H] 644 (columna Chromolith Performance 18e 4.6 x 100 mm, 10-90% metanol, agua con gradiente de ácido trifluoroacético 0.1% durante 2 min, 5 ml/min)




A una suspensión de fluoruro de (R)-4-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)benzoilo (20 mg, 0.03 mmoles) en acetonitrilo (1 ml) se le agregó amoníaco (7 M en metanol, 20 µL, 0.14 mmoles). La mezcla de reacción se agitó durante 24 h. La mezcla de reacción se concentró y el residuo se purificó por Cromatografía de vaporización instantánea (4 g gel de sílice; 0-100% acetato de etilo, gradiente de hexanos durante 14 min., 18 ml/min) para proporcionar (R)-N-(1-(4-carbamoilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 320, 13 mg, 65% de

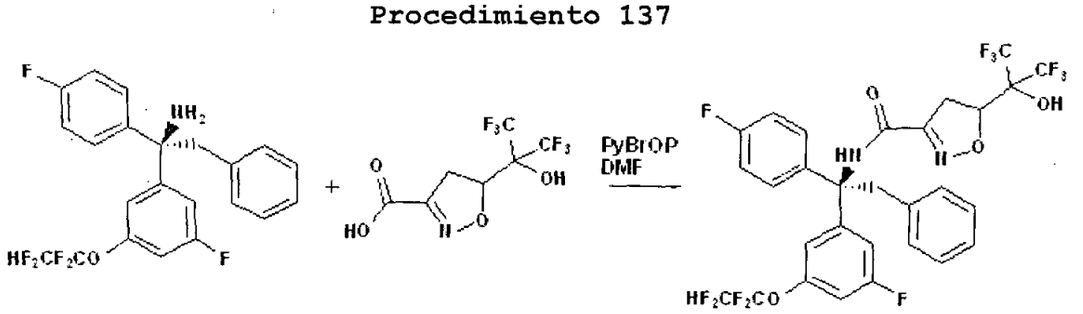
rendimiento). CLEM: TR = 1.81 min [M+H] 631 (columna Chromolith Performance 18e 4.6 x 100 mm, 50-90% metanol, agua con ácido trifluoroacético 0.1% gradiente durante 2 min, 5 ml/min). $^1$H RMN (400 MHz, $CDCl_3$) ppm 7.86 (1 H, d, *J*=4.83 Hz), 7.77 (1 H, dt, *J*=8.35, 2.20 Hz), 7.71 (2 H, d, *J*=8.35 Hz), 7.14 - 7.25 (3 H, m), 7.08 (3 H, t, *J*=7.47 Hz), 6.85 - 6.90 (3 H, m), 6.71 (1 H, s), 6.63 (2 H, d, *J*=7.03 Hz), 6.05 (1 H, s), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 5.70 (1 H, s), 3.86 (2 H, dd, *J*=37.4, 13.2 Hz).

**EJEMPLO 321**



**N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-5-(1,1,1,3,3,3-hexafluoro-2-hidroxipropan-2-il)-4,5-dihidroisoxazol-3-carboxamida**

**Procedimiento 137**

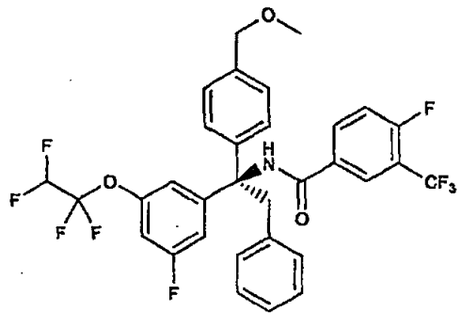



(R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina se preparó por los métodos

descritos en el Procedimiento 3, 4, 5 y 6. El ácido 5-(1,1,1,3,3,3-Hexafluoro-2-hidroxipropan-2-il)-4,5-dihidroisoxazol-3-carboxílico se preparó como se describe en Journal of Medicinal Chemistry, 2006, 49, 14, 4055. A una solución de (R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (60 mg, 0.14 mmoles), en DMF anhidro (1 ml) se le agregó N-metilmorfolina (26 mg, 0.28 mmoles), PyBrOP (73 mg, 0.14 mmoles) y ácido 5-(1,1,1,3,3,3-hexafluoro-2-hidroxipropan-2-il)-4,5-dihidroisoxazol-3-carboxílico (40 mg, 0.14 mmoles). La solución resultante se agitó a temperatura ambiente durante 16 h. La solución resultante se diluyó con MeOH (0.5 ml) y se purificó por CLAR preparativa (columna YMC Sunfire 30 x 100 mm, eluyendo con 10-90% MeOH/$H_2O$ durante 10 minutos que contiene TFA 0.1%; 40 ml/min, observando a 220 nm). La (N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-5-(1,1,1,3,3,3-hexafluoro-2-hidroxipropan-2-il)-4,5-dihidroisoxazol-3-carboxamida (Ejemplo 321, 3 mg, 3% de rendimiento) se aisló como un aceite incoloro a un tiempo de retención de 11.29 min. CLEM: TR = 2.18 min [M+H] 689.45 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); CLAR: TR = 4.14 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que

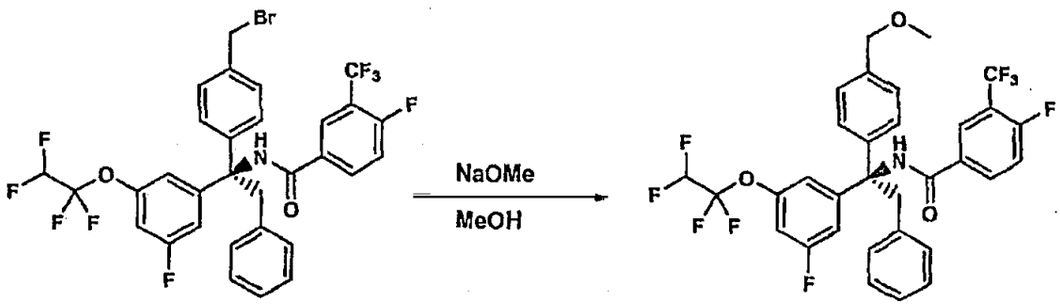
contiene PPA 0.2%; 4 ml/min, observando a 220 nm) RMN: 400 MHz $^1H$ ($CDCl_3$) La relación diaestereomérica es 1:1; 7.28 - 6.86 ppm, 24 H, m; 6.64 ppm, 1 H, m; 6.61 ppm, 1 H, m; 5.88 ppm, 2 H, t, J=60.0 Hz; 5.16 ppm, 2 H, t, J=16.0 Hz; 3.94 ppm, 1 H, d, J=12.0 Hz; 3.88 ppm, 1 H, d, J=12.0 Hz; 3.75 ppm, 1 H, d, J=12.0 Hz; 3.68 ppm, 1 H, d, J=12.0 Hz; 3.61 ppm, 2 H, m; 3.40 ppm, 1 H, dm, J=12.0 Hz; 3.33 ppm, 1 H, dm, J=12.0 Hz.

**EJEMPLO 322**



**(R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-(metoximatil)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

**Procedimiento 138**

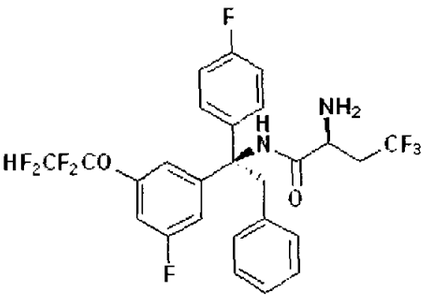



La (R)-N-(1-(4-(bromometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-

(trifluorometil)benzamida (preparada como se describe en el Procedimiento 3, 4, 5, 6, 7, 56, 57, 100 y 32, 24 mg, 0.035 mmoles) se disolvió en 0.5 ml de metanol. A esta solución se agregó metóxido de sodio (25% en peso, 0.5 ml) y la mezcla de reacción se agitó durante 40 min. La reacción se apagó con HCl 1.0 M y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El aceite resultante se purificó por Cromatografía de vaporización instantánea (columna de gel de sílice 4 g, 0-100% EtOAc/gradiente de hexanos durante 11 min., relación de flujo 18 ml/min) para proporcionar (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-(metoximatil)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 321) como un sólido blanco (15 mg, 67% de rendimiento). CL/EM: TR = 1.62 min [M+H] 642 (columna Chromolith Performance 18e 4.6 x 100 mm, 50-90% acetonitrilo, agua con ácido trifluoroacético 0.1% gradiente durante 2 min, 5 ml/min); $^1$H RMN (400 MHz, $CDCl_3$) ppm 7.91 (1 H, d, $J$=7.15 Hz), 7.77 - 7.87 (1 H, m), 7.08 - 7.44 (7 H, m), 6.97 - 7.05 (2 H, m), 6.92 (1 H, d, $J$=8.79 Hz), 6.66 - 6.75 (3 H, m), 5.87 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 4.47 (2 H, s), 4.09 (1 H, d, $J$=13.2 Hz), 3.81 (1 H, d, $J$=13.2 Hz), 3.42 (3 H, s).

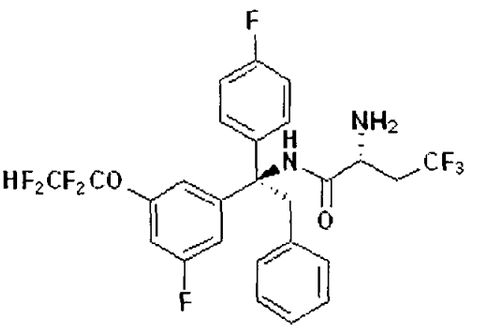
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**EJEMPLO 323A**



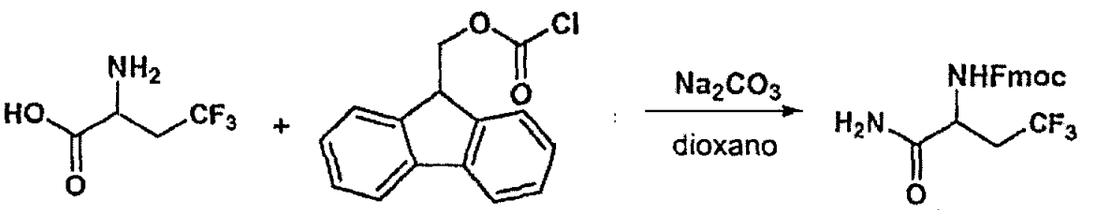
**(S)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida**

**EJEMPLO 323B**



**(R)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida**

**Procedimiento 139**

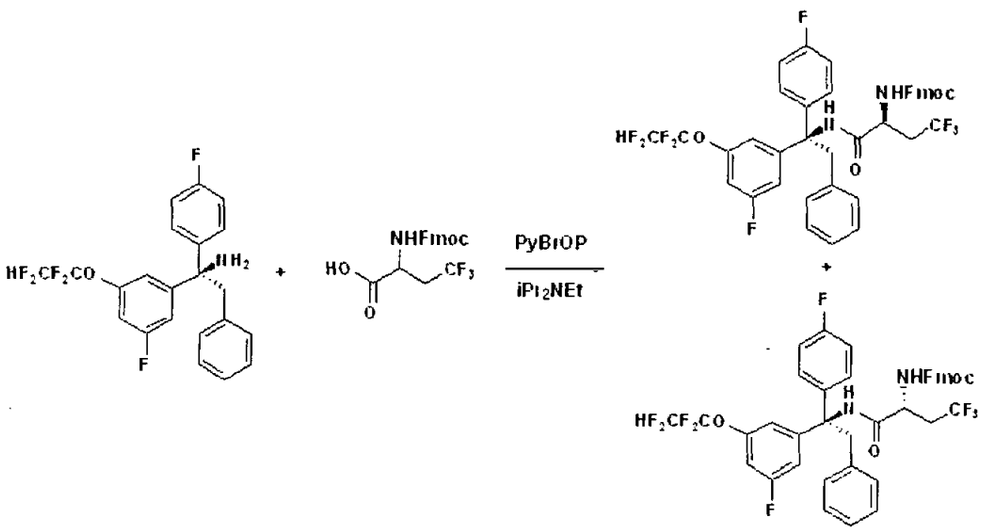



A una solución de ácido 2-amino-4,4,4-trifluorobutanoico (239.0 mg, 1.52 mmoles)) en dioxano (6 ml)

1490

se le agregó $Na_2CO_3$ al 10%, seguido por clorhidrato de (9H-fluoren-9-il)metil carbono (394.0 mg, 1.52 mmoles). La mezcla de reacción se agitó a 0°C durante 1 h, luego a temperatura ambiente durante 1 h. La mezcla de reacción se vació dentro de una mezcla de éter y agua. La capa acuosa se trató con HCl concentrado, luego se extrajo con 3 x EtOAc. Las capas orgánicas se combinaron y se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía ISCO (columna 10 g, eluyendo con 0-30% EtOAc/hexano que contiene AcOH 0.1%) para producir 1-amino-4,4,4-trifluoro-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo como un sólido blanco (260.0 mg, rendimiento 45%). CLEM: TR = 3.06 min [M+H] 380.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm).

**Procedimiento 140**



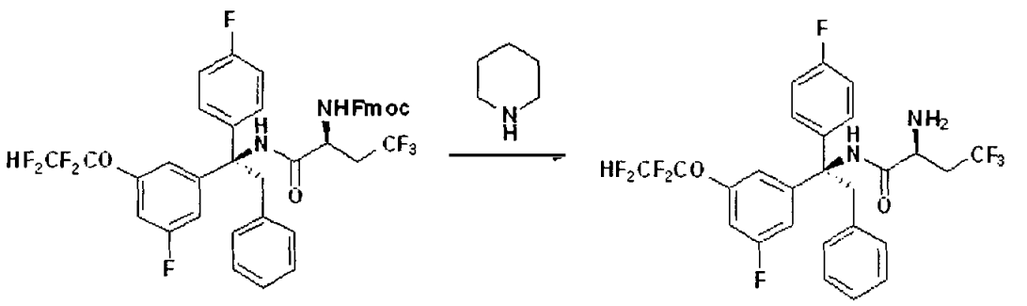

A una solución de (R)-1-(3-fluoro-5-(1,1,2,2-

tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletanamina (31 mg, 0.07 mmoles), preparada como se describe en el Procedimiento 3, 4, 5 y 6, en DCM (1 ml) se le agregó 1-amino-4,4,4-trifluoro-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo (31 mg, 0.08 mmoles), seguido por PyBrOP y $iPr_2NEt$. La mezcla de reacción se agitó a temperatura ambiente durante 72 h y se concentró. El residuo se purificó por CLAR preparativa (columna Axia, 30 x 100 mm, 60-100% MeOH/$H_2O$ con TFA 0.1% durante 12 min, relación de flujo 40 ml/min, observando a 220 nm) para producir 4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo como un sólido blanco (20 mg, 38% de rendimiento). CLEM: TR = 4.5 min [M+H] 787.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). Esta mezcla diaestereomérica se separó por columna Chiralpak AD eluyendo con 10% MeOH/EtOH(1:1)/90% heptano con relación de flujo 20 ml/min. El (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo se eluyó a un tiempo de retención de 8.26 min y se aisló como un sólido blanco (10 mg). El (R)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-

1492

1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo se eluyó a un tiempo de retención de 12.97 min y se aisló como un sólido blanco (10 mg). La estereoquímica de (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo y (R)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo se asignó arbitrariamente.

**Procedimiento 141**



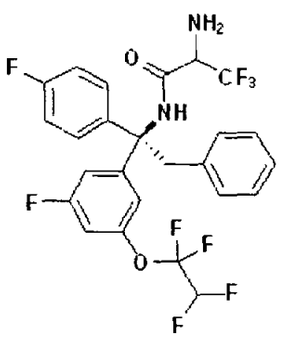

A una solución de (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-1-oxobutan-2-ilcarbamato de (9H-fluoren-9-il)metilo (10 mg, 0.01 mmoles) en DCM (0.5 ml) se le agregó piperidina (20 mg, 0.1 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h y se concentró. El residuo se purificó por CLAR preparativa (columna Axia, 30 x 100 mm, 30-100% MeOH/$H_2O$ con TFA 0.1% durante 12 min, relación de flujo 40 ml/min, observando a 220 nm) para

producir (S)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida (Ejemplo 323A) como un sólido blanco (6 mg, 82% de rendimiento). CLEM: TR = 3.1 min [M+H] 565.22 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 8.14 (1 H, s), 7.17 - 7.22 (1 H, m), 7.12 (2 H, t, *J*=7.33 Hz), 7.03 - 7.08 (2 H, m), 6.96 - 7.02 (2 H, m), 6.88 (3 H, s), 6.59 (2 H, d, *J*=7.07 Hz), 5.85 (1 H, t, *J*=2.53 Hz), 4.09 (1 H, s), 3.91 (1 H, d, *J*=13.14 Hz), 3.71 (1 H, d, *J*=13.39 Hz), 2.66 (2 H, m). (R)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida (Ejemplo 323B) se preparó en el mismo método aquí y se aisló como un sólido blanco (6 mg, 82% de rendimiento). CLEM: TR = 3.1 min [M+H] 565.22 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.80 (1 H, s), 7.19 (1 H, t, *J*=7.33 Hz), 7.08 - 7.15 (4 H, m), 6.93 - 7.00 (2 H, m), 6.84 - 6.92 (2 H, m), 6.81 (1 H, s), 6.58 (2 H, d, *J*=7.07 Hz), 5.84 (1 H, t, *J*=2.65 Hz), 4.26 (1 H, d, *J*=5.56 Hz), 3.76 - 3.86 (2 H, m), 2.53 (1 H, d, *J*=10.61 Hz), 2.43 - 2.49 (1 H, m). La estereoquímica de (S)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-

1494

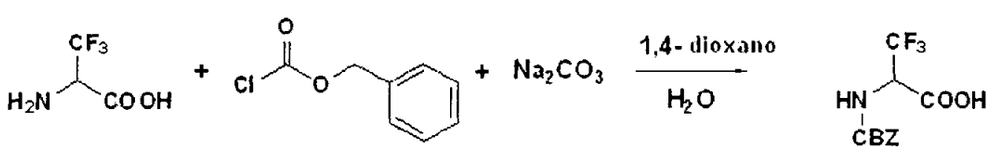
fluorofenil)-2-feniletil)butanamida (Ejemplo 323A) y (R)-2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-butanamida (Ejemplo 323B) se asignó arbitrariamente.

**EJEMPLO 324**



**2-amino-3,3,3-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)propanamida**

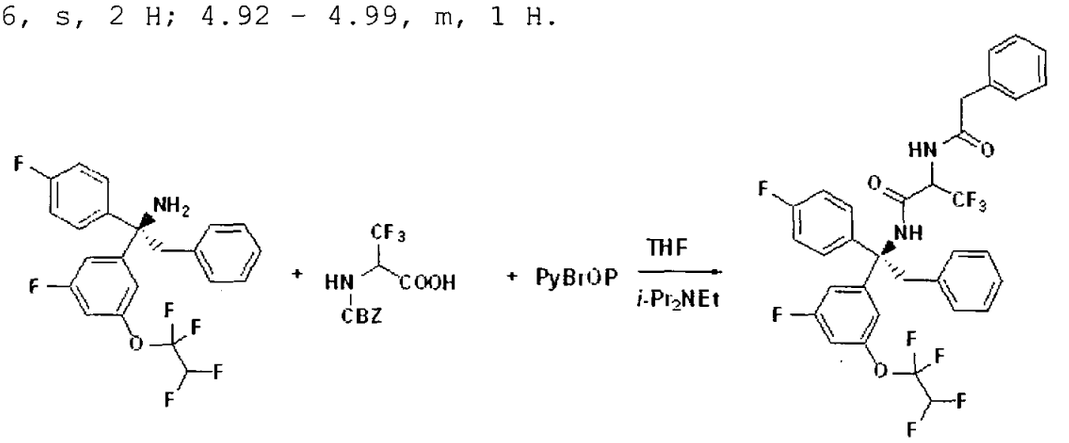
**Procedimiento 142**



A 0°C, a una solución de ácido 2-amino-3,3,3-difluoropropanoico (143 mg, 0.1 mmoles) en 1,4-dioxano (1.3 ml) se le agregó $Na_2CO_3$ acuoso al 10% (2.6 ml), seguido por adición gota a gota de clorhidrato de bencil carbono (170 mg, 0.1 mmoles) en 1,4-dioxano (2.6 ml). La mezcla de reacción se agitó a 0°C durante 1 h, luego se permitió entibiar hasta temperatura ambiente y se agitó a temperatura ambiente durante 72 h. La mezcla de reacción se concentró y el residuo

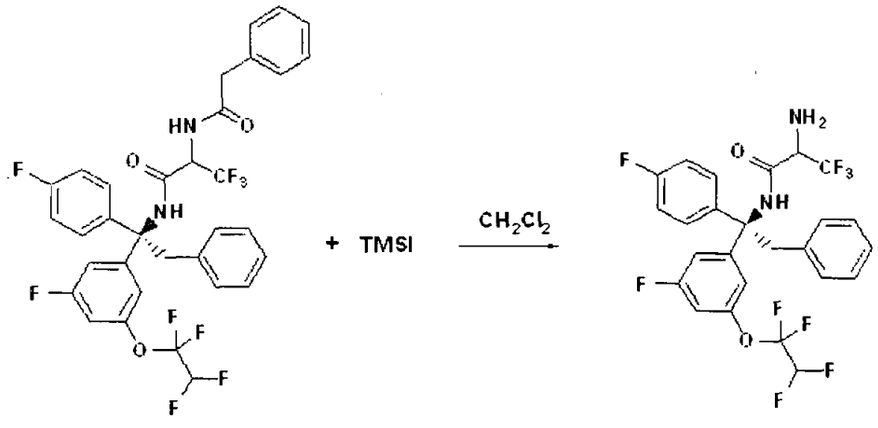
1495

se purificó por CLAR preparativa (Phenomenex Luna AXIA 5 µ 21.2 x 100 mm, 10% - 90% ACN/$H_2O$ que contiene TFA 0.1%, relación de flujo 20 ml/min, tiempo de gradiente 10 min) para producir ácido 2-(benciloxicarbonilamino)-3,3,3-trifluoropropanoico como un sólido blanco (108 mg, 76% de rendimiento). CLAR: TR = 2.64 min [M+Na] 300.1 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.12 - 7.22, m, 5 H; 4.96, s, 2 H; 4.92 - 4.99, m, 1 H.




Siguiendo el procedimiento 140, 1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-3-oxopropan-2-ilcarbamato de bencilo se preparó como un sólido amarillo (13 mg, 25% de rendimiento). CLAR: TR = 4.15 min [M+H] 685.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.26 - 7.51, m, 6 H; 7.18 - 7.23, m, 1 H; 6.97 - 7.15, m, 7 H; 6.84 - 6.93, m, 3

H; 6.58 - 6.61, m, 2 H; 5.71 - 5.98, t, *J* = 34, 1 H; 5.73, m, 1 H; 5.07 - 5.11, m, 2 H; 4.87, m, 1 H; 3.81 - 3.90, m, 1 H; 3.69 - 3.73, m, 1 H.

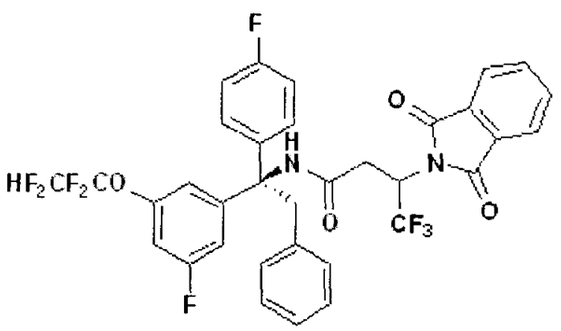



A una solución de 1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletilamino)-3-oxopropan-2-ilcarbamato de bencilo (10 mg, 0.014 mmoles) en $CH_2Cl_2$ (0.5 ml) se le agregó TMSI (18 mg, 0.094 mmoles). La mezcla de reacción se selló y se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por CLAR preparativa (Phenomenex Luna AXIA 5 µ 21.2 x 100 mm, 10% - 90% ACN/$H_2O$ que contiene TFA 0.1%, relación de flujo 20 ml/min, tiempo de gradiente 10 min) para producir 2-amino-3,3,3-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)propanamida (Ejemplo 324) como un sólido blanco (5 mg, 65% de rendimiento). CLAR: TR = 1.90 min [M+H] 551.5 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90%

1497

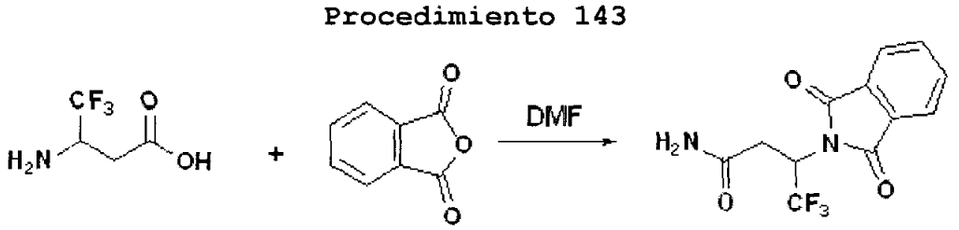
MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.82 - 7.85, m, 1 H; 7.19 - 7.23, m, 1 H; 7.11 - 7.17, m, 2 H; 7.07 - 7.11, m, 1 H; 6.98 - 7.03, m, 3 H; 6.89 - 6.93, m, 2 H; 6.80 - 6.86, m, 1 H; 6.61 - 6.64, m, 2 H; 5.73 - 5.99, t, *J* = 52, 1 H; 4.00 - 4.03, *J* = 12, d, 1 H; 3.98, m, 1 H; 3.63 - 3.67, d, *J* = 12, 1 H;

**EJEMPLO 325**




**3-(1,3-dioxoisoindolin-2-il)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida**

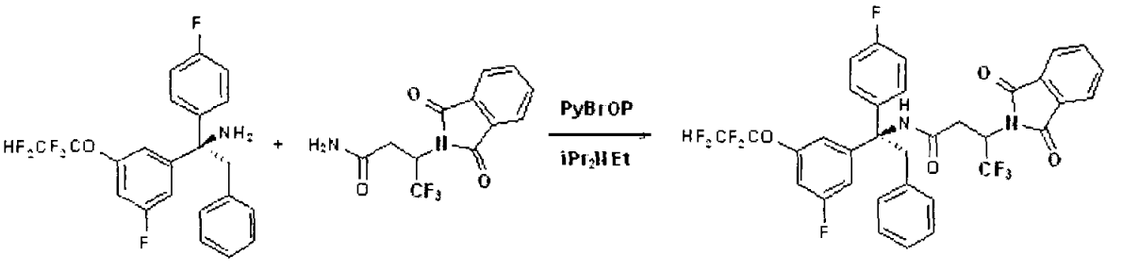
**Procedimiento 143**




Una solución de ácido 3-amino-4,4,4-trifluorobutanoico (628 mg, 4 mmoles) y isobenzofuran-1,3-diona (592 mg, 4 mmoles) en DMF (5 ml) se calentó a 140°C bajo radiación por microondas durante 15 min. La mezcla de

1498

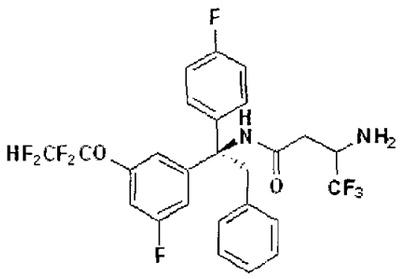
reacción se purificó por CLAR preparativa (columna Axia luna, 30 x 75 mm, 10-100% ACN/$H_2O$ con TFA 0.1% durante 10 min, relación de flujo 40 ml/min, observando a 220 nm) para producir 3-(1,3-dioxoisoindolin-2-il)-4,4,4-trifluorobutanamida (620 mg, 54% de rendimiento). CLEM: TR = 1.54 min [M+H] 288.2 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).




3-(1,3-Dioxoisoindolin-2-il)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida (Ejemplo 325) se preparó como un sólido blanco (12 mg, 27% de rendimiento) como se describe en el Procedimiento 140. CLEM: TR = 3.62 min [M+H] 695.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.76 - 7.88 (4 H, m), 7.15 - 7.01 (3 H, m), 6.91 - 6.97 (2 H, m), 6.80 - 6.86 (2 H, m), 6.61 - 6.72 (3 H, m), 6.54 (2 H, dd, *J*=13.26, 7.71 Hz), 6.21 (1 H, d, *J*=4.55 Hz), 5.84 (1 H, t, *J*=2.78 Hz), 5.25 (1 H, m), 3.87 (1 H, d, *J*=13.14 Hz), 3.71 (1 H, ddd, *J*=15.66, 11.49, 4.42 Hz), 3.62 - 3.55 (1 H, m),

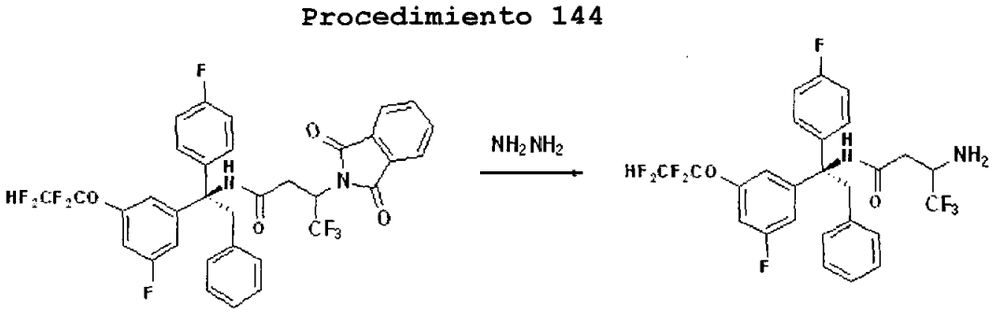
2.85 - 2.95 (1 H, m).

**EJEMPLO 326**



**3-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida**

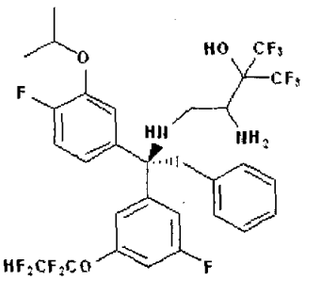
**Procedimiento 144**



A una solución de 3-(1,3-dioxoisoindolin-2-il)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida (Ejemplo 325, 30 mg, 0.04 mmoles) en MeOH (1 ml) se le agregó hidracina (0.03 ml, 1 mmoles) y la mezcla de reacción se calentó a 50°C durante 4 h. La mezcla de reacción se purificó por CLAR preparativa (columna Axia luna, 30 x 75 mm, 10-100% ACN/$H_2O$ con TFA 0.1% durante 10 min, relación de flujo 40 ml/min, observando a 220 nm) para producir 3-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-

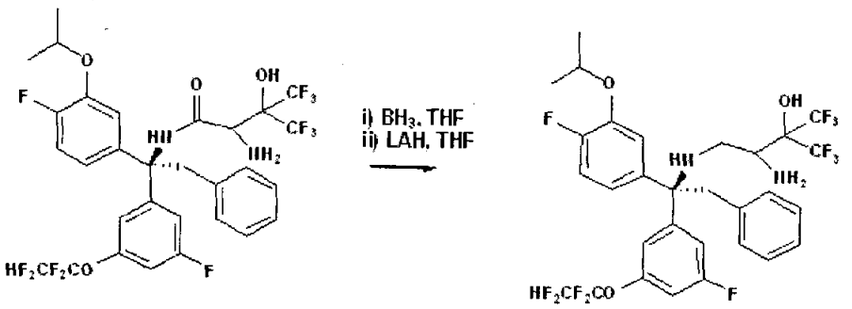
feniletil)butanamida (Ejemplo 326) como un sólido blanco (7 mg, 24% de rendimiento). CLEM: TR = 3.62 min [M+H] 565.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.34 (1 H, d, *J*=17.94 Hz), 7.13 - 7.24 (3 H, m), 6.96 - 7.11 (4 H, m), 6.82 - 6.92 (3 H, m), 6.62 (2 H, d, *J*=7.83 Hz), 5.86 (1 H, t, *J*=1.77 Hz), 3.88 (1 H, t, *J*=12.63 Hz), 3.75 - 3.84 (1 H, m), 3.70 (1 H, d, *J*=13.14 Hz), 2.82 - 2.93 (1 H, m), 2.77 (1 H, m).

**EJEMPLO 327**




**3-amino-1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)-2-(trifluorometil)butan-2-ol**

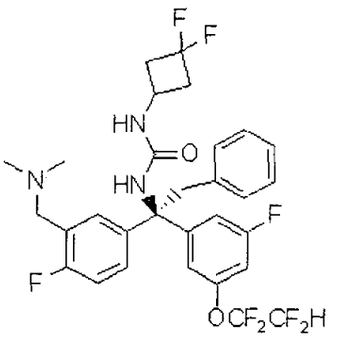
**Procedimiento 145**



A una solución de 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil)butanamida, se preparó como se describe en el Ejemplo 293, (20 mg, 0.028 mmoles) en THF (0.5 ml) se le agregó borano (0.2 ml, solución 1.0 M en THF). Después de que la evolución de hidrógeno terminó, la solución se calentó en un vial de microondas sellado bajo radiación por microondas a 100°C durante 5 min. Los solventes se retiraron bajo una corriente de nitrógeno luego THF (0.5 ml) se agregó al residuo seguido por $BF_3 \cdot Et_2O$ (30 mg, 0.21 mmoles) y LAH (0.2 ml, solución 1.0 M en THF). Después de que terminó la evolución de gas de hidrógeno, el vial de microondas sellado se calentó a 100°C durante 10 min. Los solventes se retiraron bajo una corriente de nitrógeno y el residuo se disolvió en $NH_4OH$ (ca. 10 ml). El LiCl (10%, ca. 10 ml) se agregó y el acuoso se extrajo con DCM (3 x 10 ml). Las porciones orgánicas combinadas se concentraron bajo presión reducida y se purificaron por CCD preparativa (25 x 25 mm, gel de sílice 1 mm elución con hexano: EtOAc 4:1). El 3-Amino-1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)-2-(trifluorometil)butan-2-ol (Ejemplo 327, 5 mg, 20% de rendimiento) se aisló como un aceite incoloro a $R_f$ de 0.5. CLEM: TR = 3.88 min [M+H] 693.1 (columna Phenomenex Luna C18,

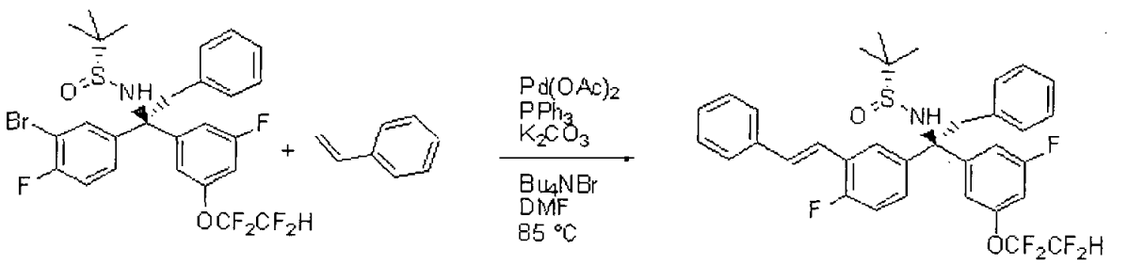
4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); CLAR: TR = 3.88 min, Pureza 91% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.15 ppm, 3 H, m; 7.05 ppm, 1 H, m; 6.86 ppm, 2H, d, J=8.0Hz; 6.83 ppm, 3 H, m; 6.61 ppm, 2H, d, J=8.0Hz; 5.87 ppm, 1H, t,t, J=52.0Hz y J=4.0Hz; 4.41 ppm, 1H, sept, J=8.0Hz; 3.57 ppm, 1H, d, J=12.0Hz; 3.48 ppm, 1H, d, J=12.0Hz; 2.99 ppm, 2H, m; 2.53 ppm, 1H, brt; 1.27 ppm, 3H, d, J=8.0Hz; 1.25 ppm, 3H, d, J=8.0Hz.

**EJEMPLO 328**



**(R)-1-(3,3-difluorociclobutil)-3-(1-(3-((dimetilamino)metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea**

**Procedimiento 146**

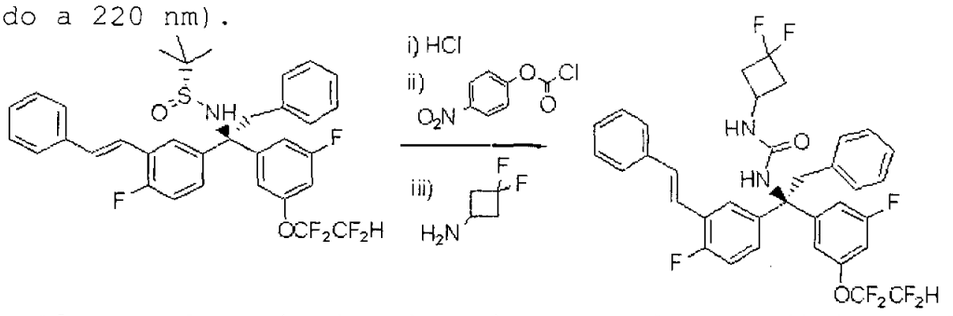


Siguiendo el procedimiento 3, 62, 5 y 6, N-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se preparó y la mezcla de diaestereómeros se separó por CLAR quiral preparativa (columna Chiralpak AD, 5 x 50 cm elución isocrática con 60% IPA/heptano, 50 ml/min, observando a 254 nm) para producir (R)-N-((S)-1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma blanca (3.92 g, 33% de rendimiento) con un tiempo de retención de 40 min.

A una suspensión de $Pd(OAc)_2$ (9 mg, 0.04 mmoles) y $PPh_3$ (2 mg, 0.008 mmoles) en DMF se le agregó $Bu_4NBr$ (265 mg, 0.8 mmoles), (R)-N-((S)-1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida, preparada como se describe en el Procedimiento 62, (500 mg, 0.8 mmoles), estireno (137 mg, 1.3 mmoles) y $K_2CO_3$ (136 mg, 1.0 mmoles). La mezcla de reacción se desgasificó y se rellenó con argón varias veces. La mezcla de reacción se calentó a 85°C durante 16 h. La mezcla de reacción se vació luego en $NH_4Cl$ saturado y la fase acuosa se extrajo con EtOAc. Las porciones orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó por cromatografía ISCO (columna 12 g, 0-30% EtOAc/hexano) para producir (R)-N-

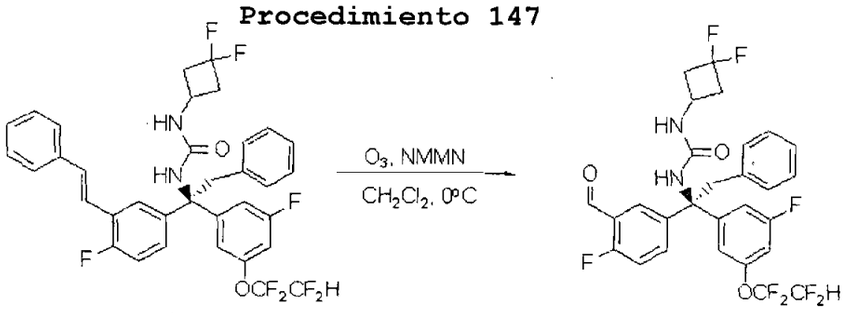
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((R)-1-(4-fluoro-3-estirilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (119 mg, 23% de rendimiento). CLEM: TR = 4.62 min [M+H] 632 (Phenomenex Luna C18, 50 x 4.6 mm, 10%-90% $H_2O$/ACN con TFA 0.1%, 4 min gradiente, relación de flujo 4 ml/min, observando a 220 nm).




Al usar los métodos descritos en el Procedimiento 6 y 12, (R,E)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-estirilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea se preparó como un aceite transparente (170 mg, 57% de rendimiento). CLEM: TR = 4.19 min [M+H] 661 (Phenomenex Luna C18, 50 x 4.6 mm, 10%-90% $H_2O$/ACN con TFA 0.1%, 4 min gradiente, relación de flujo 4 ml/min, observando a 220 nm).

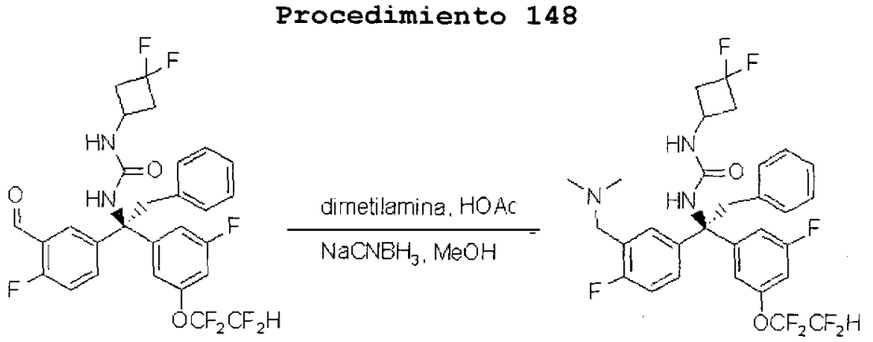
**Procedimiento 147**




A una solución de (R,E)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-estirilfenil)-1-(3-fluoro-5-(1,1,2,2-

tetrafluoroetoxi)fenil)-2-feniletil)urea (509 mg, 0.8 mmoles) en DCM (10 ml) a 0°C se le agregó N-óxido de 4-metilmorfolina (104 mg, 0.8 mmoles). El ozono se burbujeó a través de la solución amarilla resultante durante 10 min. El solvente de la reacción se retiró y el residuo se purificó por cromatografía ISCO (columna 12 g, 0-30% EtOAc/hexano) para producir (R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-formilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea como un aceite incoloro (106 mg, 23% de rendimiento). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 10.22 (s, 1 H), 8.06 (m, 1 H), 7.67 (dd, *J*=6.19, 2.65 Hz, 1 H), 7.16 (m, 4 H), 6.85 (m, 3 H), 6.69 (m, 3 H), 5.85 (m, 1 H), 5.40 (d, *J*=6.57 Hz, 1 H), 4.00 (m, 1 H), 2.90 (m, 2 H).

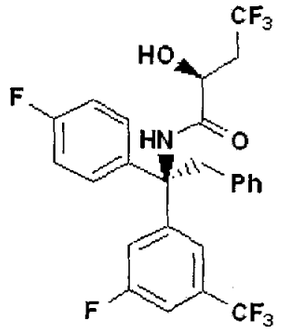
**Procedimiento 148**




A una solución de (R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-formilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea (20 mg, 0.03 mmoles) en MeOH (2 ml) se le agregó $NHMe_2$ (0.009 ml) y una gota de ácido acético. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, seguido por la adición de $NaCNBH_3$ (2

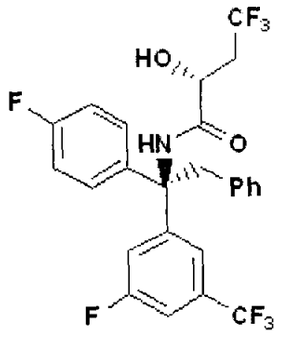
mg, 0.03 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. El solvente se retiró bajo presión reducida y el residuo se dividió entre $NaHCO_3$ saturado y EtOAc. La fase orgánica se concentró y se purificó por CLAR preparativa (columna Phemomenex Luna 5u C18 Axia, 21 x 100 mm, 10%-90% $H_2O$/ACN con TFA 0.1%/, observando a 220 nm) para producir (R)-1-(3,3-difluorociclobutil)-3-(1-(3-((dimetilamino)metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea (Ejemplo 328, 8 mg, 44% de rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.28 (d, *J*=2.27 Hz, 1 H), 7.09 (m, 7 H), 6.88 (d, *J*=8.84 Hz, 1 H), 6.63 (d, *J*=7.07 Hz, 2 H), 6.51 (br. s., 1 H), 5.88 (m, 1 H), 4.34 (d, *J*=12.63 Hz, 1 H), 4.10 (m, 2 H), 3.87 (m, 1 H), 3.31 (d, *J*=12.63 Hz, 2 H), 2.92 (m, 3 H), 2.74 (d, *J*=2.78 Hz, 3 H), 2.70 (d, *J*=3.28 Hz, 3 H), 2.46 (m, 2 H).

**EJEMPLO 329A**



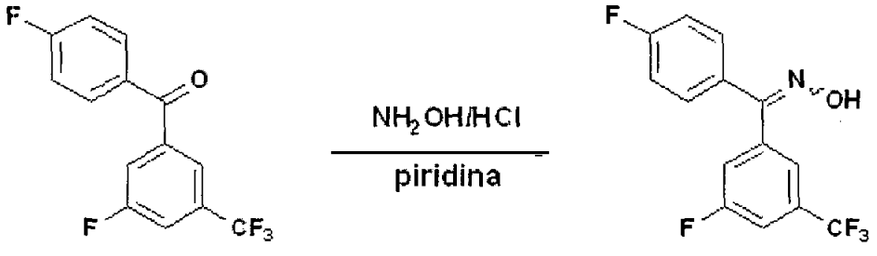

**(S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida**

**EJEMPLO 329B**



**(R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida**

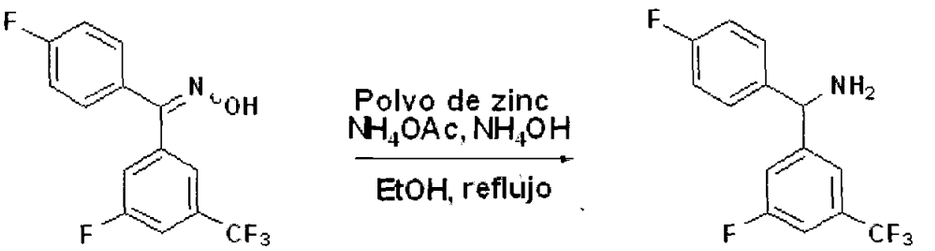
**Procedimiento 149**




A una solución de (3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metanona, preparada como se describe en el Procedimiento 4, (860 mg, 3.0 mmoles) en piridina (6 ml) se agregó clorohidrato de hidroxilamina (830 mg, 12.0 mmoles) y la mezcla de reacción se calentó a 100°C durante 2 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se disolvió en EtOAc (50 ml), se lavó con HCl 1N (2 x 20 ml), agua (20 ml) y NaCl saturado (20 ml), luego se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida para producir oxima de (3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metanona (912 mg, 100%

de rendimiento) como un sólido blanco. El CCD (30% EtOAc/hexano) muestra dos etapas, los isómeros cis y trans de oxima de (3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metanona, que no fueron separados. CLEM: TR = 1.59 min [M+H] 302.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

**Procedimiento 150**

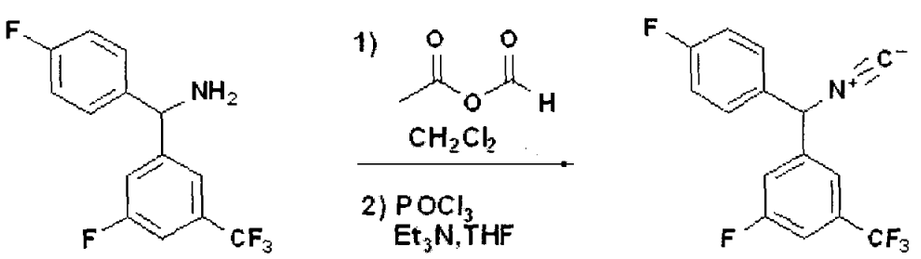



A una suspensión de oxima de (3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metanona (904 mg, 3.0 mmoles) en EtOH (3 ml) y $NH_4OH$ concentrado (15 ml) se le agregó acetato de amonio (120 mg, 1.6 mmoles) seguido por polvo de zinc (1.05 g, 16.2 mmoles) y la mezcla de reacción se calentó a reflujo durante 2 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente luego se filtró. El sólido filtrado se lavó con NaOH 10 N (15 ml) y EtOAc (15 ml). El filtrado combinado se extrajo con EtOAc (2 x 30 ml). Las fracciones orgánicas combinadas se lavaron con NaCl saturado (2 x 10 ml) luego se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida para

1510

producir (3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metanamina (804 mg, 93% de rendimiento) como un aceite incoloro, transparente. CLEM: TR = 0.96 min [M-$NH_2$] 271.0 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) δ ppm 1.68 (bs, 2 H), 5.25 (s, 1 H), 7.03 (t, *J*=8.57 Hz, 2 H), 7.19 (d, *J*=7.91 Hz, 1 H), 7.29 - 7.35 (m, 3 H), 7.48 (s, 1 H).

**Procedimiento 151**

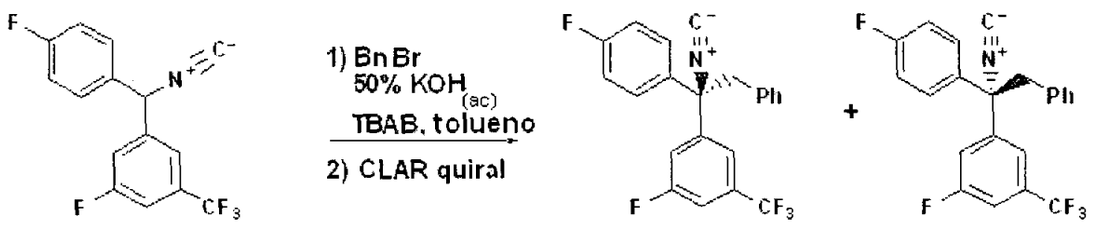



A una solución de (3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metanamina (315 mg, 1.1 mmoles) en $CH_2Cl_2$ (2 ml) a 0°C se le agregó anhídrido fórmico acético (314 ul, formado al calentar una relación 2:1 v/v de anhídrido acético y ácido fórmico a 60°C durante 2 h). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 0.5 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó en una columna 40 g de gel de sílice, eluyendo con 0 hasta 100% EtOAc/hexano, para dar N-((3-fluoro-5-

(trifluorometil)fenil)(4-fluorofenil)metil)formamida (327 mg, 94% de rendimiento) como un aceite viscoso, transparente. CLEM: TR = 1.37 min [M+H] 316.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) $\delta$ ppm 6.13 (bs, 1 H), 6.34 (d, $J$=7.47 Hz, 1 H), 7.05 - 7.20 (m, 5 H), 7.27 - 7.34 (m, 2 H), 8.35 (s, 1 H). A una solución de N-((3-fluoro-5-(trifluorometil)fenil)(4-fluorofenil)metil)formamida (327 mg, 1.04 mmoles) en THF (5 ml) a 0°C se le agregó $Et_3N$ (0.79 ml, 5.7 mmoles) seguido por oxicloruro de fósforo (0.125, 1.35 mmoles). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 16 h. La mezcla de reacción se diluyó con hielo-agua (25 ml) y se extrajo con $Et_2O$ (3 x 20 ml). Las capas orgánicas combinadas se lavaron con NaCl saturado (20 ml), se secaron sobre $Na_2SO_4$ anhidro, el se filtró a través de alúmina básica. El producto filtrado se concentró para dar 1-fluoro-3-((4-fluorofenil)(isociano)metil)-5-(trifluorometil)benceno (268 mg, 93% de rendimiento) como un aceite café claro. CLEM: TR = 1.71 min [M-NC] 271.0 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); IR $\nu_{max}$ $cm^{-1}$ puro: 2139 (N=C); RMN: 500 MHz $^1H$ ($CDCl_3$) $\delta$ ppm 5.94 (s, 1 H), 7.12 (t, $J$=8.52 Hz, 2 H), 7.25 - 7.29 (m,

1 H), 7.30 - 7.35 (m, 3 H), 7.41 (s, 1 H).

**Procedimiento 152**



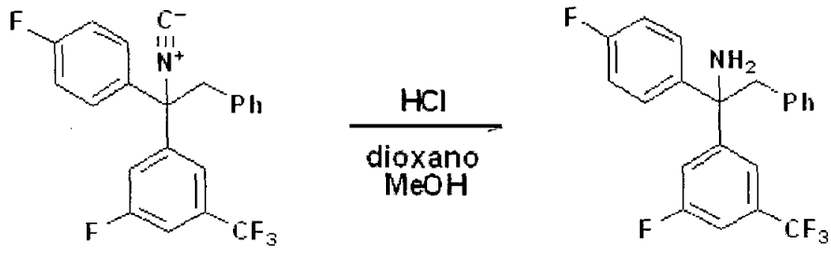

A una solución de 1-fluoro-3-((4-fluorofenil)(isociano)metil)-5-(trifluorometil)benceno (234 mg, 0.79 mmoles) en tolueno (8 ml) se agregó bromuro de tetrabutilamonio (75 mg, 0.23 mmoles) y bromuro de bencilo (0.185 ml, 1.56 mmoles) seguido por KOH(ac) 50% (2.5 ml). La mezcla de reacción se agitó vigorosamente durante 3 minutos. La mezcla de reacción se transfirió a un embudo separador y se lavó con $H_2O$ (2.5 ml). La fracción orgánica se secó sobre $Na_2SO_4$, se filtró a través de una almohadilla de alúmina básica y se concentró bajo presión reducida. El residuo se purificó por CLAR preparativa quiral (columna Chiralcel OD-H, 20 x 250 mm elución isocrática con alcohol de isopropilo (10%) y heptano, 20 ml/min, observando a 254 nm) para dar (R)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno (TR = 6.2 minutos, 128 mg, 42% de rendimiento) y (S)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno (TR = 7.8 minutos, 128 mg, 42% de rendimiento) como aceites transparentes e incoloros. CLEM: TR = 1.94 min [M-NC] 361.1 (2 min Columna

1513

Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) δ ppm 3.61 (d, *J*=13.18 Hz, 1 H), 3.67 (d, *J*=13.18 Hz, 1 H), 6.83 (d, *J*=7.47 Hz, 2 H), 7.08 (t, *J*=8.57 Hz, 2 H), 7.17 - 7.34 (m, 8 H).

La reacción se correrá en 16% ee del isómero (R) al substituir cloruro de N-bencilcinconinio en lugar de bromuro de tetrabutilamonio y correr la reacción a 0°C durante 1 h.

**Procedimiento 153**

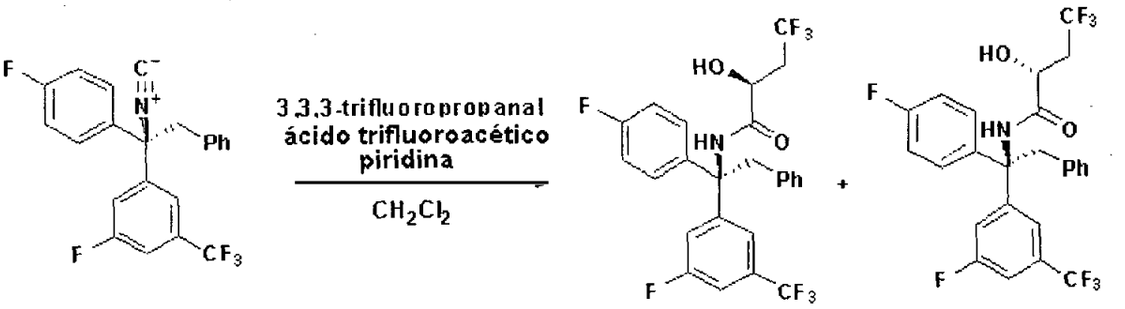



A una solución de 1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno (20 mg, 0.052 mmoles) en MeOH (0.4 ml) se agregó HCl 4 N en dioxano (0.3 ml) y la mezcla de reacción se agitó durante 3 minutos. El solvente de la reacción se evaporó bajo una corriente de nitrógeno. El residuo se diluyó con NaOH 1 N (5 ml) y la porción acuosa se extrajo con $Et_2O$ (3 x 5 ml). Las fracciones orgánicas combinadas se lavaron con NaCl saturado (5 ml), se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron bajo vacío para producir 1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletanamina (19 mg, 97% de rendimiento)

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como un vidrio claro.

**Procedimiento 154**

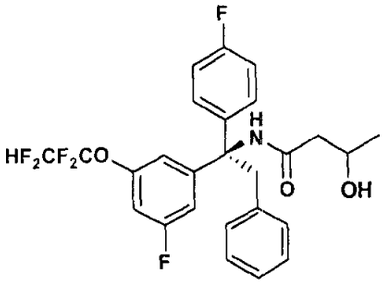



A una solución de (R)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno (22 mg, 0.057 mmoles) en $CH_2Cl_2$ (0.10 ml) se agregó 3,3,3-trifluoropropanal (0.010 ml, 0.11 mmoles) y piridina (0.018 ml, 0.23 mmoles) seguido por ácido trifluoroacético (0.009 ml, 0.11 mmoles). La mezcla de reacción se calentó a 40°C durante 4 h. El 3,3,3-trifluoropropanal adicional (0.010 ml, 0.11 mmoles) se agregó y continuó el calentamiento a 40°C durante 2 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y el solvente se retiró bajo una corriente de nitrógeno. El residuo se purificó por placa CCD preparativa, eluyendo con 40% $Et_2O$/hexano, para producir (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 329A, 11 mg, 36% de rendimiento) y (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 329B, 11 mg, 36% de rendimiento)

como aceites transparentes e incoloros. La (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 329A): CLEM: TR = 1.81 min [M+H] 518.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.24-2.36 (m, 1 H) 2.81-2.91 (m, 2 H), 3.74 (d, *J*=13.18 Hz, 1 H), 3.99 (d, *J*=13.18 Hz, 1 H), 4.43 (dd, *J*=10.11, 3.52 Hz, 1 H), 6.60 (d, *J*=7.47 Hz, 2 H), 6.99-7.07 (m, 4 H), 7.12-7.28 (m, 6 H), 7.70 (s, 1 H). (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 329B): CLEM: TR = 1.82 min [M+H] 518.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.23 - 2.35 (m, 1 H), 2.77 - 2.88 (m, 2 H), 3.73 (d, *J*=12.75 Hz, 1 H), 3.99 (d, *J*=12.74 Hz, 1 H), 4.45 (dd, *J*=8.35, 3.95 Hz, 1 H), 6.61 (d, *J*=7.47 Hz, 2 H), 6.98 - 7.04 (m, 4 H), 7.16 - 7.28 (m, 6 H), 7.69 (s, 1 H). La estereoquímica de (S)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 329A) y (R)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 329B) se asignó

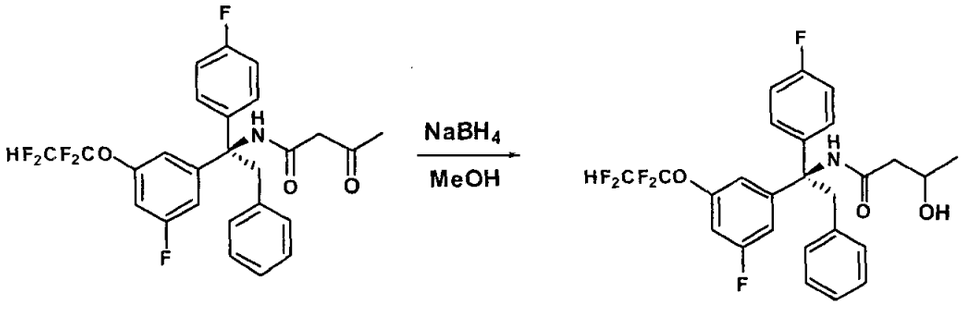
arbitrariamente.

**EJEMPLO 330**




**N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxibutanamida**

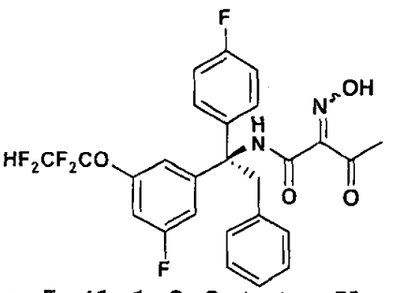
**Procedimiento 155**




A una solución de (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-oxobutanamida (Ejemplo 251, 51 mg, 0.1 mmoles), en MeOH (1 ml) se agregó $NaBH_4$(10 ml, 0.26 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se concentró bajo presión reducida. El residuo se purificó por CLAR preparativa (Columna Axia luna, 30 x 100 mm, 40-100% MeOH/$H_2O$ con TFA 0.1% durante 10 min, relación de flujo 40 ml/min, observando a 220 nm) para producir N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxibutanamida (Ejemplo 330) como un aceite

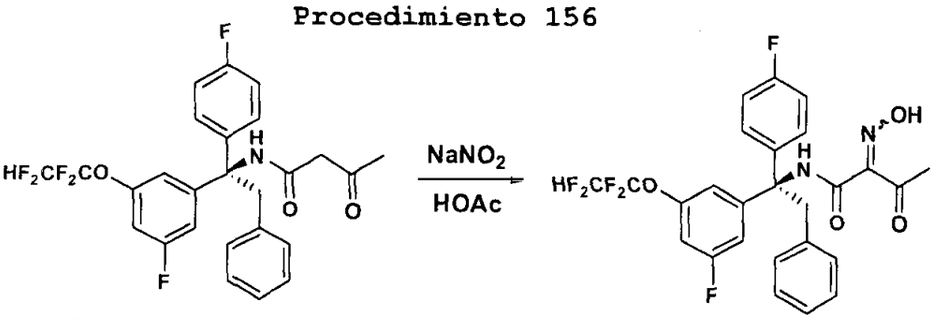
amarillo pálido (28 mg, 55% de rendimiento). CLEM: TR = 2.66 min [M+H] 512.2 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.13 - 7.23 (3 H, m), 7.02 - 7.08 (2 H, m, *J*=4.96, 4.56, 4.56, 2.43, 2.43 Hz), 6.96 - 7.02 (2 H, m), 6.85 - 6.93 (4 H, m), 6.67 (2 H, d, *J*=7.07 Hz), 5.87 (1 H, t, *J*=2.78 Hz), 4.10 - 4.20 (1 H, m), 3.95 (1 H, dd, *J*=12.76, 10.74 Hz), 3.73 (1 H, dd, *J*=12.76, 10.74 Hz), 2.32 - 2.38 (2 H, m), 1.22 (3 H, d, *J*=6.32 Hz).

**EJEMPLO 331**



**(R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-(hidroxiimino)-3-oxobutanamida**

**Procedimiento 156**

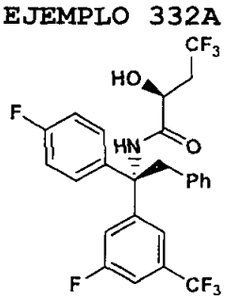



A una solución de (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-oxobutanamida (Ejemplo 251, 62 mg, 0.12 mmoles), en ácido

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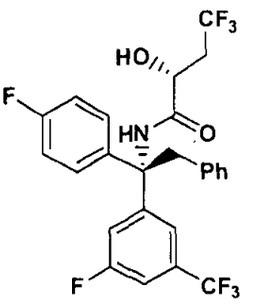
acético (0.5 ml) se agregó gota a gota una solución de $NaNO_2$ (25 mg, 0.36 mmoles) en $H_2O$ (0.5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 10 min y se diluyó con $H_2O$ (10 ml). La porción acuosa se extrajo con EtOAc (3 x 10 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida para producir la (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-2-(hidroxiimino)-3-oxobutanamida (Ejemplo 331) como un sólido amarillo (65 mg, 100% de rendimiento). CLEM: TR = 1.99 min [M+H] 539.4 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 10.07 (1 H, s), 7.15 - 7.21 (2 H, m), 7.07 - 7.14 (7 H, m), 7.00 - 7.05 (4 H, m), 6.84 - 6.96 (6 H, m), 6.55 - 6.60 (2 H, m), 5.88 (1 H, t, *J*=2.78 Hz), 3.91 (1 H, d, *J*=13.14 Hz), 3.72 - 3.80 (1 H, m), 2.52 (3 H, s).

**EJEMPLO 332A**



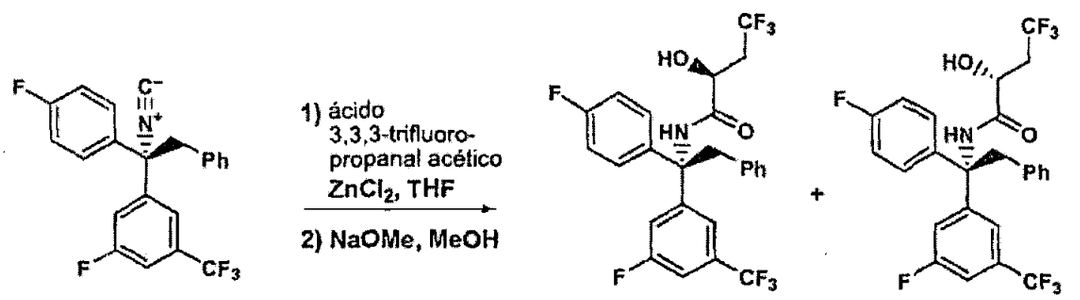

**(S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida**

**EJEMPLO 332B**



**(R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida**

**Procedimiento 157**

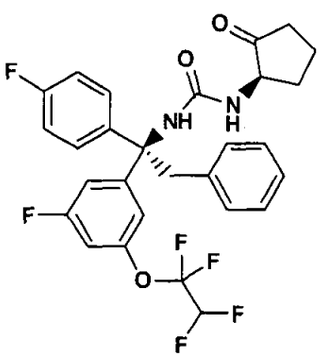



A una solución de (S)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno preparada como se describe en el Procedimiento 149, 150, 151 y 152 (23 mg, 0.060 mmoles) en THF (0.25 ml) se le agregó 3,3,3-trifluoropropanal (0.006 ml, 0.071 mmoles) y ácido acético (0.004 ml, 0.071 mmoles) seguido por una solución 0.5M de cloruro de zinc en THF (0.142 ml, 0.071 mmoles). La mezcla de reacción se calentó a 55°C durante 16 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente, luego una solución de NaOMe 25%

en MeOH (25 ul) se agregó y la mezcla de reacción se calentó a 40°C durante 18 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente, luego una gota de ácido acético se agregó y el solvente se retiró bajo una corriente de nitrógeno. El residuo se purificó por placa CCD preparativa, eluyendo con 25% EtOAc/hexanos, para producir (S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 332A, 7 mg, 22% de rendimiento) y (R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 332B, 6 mg, 18% de rendimiento) como aceites transparentes e incoloros. (S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 332A): CLEM: TR = 1.82 min [M+H] 518.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) $\delta$ ppm 2.23 - 2.35 (m, 1 H) 2.77 - 2.88 (m, 2 H) 3.73 (d, $J$=12.75 Hz, 1 H) 3.99 (d, $J$=12.74 Hz, 1 H) 4.45 (dd, $J$=8.57, 4.17 Hz, 1 H) 6.61 (d, $J$=7.47 Hz, 2 H) 6.98 - 7.04 (m, 4 H) 7.16 - 7.28 (m, 6 H) 7.69 (s, 1 H). (R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 332B): CLEM: TR = 1.81 min [M+H]

518.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) δ ppm 2.23 - 2.34 (m, 1 H) 2.77 - 2.88 (m, 2 H) 3.73 (d, *J*=12.75 Hz, 1 H) 3.99 (d, *J*=12.74 Hz, 1 H) 4.44 - 4.47 (m, 1 H) 6.61 (d, *J*=7.47 Hz, 2 H) 6.98 - 7.07 (m, 4 H) 7.14 - 7.28 (m, 6 H) 7.69 (s, 1 H). La estereoquímica de (S)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 332A) y (R)-4,4,4-trifluoro-N-((S)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxibutanamida (Ejemplo 332B) se asignó arbitrariamente.

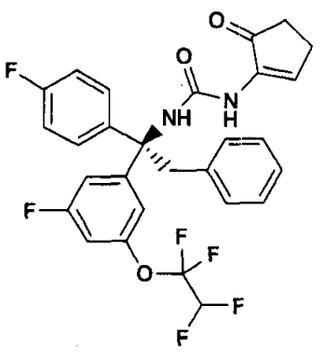
**EJEMPLO 333**




**1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((R)-2-oxociclopentil)urea**

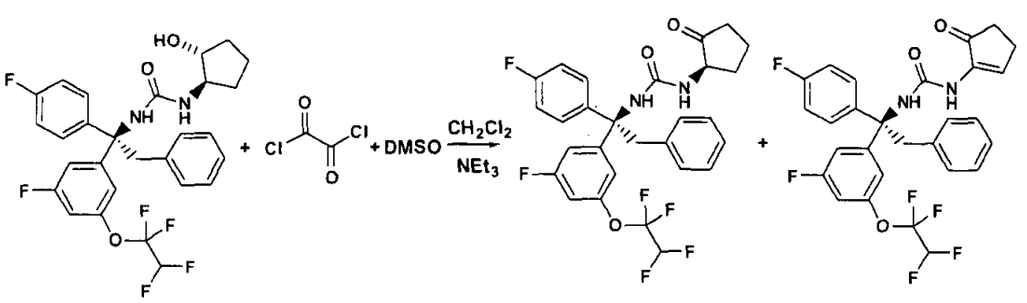
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**EJEMPLO 334**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(5-oxociclopent-1-enil)urea**

**Procedimiento 158**

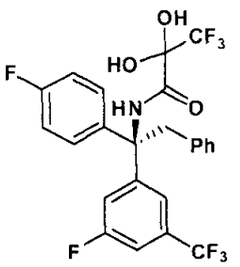


A una solución de cloruro de oxalilo (2 M en $CH_2Cl_2$, 150 ul) a -78°C se le agregó DMSO (47 mg, 0.60 mmoles) gota a gota. La mezcla de reacción se agitó a -78 °C durante 15 min, luego la 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1R,2R)-2-hidroxiciclopentil)urea (Ejemplo 246, 113 mg, 0.20 mmoles) en $CH_2Cl_2$ (1 ml) se agregó gota a gota. La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 16 h. La mezcla de reacción se concentró bajo presión reducida y se purificó Cromatografía de vaporización

instantánea ISCO con EtOAc y hexano como solvente eluyente para producir (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(5-oxociclopent-1-enil)urea (Ejemplo 333) como un sólido blanco (15 mg, 14% de rendimiento) y 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((R)-2-oxociclopentil)urea (Ejemplo 334) como un sólido blanco (66 mg, 60% de rendimiento). (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(5-oxociclopent-1-enil)urea: CLAR: TR = 3.99 min [M+H] 551.09 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 1.24 - 1.37 (m, 1 H), 1.36 - 1.58 (m, 1 H), 1.68 - 1.84 (m, 1 H), 1.84 - 2.00 (m, 2 H), 2.12 - 2.30 (m, 3 H), 2.48 - 2.73 (m, 1 H), 3.58 - 4.05 (m, 3 H), 5.35 - 5.52 (m, 1 H), 5.64 - 6.03 (m, 2 H), 6.62 - 6.78 (m, 2 H), 6.78 - 7.02 (m, 5 H), 7.04 - 7.23 (m, 5 H). 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-((R)-2-oxociclopentil)urea: CLAR: TR = 4.09 min [M+H] 549.1 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm); $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 1.84 - 1.94 (m, 2 H), 2.43 - 2.62 (m, 2 H) 3.92 (dd, 2 H) 5.82 (t, 1 H) 6.62 - 6.78 (m, 2 H) 6.79 - 6.88 (m,

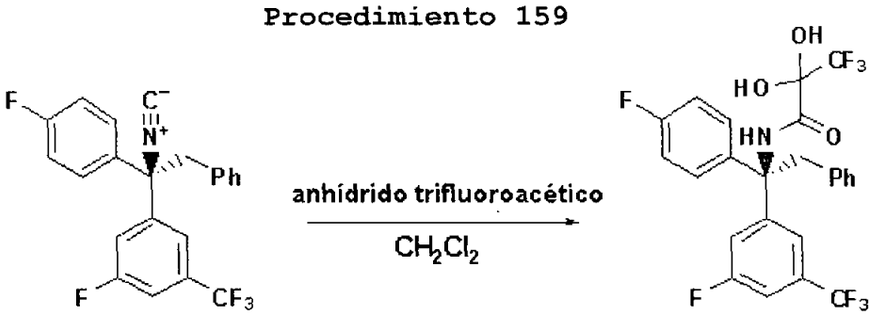
1 H) 6.90 - 7.01 (m, 5 H), 7.01 - 7.15 (m, 3 H), 7.14 - 7.25 (m, 2 H), 7.62 - 7.74 (m, 1 H), 8.09 - 8.25 (m, 1 H).

**EJEMPLO 335**




**(R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2,2-dihidroxipropanamida**

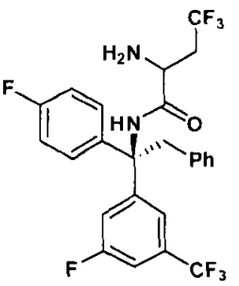
**Procedimiento 159**




A una solución de (R)-1-fluoro-3-(1-(4-fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno (26 mg, 0.067 mmoles) preparada como se describe en el Procedimiento 4, 149, 150, 151 y 152, en $CH_2Cl_2$ (0.7 ml) a -78°C se agregó anhídrido trifluoroacético (0.06 ml, 0.42 mmoles) y la mezcla de reacción se permitió entibiar hasta -40 °C durante 6 h. La mezcla de reacción se apagó por la adición de $H_2O$ (5 ml) luego se permitió entibiar hasta temperatura ambiente. La mezcla se extrajo con $CH_2Cl_2$ (3 x 5 ml) luego se secó sobre $Na_2SO_4$, se filtró y los volátiles se removieron bajo vacío. El residuo se purificó al usar gel

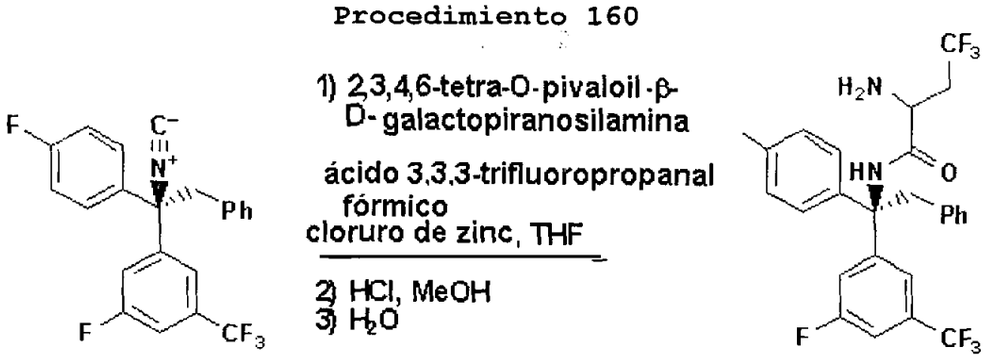
de sílice (4 g), eluyendo con 0 hasta 100% $Et_2O$/hexano, para dar (R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-2,2-dihidroxipropanamida (Ejemplo 335, 11 mg, 32%) como un vidrio incoloro claro. CLEM: TR = 1.69 min [M-H] 518.0 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene 0.1% $NH_4Ac$; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) δ ppm 3.71 (d, J=13.18 Hz, 1 H) 3.92 (d, J=13.18 Hz, 1 H) 6.61 (d, J=7.47 Hz, 2 H) 6.98 - 7.06 (m, 4 H) 7.12 - 7.30 (m, 7 H).

**EJEMPLO 336**




**2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida**

**Procedimiento 160**

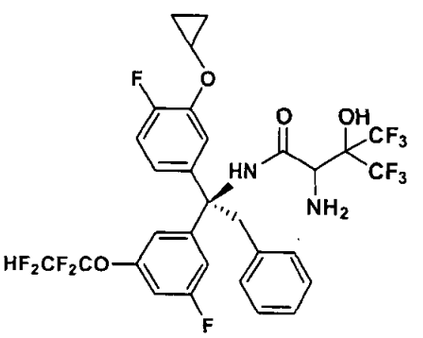



A una solución de (R)-1-fluoro-3-(1-(4-

fluorofenil)-1-isociano-2-feniletil)-5-(trifluorometil)benceno (35 mg, 0.09 mmoles) preparada como se describe en el Procedimiento 4, 149, 150, 151 y 152, en THF (0.7 ml) se agregó 3,3,3-trifluoropropanal (0.008 ml, 0.095 mmoles), 2, 3, 4, 6-O-pivaloil-β-D-galactopiranosilamina (49 mg, 0.095 mmoles) y ácido fórmico (0.004 ml, 0.10 mmoles). La mezcla de reacción se enfrió hasta - 20°C luego una solución 0.5M de cloruro de zinc en THF (0.19 ml, 0.095 mmoles) se agregó y la mezcla de reacción se agitó a 0°C durante 16 h. El 3,3,3-trifluoropropanal adicional (0.016 ml, 0.19 mmoles), 2, 3, 4, 6-O-pivaloil-β-D-galactopiranosilamina (98 mg, 0.19 mmoles), ácido fórmico (0.008 ml, 0.20 mmoles) y solución de cloruro de zinc (0.38 ml, 0.19 mmoles) se agregaron y la mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 3 h. Los volátiles se retiraron bajo vacío y el residuo se disolvió en $CH_2Cl_2$ (5 ml) y se lavó con $NaHCO_3$ saturado (2 x 10 ml) y $H_2O$ (10 ml) luego se secó sobre $MgSO_4$, se filtró y los volátiles se removieron bajo vacío. El matraz que contiene el residuo se enfrió en un baño con hielo luego HCl saturado en metanol (2 ml) se agregó y la mezcla de reacción se agitó durante 0.5 h a 0°C luego a temperatura ambiente durante 1.5 h. $H_2O$ (0.5 ml) y MeOH (1.5 ml) se agregaron y la mezcla de reacción se agitó durante 24 h. La mayoría del MeOH se retiró bajo una corriente de nitrógeno

luego la mezcla de reacción se diluyó con NaOH 1 N (5 ml) y se extrajo con $CH_2Cl_2$ (3 x 5 ml). Las fracciones orgánicas combinadas se lavaron con $H_2O$ (5 ml), se secó sobre $Na_2SO_4$, se filtró y los volátiles se removieron bajo vacío. El residuo se purificó por CLAR preparativa (TR = 6.2 min al usar columna Axia Luna 5µ C18 30 x 100 mm con relación de flujo de 40 ml/min durante un periodo de 10 min. 20 hasta 100% solvente B. Solvente A = 10/90/0.1% ACN/$H_2O$/TFA. Solvente B = 90/10/0.1%) para dar la sal del ácido trifluoroacético de 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida (Ejemplo 336, 9 mg, 15% de rendimiento) como un vidrio incoloro claro. CLEM: TR = 1.34 min [M+H] 517.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% acetonitrilo/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400MHz $^1H$ ($CD_3Cl$)δ ppm 2.59 - 2.70 (m, 1 H), 2.72 - 2.84 (m, 1 H), 3.93 - 4.03 (m, 2 H), 4.34 (dd, J=9.01, 3.73 Hz, 1 H), 6.68 - 6.72 (m, 2 H), 7.02 - 7.09 (m, 2 H), 7.11 - 7.22 (m, 3 H), 7.25 - 7.40 (m, 5 H).

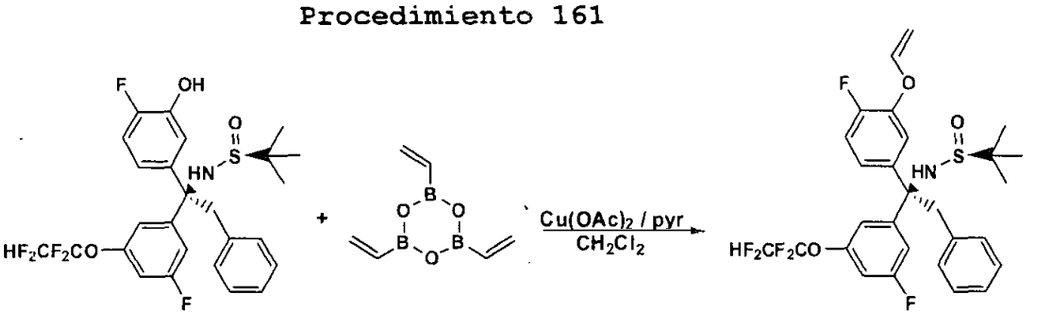
**EJEMPLO 337**




**2-amino-N-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4,4,4-**

**trifluoro-3-hidroxi-3-(trifluorometil)butanamida**

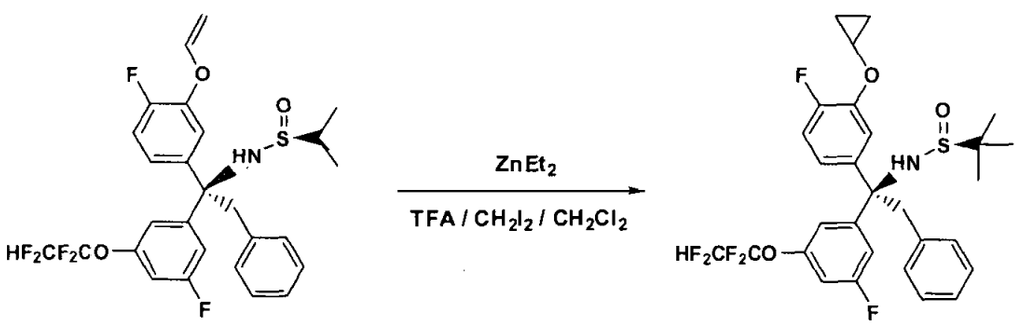
**Procedimiento 161**




A una solución de (S)-N-((R)-1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida, preparada como se describe en el Procedimiento 109, 110, 111, 112, 113, 114, (0.545 g , 1 mmoles) en $CH_2Cl_2$ (10 ml) se agregó $Cu(OAc)_2$ (0.182 g, 1 mmoles), seguido por piridina (0.79 g, 10 mmoles) y 2,4,6-trivinil-1,3,5,2,4,6-trioxatriborinano (0.159 g, 0.66 mmoles). La mezcla de reacción se agitó durante la noche bajo aire ambiente y se filtró a través de un tapón de celite y alúmina neutral. El sólido se lavó con acetato de etilo y el producto filtrado se concentró bajo presión reducida para producir (S)-N-((R)-1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma blanca opaca (0.495 g, 87% de rendimiento). CLEM: TR = 3.653 min [M+H] 572.2 (columna Phenomenex Luna C18 5 µ, eluyendo con 10-90% acetonitrilo acuoso que contiene 0.1% ácido trifluoroacético durante un gradiente de 4 minutos, observando a 220 nM). $^1H$ RMN ($CDCl_3$) ppm 7.2-7.1 (m, 5 H), 7.02 (d, J=6.2 Hz, 1 H),

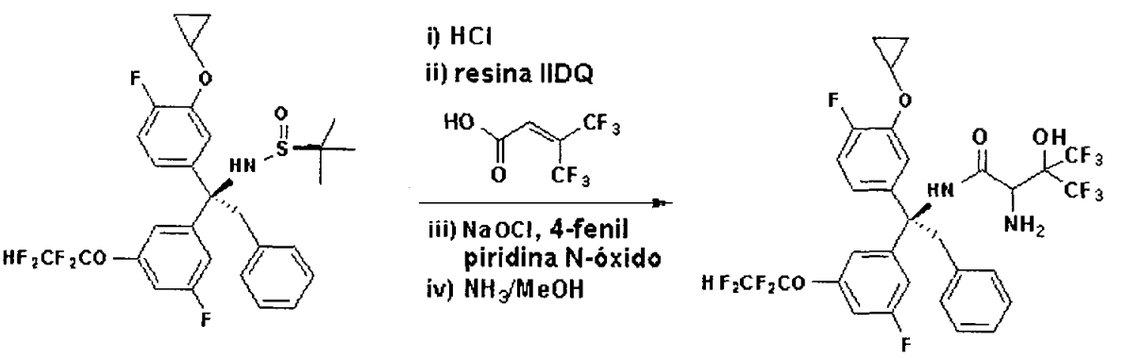
1524

6.89 ( d, J=6.2 Hz, 2 H), 6.82 (d, J=8.8 Hz, 1H), 6.68 (br, 2 H), 6.54 (dd, J=6.2 Hz, 13.6Hz, 1 H), 5.84 (t, J=52.7 Hz, 1 H), 4.62 (dd, J=2.2 Hz, 13.6 Hz, 1 H), 4.40 (dd, J=2.2Hz, 5.7 Hz, 1 H), 4.21 (s, 1 H), 3.95 (d, J=12.8 Hz, 1H), 3.55 (d, J=12.7 Hz, 1 H), 1.19 (s, 9 H).




A un matraz secado al horno de 3 cuellos de 25 ml RB bajo nitrógeno se agregó $CH_2Cl_2$ (3.5 ml) y solución de dietilzinc 1 M en hexano (3.43 ml, 3.43 mmoles). El matraz se enfrió en un baño de hielo y una solución de ácido trifluoroacético (0.391 g, 3.43 mmoles) en $CH_2Cl_2$ (1 ml) se agregó gota a gota por medio de jeringa. Después de agitar durante 15 min, una solución de diyodometano (0.918 g, 3.43 mmoles) en $CH_2Cl_2$ (1 ml) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 15 min, seguido por la adición de (S)-N-((R)-1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (0.495 g, 0.87 mmoles) en $CH_2Cl_2$ (1 ml). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 4 h. La mezcla de reacción se diluyó con $CH_2Cl_2$ y se lavó sucesivamente con

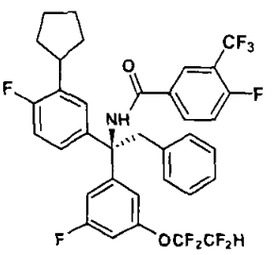
bicarbonato de sodio saturado, agua, NaCl saturado, se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por ISCO al usar un gradiente de 5-70% EtOAc/hexano como eluyente para producir (S)-N-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropan-2-sulfinamida como una espuma blanca (0.347 g, 71% de rendimiento). CLAR: TR = 3.668 min [M+H] 586.3 (columna Phenomenex Luna C18 5µ, eluyendo con 10-90% acetonitrilo acuoso que contiene ácido trifluoroacético 0.1% durante un gradiente de 4 minutos, observando a 220 nm). $^1H$ RMN ($CDCl_3$) ppm 7.2-7.05 (m, 6 H), 6.91 (d, J=6.6 Hz, 2H), 6.83 (d, J=8.4 Hz, 1 H), 6.71 (m, 2 H), 5.84 (t, J=53.1 Hz, 1 H), 4.21 (s, 1 H), 3.99 (d, J=12.3 Hz, 1 H), 3.62 (m, 1 H), 3.56 (d, J=12.8 Hz, 1 H), 1.22 ( s, 9 H), 0.72-0.65 (m, 4 H).




Siguiendo el procedimiento 6, 90, 91 y 92, la 2-amino-N-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4,4,4-trifluoro-3-hidroxi-3-(trifluorometil)butanamida (Ejemplo

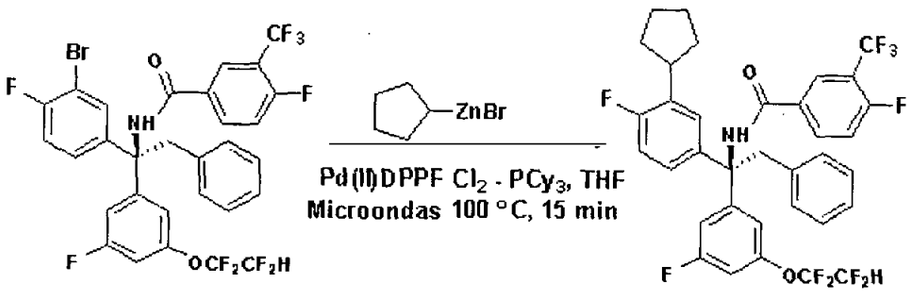
337) se preparó. CLAR: TR = 3.466 min [M+H] 705.3 (columna Phenomenex Luna C18 5 µ, eluyendo con acetonitrilo acuoso 10-90% que contiene 0.1% ácido trifluoroacético durante un gradiente de 4 minutos, observando a 220 nM). $^1$H RMN($CD_2Cl_2$) ppm 8.97 (s, 1 H), 7.14-6.5 (m, 11 H), 5.84 (t, J=53.1 Hz, 1 H), 3.79 (d, J=12.3Hz, 1 H), 3.67 (s, 1 H), 3.62 (d, J=13.1 Hz, 1 H), 3.52 (m, 1 H), 1.48 (br, 1 H), 0.55 (m, 4 H).

**EJEMPLO 338**




**(R)-N-(1-(3-ciclopentil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 162**

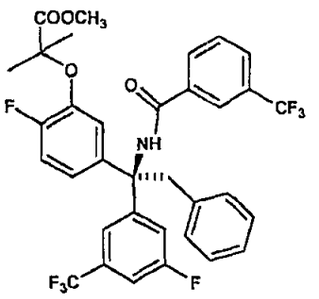



A una solución de (S)-N-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida, preparada como se describe en el Procedimiento 3, 62, 5, 6 y 7 en THF (0.1 M,

0.5 ml, 0.05 mmoles) se le agregó diclorometano de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) (4 mg, 0.0054 mmoles) y triciclohexilfosfina (1.0 M en tolueno, 0.05 ml, 0.05 mmoles), seguido por bromuro de ciclopentil zinc (0.5 M en THF, 0.04 ml, 0.2 mmoles). La mezcla de reacción se calentó a 100°C bajo radiación por microondas durante 15 min. La mezcla de reacción se enfrió y se filtró a través de un tapón de sílice. El sólido se lavó con THF (2 ml) y el producto filtrado se concentró bajo presión reducida. El residuo se disolvió en metanol (1 ml) y se purificó por CLAR preparativa (TR = 14.89 min, Sunfire Prep C18 OBD 19x100 mm eluyendo con 18-90% MeCN/$H_2O$ durante 12 minutos y a 90% durante 8 minutos adicionales que contiene TFA 0.1%; 20 ml/min, observando a 220 nm) para producir (R)-N-(1-(3-ciclopentil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 338) como una goma incolora (13 mg, 19% de rendimiento). CLEM: TR = 4.56 min [M+H] 684.3 (4 min columna Sunfire S5 C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1H$ RMN (500 MHz, $CD_3Cl$) δ ppm 7.90 (1 H, d, J=6.60 Hz), 7.84 (1 H, dd, J=8.25, 4.40 Hz), 7.28 (1 H, t, J=9.07 Hz), 7.23 (1 H, t, J=7.42 Hz), 7.16 (2 H, t, J=7.42 Hz), 7.01-7.05 (2 H, m), 6.92-6.96 (2 H, m), 6.86 (1 H, dd, J=6.60, 2.75 Hz), 6.79-6.82 (1 H, m), 6.69

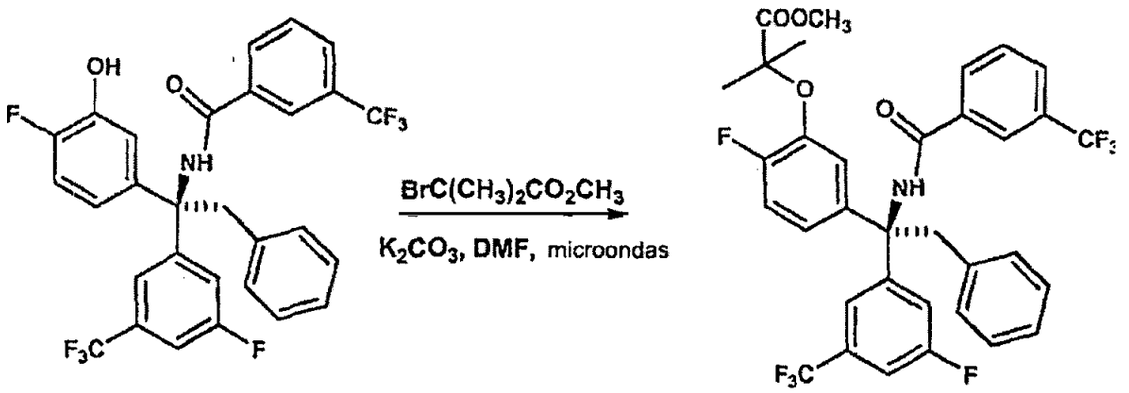
(2 H, d, J=7.15 Hz), 6.65 (1 H, s), 5.75-5.98 (1 H, t), 4.12 (1 H, d, J=13.20 Hz), 3.66 (1 H, d, J=13.20 Hz), 3.14-3.21 (1 H, m), 1.94-2.03 (2 H, m), 1.62-1.72 (4 H, m), 1.43-1.48 (1 H, m), 1.36-1.42 (1 H, m).

**EJEMPLO 339**




**2-(2-Fluoro-5-(1-(3-fluoro-5-(trifluorometil)fenil)-2-fenil-1-(3-(trifluorometil)benzamido)etil)fenoxi)-2-metilpropanoato de (*R*)-metilo**

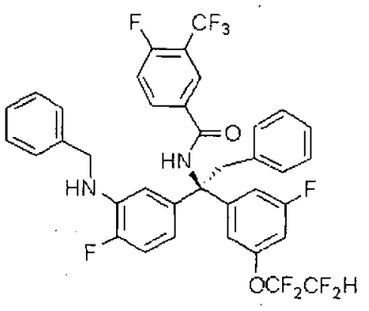
**Procedimiento 163**




Una solución de (R)-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-(trifluorometil)benzamida, preparada como se describe en el Ejemplo 264, (226 mg, 0.4

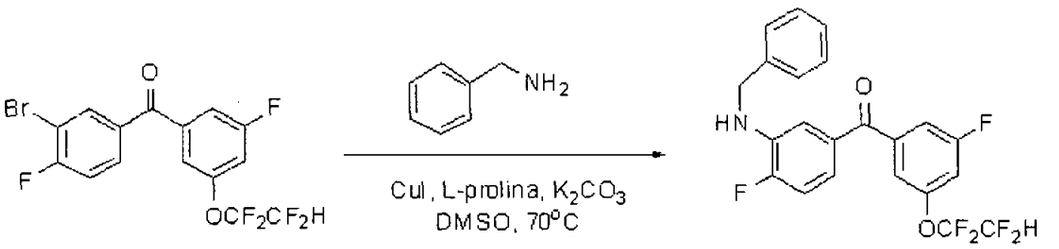
mmoles), 2-bromo-2-metilpropanoato de metilo (0.10 ml) y $K_2CO_3$ (326 mg, 2.36 mmoles) en DMF (1 ml) se calentó a 180°C bajo condición de microondas durante 1200 segundos. La mezcla de reacción se permitió hasta enfriar, se diluyó con EtOAc y la capa orgánica se lavó con $H_2O$ (2 x), NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se purificó por Cromatografía de vaporización instantánea ISCO (gel de sílice, hexanos/EtOAc) para dar 2-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil)fenil)-2-fenil-1-(3-(trifluorometil)benzamido)etil)fenoxi)-2-metilpropanoato de (R)-metilo (Ejemplo 273, 76 mg, rendimiento: 29%). CLEM: TR = 2.26 min [M+H] 666.4 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

**EJEMPLO 340**



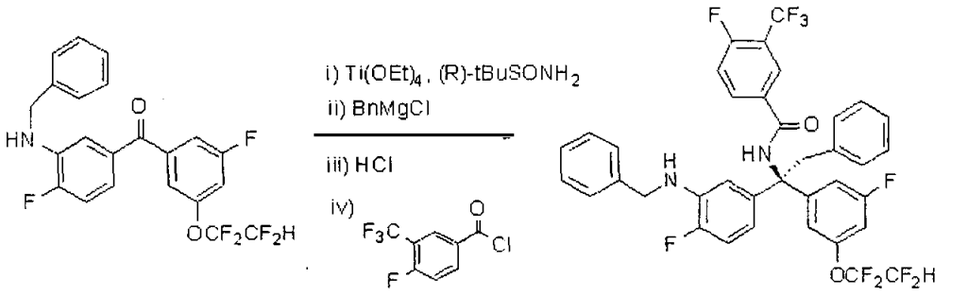

**(R)-N-(1-(3-(bencilamino)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 164**



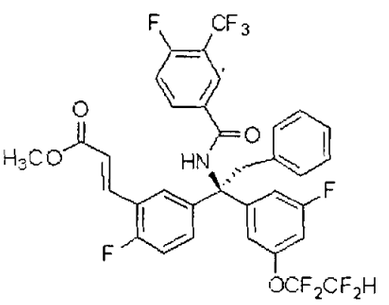

A una solución de (3-bromo-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)-fenil)metanona, preparada como se describe en el Procedimiento 62, (110 mg, 0.27 mol) en DMSO (2 ml) a temperatura ambiente se le agregó bencilamina (43 µL, 0.4 mol), yoduro de cobre (I) (5 mg, 0.03 mol), L-prolina (23 mg, 0.05 mol), y carbonato de potasio (55 mg, 0.4 mol). La mezcla de reacción se desgasificó y calentó durante 4 h a 70°C. Después del enfriamiento hasta temperatura ambiente, la mezcla de reacción se dividió entre agua y EtOAc. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por medio de cromatografía ISCO (4 g columna, 0-30% EtOAc/hexano) para producir (3-(bencilamino)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona como un aceite incoloro, transparente (95 mg, 81% de rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, J=6.57, 2.02 Hz, 1 H), 7.79 (m, 1 H), 7.27 (m, 10 H), 6.95 (m, 3 H), 6.87 (dd, J=8.59, 2.53 Hz, 1 H), 6.73 (d, J=7.07 Hz, 2 H),

6.54 (m, 2 H), 5.87 (m, 1 H), 4.40 (s, 2 H), 3.75 (d, J=13.14 Hz, 1 H).




Al usar los métodos descritos en los Procedimientos 5, 6 y 7, (R)-N-(1-(3-(bencilamino)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 340) se preparó como un sólido blanco (8 mg, 59% de rendimiento). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.90 (dd, J=6.57, 2.02 Hz, 1 H), 7.79 (m, 1 H), 7.27 (m, 10 H), 6.95 (m, 3 H), 6.87 (dd, J=8.59, 2.53 Hz, 1 H), 6.73 (d, J=7.07 Hz, 2 H), 6.54 (m, 2 H), 5.87 (m, 1 H), 4.40 (s, 2 H), 3.75 (d, J=13.14 Hz, 1 H).

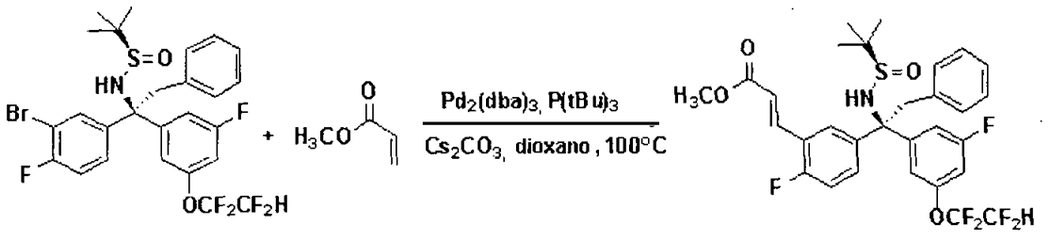
**EJEMPLO 341**



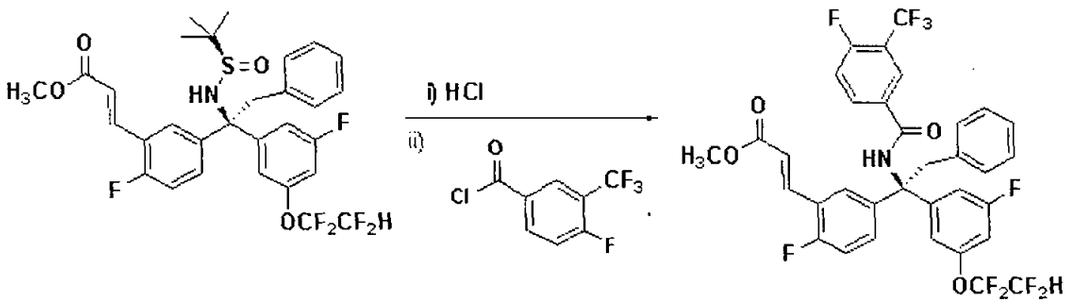

**3-(2-fluoro-5-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)fenil)acrilato de (R,E)-metilo**

1537

**Procedimiento 165**

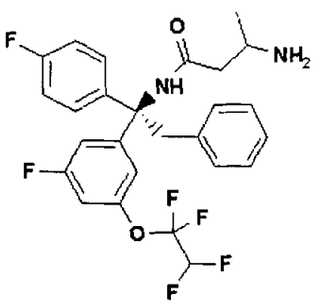



A una solución de (R)-N-((S)-1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)-fenil)-2-feniletil)-2-metilpropano-2-sulfinamida, preparada como se describe en el Procedimiento 3, 62, 5 y 6, (500 mg, 0.82 mmoles) en DMF (5 ml) a temperatura ambiente se agregó acrilato de metilo (0.74 ml, 8.22 mmoles), $Pd_2(dba)_3$ (75 mg, 0.082 mmoles), fosfina de tri-t-butilo (89 µl, 0.33 mmoles), y carbonato de cesio (536 mg, 1.64 mmoles). La mezcla de reacción se desgasificó con argón y se calentó a 100°C durante 4 h. La mezcla de reacción se vació dentro de agua y la fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por cromatografía ISCO (4 g columna, 0-40% EtOAc/hexano) para producir 3-(5-((R)-1-((R)-1,1-dimetiletilsulfinamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-fluorofenil)acrilato de (E)-metilo como una espuma blanca (485 mg, 96% de rendimiento). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.77 (d, J=16.42 Hz, 1H), 7.59 (dd, J=6.69, 2.15 Hz, 1H), 7.41 (m, 1H), 7.16 (m, 4H), 6.94 (dd, J=7.33, 1.77 Hz, 2H), 6.86 (d, J=8.84 Hz, 1H), 6.73 (t, J=4.93 Hz, 2H), 6.53 (d, J=16.17 Hz, 1H), 5.88 (m, 1H), 4.29 (s, 1H), 4.03 (d, J=12.38 Hz, 1 H), 3.79 (s, 3 H), 3.62 (d, J=12.38 Hz, 1 H), 1.24 (m, 9 H).




Al usar los métodos descritos en los Procedimientos 6 y 7, 3-(2-fluoro-5-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)fenil)acrilato de (R,E)-metilo (Ejemplo 341) se preparó como un sólido blanco. CLEM: TR = 4.46 min [M+H+60] 781 (Phemonenex Luna C18, 50 x 4.6 mm, 4 min gradiente, eluyendo con 105-90% MeOH/$H_2O$ que contiene TFA 0.1%, observando a 220 nm). $^1H$ RMN (400 MHz, $CDCl_3$) δ ppm 7.92 (m, 1 H), 7.83 (m, 1 H), 7.69 (d, J=16.42 Hz, 1 H), 7.28 (m, 3 H), 7.18 (m, 2 H), 7.09 (t, J=9.35 Hz, 1 H), 6.94 (m, 3 H), 6.72 (m, 3 H), 6.51 (m, 1 H), 6.42 (d, J=16.42 Hz, 1 H), 6.42 (d, J=16.42 Hz, 1 H), 5.88 (m, 1 H), 3.95 (d, J=14.91 Hz, 1 H), 3.82 (m, 4 H).

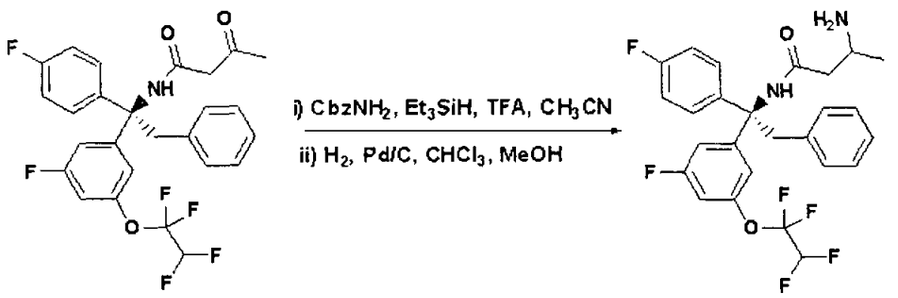
**EJEMPLO 342**



**3-amino-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida**

1539

**Procedimiento 166**

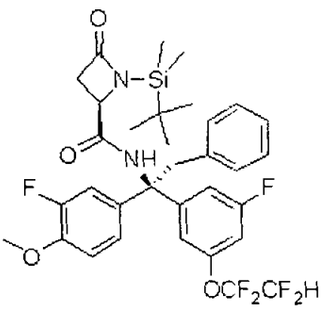



A una solución de (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-oxobutamida (Ejemplo 251, 27 mg, 0.053 mmoles) en $CH_3CN$ (1 ml) se agregó Cbz-$NH_2$ (24 mg, 0.16 mmoles), seguido por trietilsilano (0.5 ml, 3 mmoles), y TFA (0.4 ml, 5.3 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se concentró y el residuo se disolvió en una mezcla de $CH_3OH$ (1 ml) y $CHCl_3$ (1 ml) y Pd/C al 10% en peso (20 mg) se agregó. La mezcla de reacción se agitó bajo $H_2$ durante 16 h y el sólido se filtró. El producto filtrado se concentró bajo presión reducida y el residuo se purificó por CLAR preparativa (Phenomenex Luna Axia, 5u 30 x 100, eluyendo con 10%-90% MeOH/$H_2O$ que contiene TFA 0.1%, tiempo de gradiente 10 min, relación de flujo 40 ml/min, observando a 220 nm) para producir 3-amino-*N*-((*R*)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)butanamida (Ejemplo 342, 5 mg, 19% de rendimiento). CLAR: TR = 3.28 min [M+H] 511.3 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$

1590

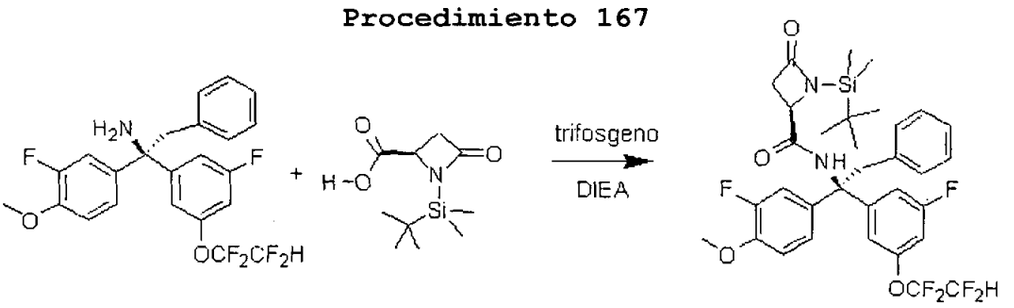
durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.15 - 7.24, m, 3 H; 6.97 - 7.10, m, 4 H; 6.83 - 6.92, m, 3 H; 6.60 - 6.64, m, 3 H; 5.73 - 6.60, t, J = 54, 3.81 - 3.91, m, 1 H; 3.67 - 3.76, m, 1 H; 3.59, m, 1 H; 2.70, m, 2 H; 1.31, m, 3 H.

**EJEMPLO 343**



**(R)-1-(ter-Butildimetilsilil)-N-((R)-1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-oxoazetidina-2-carboxamida**

**Procedimiento 167**




A una solución de ácido (R)-1-(ter-butildimetilsilil)-4-oxoazetidina-2-carboxílico (126 mg, 0.55 mmoles) en THF (1.5 ml) se agregó a una solución de trifosgeno (54 mg, 0.18 mmoles). La mezcla de reacción se agitó durante 5 min a temperatura ambiente, seguido por la adición de 2,4,6-trimetilpiridina (203 µl, 1.54 mmoles), una

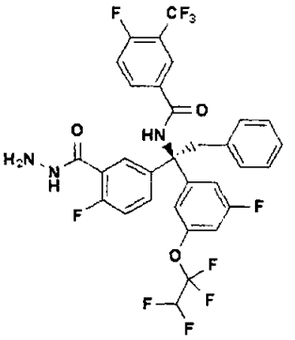
1541

solución de (R)-1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina, preparada como se describe en el Procedimiento 3, 62, 5 y 6, (50 mg, 0.11 mmoles) en THF (0.6 ml), y *N,N*-diisopropiletilamina (268 µl, 1.54 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 40 min. El agua (10 ml) se agregó y la mezcla de reacción se extrajo con diclorometano (3 x 15 ml) y las capas orgánicas combinadas se lavaron con carbonato de potasio 2 N y luego NaCl saturado. Las capas orgánicas se secaron sobre sulfato de magnesio, se filtraron y concentraron bajo presión reducida. El residuo se purificó por Cromatografía de vaporización instantánea ISCO (columna Analogix 4.2 g, eluyendo con hexano/EtOAc) para producir (R)-1-(ter-Butildimetilsilil)-N-((R)-1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-oxoazetidina-2-carboxamida (Ejemplo 343, 41 mg, 55% de rendimiento). CLEM: TR = 4.18 min [M+H] 667.1 (Phenominex, Luna C18, 4.6 X 50 mm, 10%-90% MeOH/$H_2O$ que contiene TFA 0.1%, relación de flujo 4 ml/min, 4 min gradiente, observando a 220 nm); $^1$H RMN (500 MHz, $CDCl_3$) δ ppm -0.04 (s, 3 H), 0.24 (s, 3 H), 0.91 (s, 9 H), 2.79 (dd, *J*=15.4, 2.7 Hz, 1 H), 3.32 (dd, *J*=15.4, 6.6 Hz, 1 H), 3.79 - 3.85 (m, 1 H), 3.86 - 3.90 (m, 2 H), 3.91 (s, 3 H), 5.87 (ninguno, 2 H), 6.59 (s, 1 H), 6.64 (d, *J*=7.1 Hz, 2 H), 6.75 (s, 1 H), 6.80 (d, *J*=9.3 Hz, 1 H), 6.87 - 6.94 (m, 4 H), 7.15 (t, *J*=7.4 Hz, 2 H), 7.20 (d,

1542

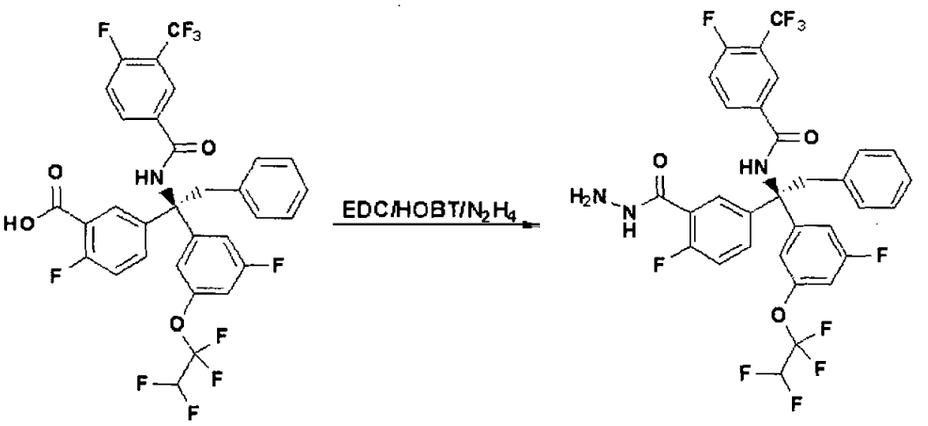
J=7.1 Hz, 1 H).

**EJEMPLO 344**



**((R)-4-fluoro-N-(1-(4-fluoro-3-(hidrazinacarbonil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

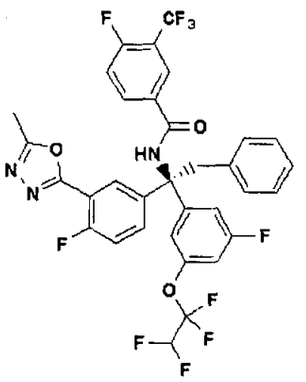
**Procedimiento 168**




A una solución de ácido (R)-2-fluoro-5-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)benzoico, preparada como se describe en los Procedimientos 3, 62, 5, 6, 7, 56, 57 y 23, (30 mg, 0.045 mmoles) en diclorometano (1 ml) se agregó hidroxibenzotriazol (8 mg, 0.058 mmoles), seguido por EDCI (11 mg, 0.058 mmoles). La mezcla de reacción se agitó durante

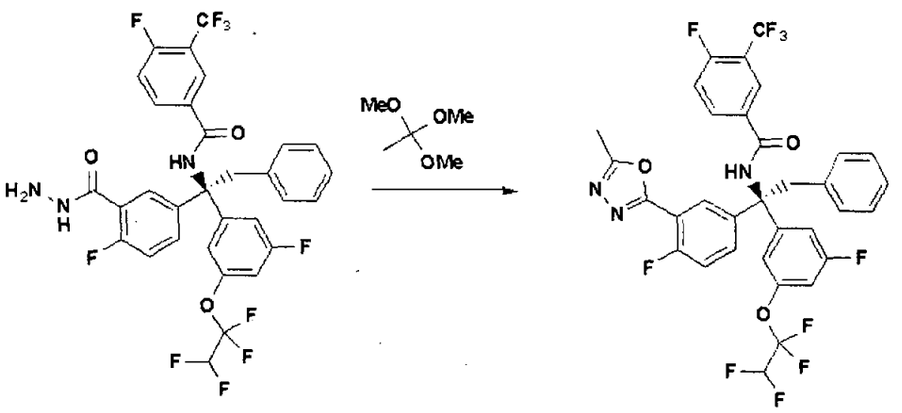
15 min a temperatura ambiente, luego hidrato de hidracina se agregó (3 µL, 0.001 mmoles) y la mezcla de reacción se agitó durante 15 min adicionales. La mezcla de reacción se cargó en un cartucho ISCO (4 g columna) y se eluyó con 0 hasta 100% EtOAc en hexano para producir (R)-4-fluoro-N-(1-(4-fluoro-3-(hidrazinacarbonil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 344, 25 mg, 81% de rendimiento) como un sólido blanco. CLEM: TR = 1.78 min [M+H] 674 (Columna Chromolith Performance RP-18e, 4.6 x 100 mm eluyendo con 10-90% ACN/$H_2O$ durante 2 minutos que contiene TFA 0.1%, 5 ml/min, observando a 220 nm).

**EJEMPLO 345**



**(R)-4-fluoro-N-(1-(4-fluoro-3-(5-metil-1,3,4-oxadiazol-2-il)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida**

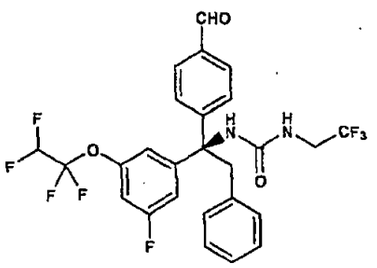
**Procedimiento 169**



Una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-(hidrazinacarbonil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 344, 35 mg, 0.052 mmoles) en ortoformiato de trimetilo (1 ml) se calentó a 100°C durante 16 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por cromatografía ISCO (4 g columna, eluyendo con 0 hasta 100% EtOAc en hexano) para producir (R)-4-fluoro-N-(1-(4-fluoro-3-(5-metil-1,3,4-oxadiazol-2-il)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 345, 16 mg, 45% de rendimiento) como un sólido blanco. CLEM TR = 2.06 min [M+H] 698 (Columna Chromolith Performance RP-18e, 4.6 X 100 mm eluyendo con 10-90% ACN/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

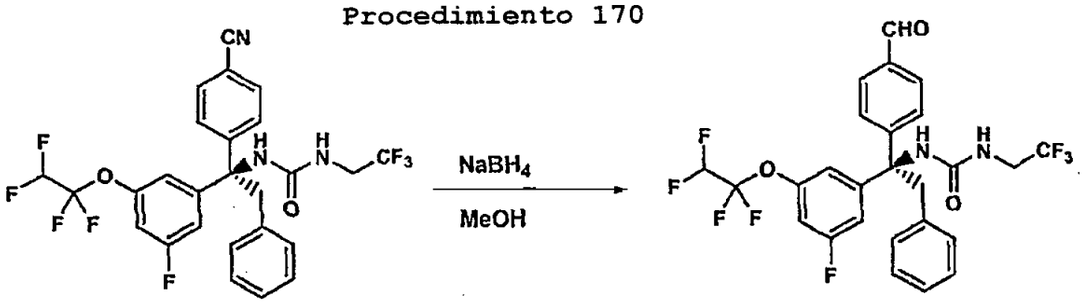
1545

**EJEMPLO 346**



**(R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-formilfenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea**

**Procedimiento 170**

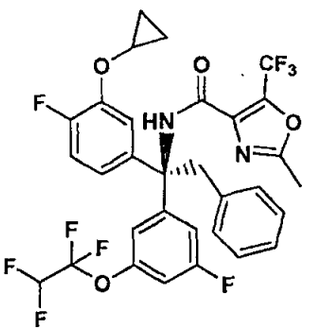



A una solución de (R)-1-(1-(4-cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea, preparada como se describe en el Procedimiento 3, 4, 5, 6, 25 y 56, (59 mg, 0.11 mmoles) en metanol (2 ml) se agregó hexahidrato de cloruro de cobalto (50 mg, 0.22 mmoles), seguido por borohidruro de sodio (40 mg, 1.1 mmoles). La mezcla de reacción se agitó durante 21 h a temperatura ambiente luego se apagó por la adición de ácido clorhídrico (1.0 M, 2 ml). La mezcla de reacción se extrajo con acetato de etilo y los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron bajo presión reducida. El residuo se purificó

1546

por Cromatografía de vaporización instantánea ISCO (12 g gel de sílice, gradiente de 0-100% acetato de etilo/hexano durante 11 min., relación de flujo 30 ml/min), luego se purificó además por CLAR preparativa (Phenomenex Onyx Monolithic 10 x 100 mm columna; 10-90% acetonitrilo/agua con gradiente 0.1% ácido trifluoroacético durante 5 min., 25 ml/min) para producir (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-formilfenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea (Ejemplo 346) como un sólido blanco (2 mg, 3% de rendimiento). CLEM: TR = 1.07 min [M+H] 561 (Columna Chromolith Performance 18e 4.6 x 100 mm, 50-90% metanol/agua con gradiente 0.1% ácido trifluoroacético durante 2 min, 5 ml/min); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 10.00 (1 H, s), 7.84 (2 H, d, $J$=8.24 Hz), 7.41 (2 H, d, $J$=8.79 Hz), 7.1 - 7.20 (5 H, m), 6.90 (3 H, m), 6.70 (2 H, d, $J$=7.15 Hz), 5.88 (1 H, tt, $J_{HH}$=2.75 Hz, $J_{HF}$=53 Hz), 5.16 (1 H, s), 4.88 (1 H, t, $J$=6.32 Hz), 3.79 (2 H, ddd, $J$=15.67, 9.07, 8.79 Hz).

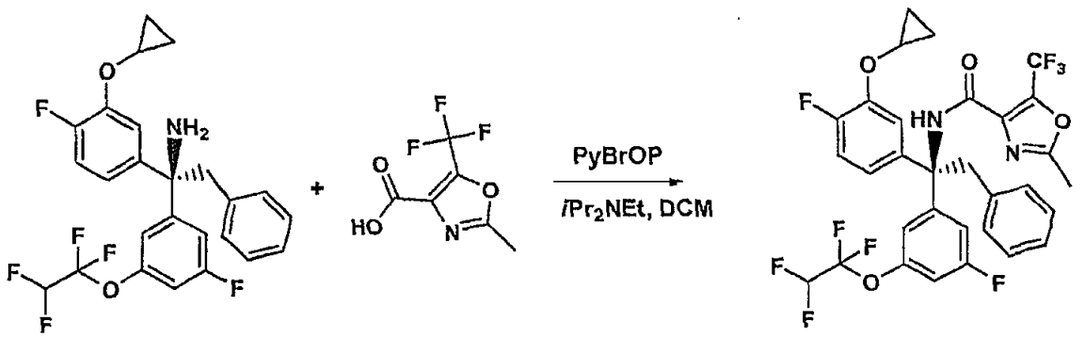
**EJEMPLO 347**




**(R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metil-5-(trifluorometil)oxazol-4-carboxamida**

1542

**Procedimiento 171**

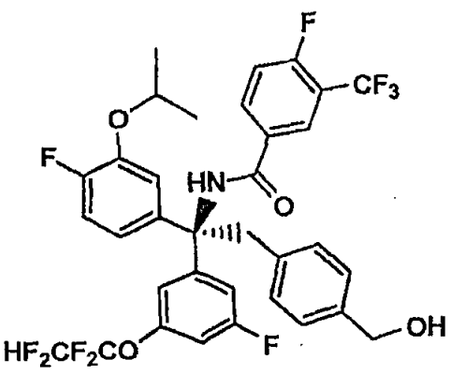



A una solución de (R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina, preparada como se describe en el Procedimiento 109, 110, 111, 112, 113, 114, 161, (24 mg, 0.05 mmoles) en $CH_2Cl_2$ (0.5 ml) se agregó ácido 2-metil-5-(trifluorometil)-oxazol-4-carboxílico (12 mg, 0.06 mmoles), seguido por PyBrOP (28 mg, 0.06 mmoles) y $iPr_2NEt$ (9 mg, 0.065 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 72 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por CLAR preparativa (Phenomenex Luna 5 µ, 30 x 100 mm, eluyendo con 10% -90% MeOH/$H_2O$ que contiene TFA 0.1%, tiempo de gradiente 10 min, relación de flujo 40 ml/min) para producir (R)-*N*-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metil-5-(trifluorometil)oxazol-4-carboxamida (Ejemplo 347) como un sólido blanco (23 mg, 70% de rendimiento). CLAR: TR = 2.18 min [M+H] 659.5 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene

1548

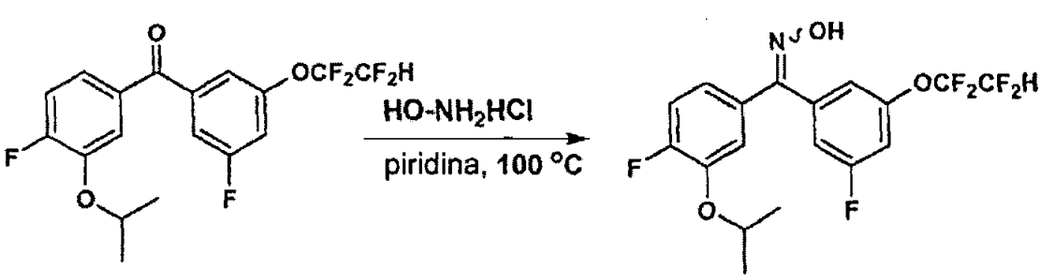
TFA 0.1%; 5 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.79, s, 1 H; 7.10 - 7.20, m, 3 H; 6.90 - 7.03, m, 5 H; 6.70, s, 1 H; 6.68, s, 1 H; 6.55 - 6.58, m, 1 H; 5.74 - 6.00, t, *J* = 52; 4.15, 4.19, d, *J* = 16, 1 H; 3.66 - 3.69, d, *J* = 12, 1 H; 3.51 - 3.54, m, 1 H; 0.73 - 0.80, m, 1 H; 0.61 - 0.69, m, 2 H; 0.55 - 0.60, m, 1 H.

**EJEMPLO 348**




**(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(hidroximatil)fenil)etil)-3-(trifluorometil)benzamida**

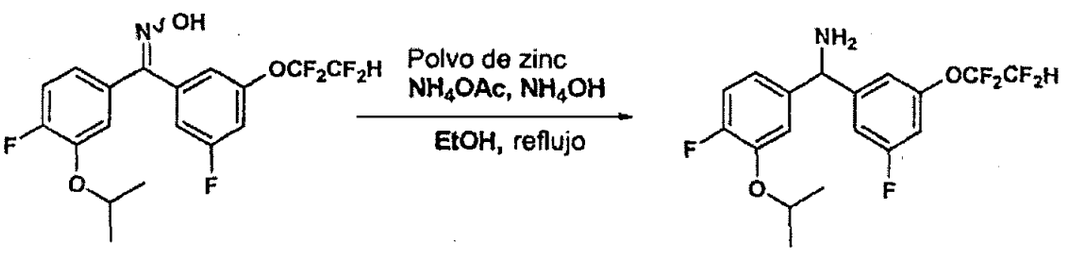
**Procedimiento 172**




A una solución de (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona, preparada como se describe en el Procedimiento 3, 4, 59 y 68, (207 mg,

0.53 mmoles) en piridina (1.5 ml) se agregó clorohidrato de hidroxilamina (192 mg, 2.8 mmoles) y la mezcla de reacción se calentó a 100°C durante 2 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se disolvió en EtOAc (50 ml). La porción orgánica se lavó con HCl 1 N (2 x 20 ml), agua (20 ml) y NaCl saturado (20 ml), luego se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por ISCO (40 g columna de gel de sílice, 0-30% EtOAc/hexano durante 30 min) para producir oxima de (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (216 mg, 77% de rendimiento) como un aceite incoloro. CLEM: TR = 2.13 min [M+H] 408.2 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

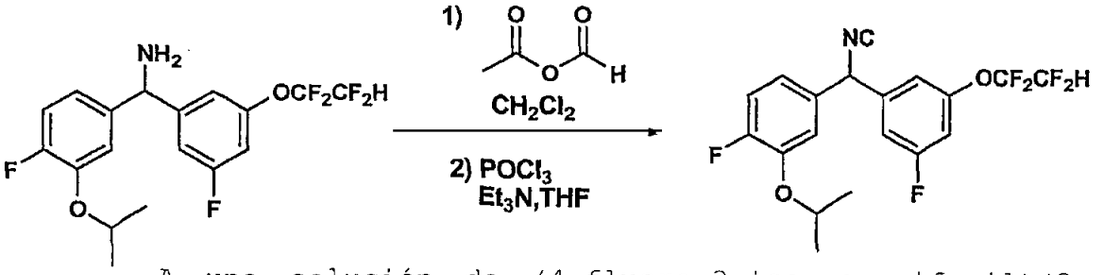
**Procedimiento 173**




A una suspensión de oxima de (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (3.5 g, 8.6 mmoles) en EtOH (30 ml) y $NH_4OH$ concentrado (50 ml) se le agregó acetato de amonio (754 mg, 19.8 mmoles), seguido por polvo de zinc (3.2

g, 49.1 mmoles) y la mezcla de reacción se calentó a reflujo durante 3 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente luego se filtró a través de celite. El sólido se lavó con NaOH 1 N (10 ml) y MeOH (10 ml). El filtrado combinado se concentró por extracción y el residuo se dividió entre EtOAc y agua. La capa orgánica se separó y se lavó con NaOH 1 N (15 ml), NaCl saturado (2 x 10 ml), se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida para producir (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanamina (2.8 g, 83% de rendimiento) como un aceite amarillo ligero. CLEM: TR = 1.76 min [M-$NH_2$] 377.1 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 6.97 - 7.09 (4 H, m), 6.81 - 6.89 (2 H, m), 5.76-6.03 (1 H, m), 5.14 (1 H, s), 4.52 (1 H, ddd, *J*=11.97, 6.15, 6.04 Hz), 1.73 (2 H, bs), 1.29 - 1.36 ( 6 H, m).

**Procedimiento 174**



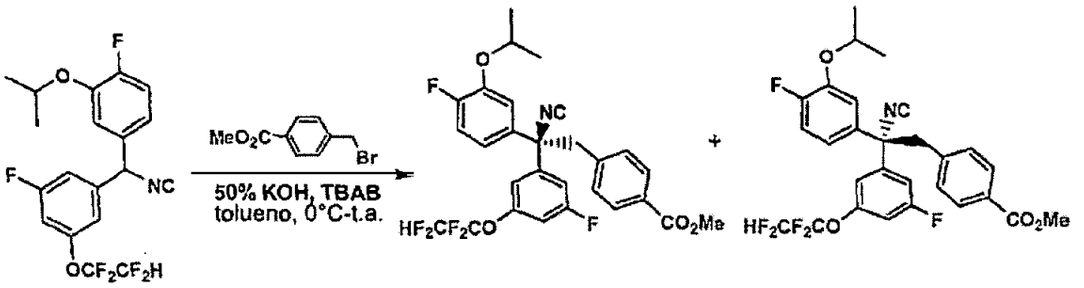

A una solución de (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanamina (2.8 g,

(551)

7.1 mmoles) en $CH_2Cl_2$ (30 ml) a 0°C se le agregó anhídrido acético fórmico (2.8 ml, formado al calentar una relación 2:1 v/v de anhídrido acético y ácido fórmico a 60°C durante 2 h). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 0.5 h. La mezcla de reacción se concentró bajo presión reducida y el residuo se purificó por ISCO (120 g columna de gel de sílice, 0 hasta 60% EtOAc/hexano durante 60 min gradiente) para dar N-((4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metil)formamida (2.56 g, 85% de rendimiento) como un aceite incoloro. CLEM: TR = 1.99 min [M+H] 422.0 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene TFA 0.1%, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm). A una solución de N-((4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metil)formamida (225 mg, 0.53 mmoles) en THF (2 ml) a 0°C se le agregó $Et_3N$ (0.4 ml, 2.9 mmoles) seguido por oxicloruro de fósforo (74 µL, 0.80 mmoles). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 4 h. La mezcla de reacción se diluyó con agua con hielo (15 ml) y se extrajo con $Et_2O$ (3 x 15 ml). Las capas orgánicas combinadas se lavaron con NaCl saturado (20 ml), se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron. El residuo se purificó por ISCO (12 g columna de gel de sílice, 0-50%

EtOAc/hexano durante 30 min) para producir 1-fluoro-4-((3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(isociano)metil)-2-isopropoxibenceno (143 mg, 67% de rendimiento) como un aceite amarillo pálido. CLEM: TR = 2.13 min [M-NC] 377 (columna Phenomenex Luna C18 4.6x30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene TFA 0.%, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.07 - 7.13 (1 H, m), 6.91 - 7.03 (4 H, m), 6.84-6.86 (1 H, m), 5.78-6.04 (1 H, m), 5.82 (1 H, s), 4.54 (1 H, ddd, *J*=11.97, 6.15, 6.04 Hz), 1.35 (6 H, t, *J*=5.05 Hz).

**Procedimiento 175**



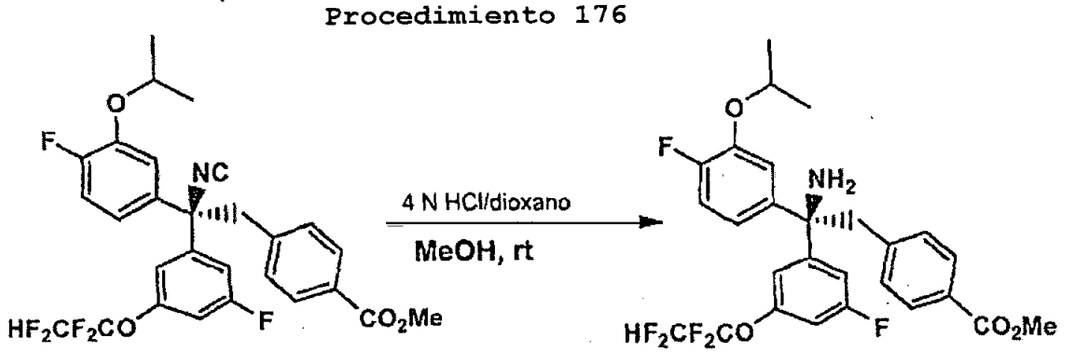

A una solución de 1-fluoro-4-((3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)(isociano)metil)-2-isopropoxibenceno (81 mg, 0.2 mmoles) en tolueno (2 ml) se agregó bromuro de tetrabutilamonio (19 mg, 0.06 mmoles) y bromuro de bencilo (50 mg, 0.22 mmoles), seguido por KOH(acuoso) 50% (650 µL). La mezcla de reacción se agitó vigorosamente durante 3 minutos. La mezcla de reacción se diluyó con EtOAc (20 ml). La capa orgánica se separó, se lavó con NaCl saturado (2 ml), se secó sobre $MgSO_4$, se filtró y se concentró bajo presión

reducida. El residuo se purificó por ISCO (12 g columna de gel de sílice, 0-40% EtOAc/hexano durante 35 min) para producir 4-(2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-isocianoetil)benzoato de (±)-metilo racémico como una película incolora (87 mg, 79% de rendimiento). CLEM TR = 2.24 min [M-NC] 525.1 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene TFA 0.%, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.87 (2 H, d, *J*=7.47 Hz), 7.08 (1 H, t, *J*=9.67 Hz), 6.93-6.99 (5 H, m), 6.87 (2 H, d, *J*=6.59 Hz), 5.76-6.03 (1 H, m), 4.40 - 4.46 (1 H, m), 3.90 (3 H, s), 3.65 (2 H, s), 1.27 (6 H, dd, *J*=17.58, 5.71 Hz).

Una solución de 4-(2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-isocianoetil)benzoato de (±)-metilo (87 mg) en alcohol de isopropilo se sometió a CLAR preparativa quiral (Columna Chiralpak AD, 5 x 50 cm elución isocrática con 10% IPA/heptano, 50 ml/min, observando a 254 nm) para producir 4-(2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-isocianoetil)benzoato de (R)-metilo (35 mg) (CLAR analítica quiral: TR = 8.9 min, Columna Chiralpak AD 4.6 x 250 mm, elución isocrática con 10% IPA/heptano) y 4-(2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-isocianoetil)benzoato de

(S)-metilo (38 mg) (CLAR analítica quiral: TR = 6.3 min, Columna Chiralpak AD 4.6 x 250 mm, elución isocrática con 10% IPA/heptano) como aceites transparentes e incoloros.

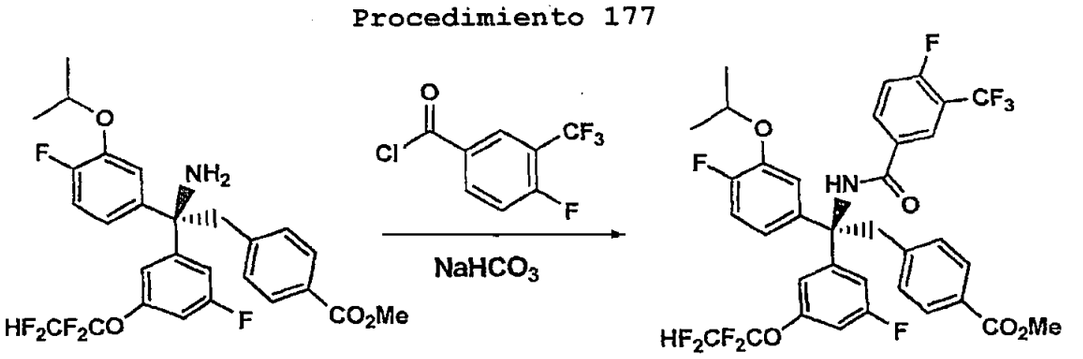
**Procedimiento 176**




A una solución de 4-(2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-isocianoetil)benzoato de (R)-metilo (120 mg, 0.22 mmoles) en MeOH (2 ml) se le agregó HCl 4 N en dioxano (0.5 ml) y la mezcla de reacción se agitó durante 3 minutos. El solvente de la reacción se evaporó bajo una corriente de nitrógeno. El residuo se diluyó con EtOAc (15 ml), se lavó con solución de bicarbonato de sodio saturado (10 ml) y NaCl saturado, se secó sobre $MgSO_4$, se filtró y se evaporó para producir 4-(2-amino-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)benzoato de (R)-metilo (103 mg, 86% de rendimiento) como un vidrio claro. CLEM: TR = 1.87 min [M-$NH_2$] 525.1 (columna Phenomenex Luna C18 4.6 x 30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene TFA 0.%, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm).

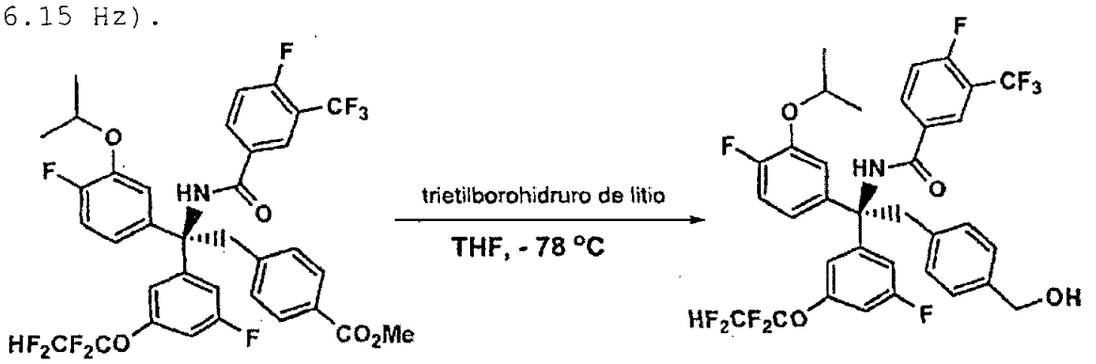
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**Procedimiento 177**




A una solución de 4-(2-amino-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)benzoato (R)-metilo (50 mg, 0.09 mmoles) en THF (2 ml) se agregó bicarbonato de sodio (30 mg, 0.36 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró y el producto filtrado se concentró bajo presión reducida. El residuo se purificó por ISCO (4 g columna de gel de sílice, 0-50% EtOAc/hexano durante 30 min) para producir 4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)benzoato de (R)-metilo (53 mg, 79% de rendimiento) como una película incolora. CLEM: TR = 2.28 min [M+H] 731.9 (columna Phenomenex Luna C18 4.6x30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene TFA 0.%, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: TR = 4.28 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene PPA 0.2%, relación de flujo 4 ml/min, longitud de onda 220 nm); $^1H$ RMN

(400 MHz, $CDCl_3$) δ ppm 7.95 (1 H, d, *J*=4.83 Hz), 7.81-7.84 (3 H, m), 7.28 - 7.32 (1 H, m), 6.94 - 7.04 (4 H, m), 6.77-6.79 (2 H, m), 6.53 - 6.63 (3 H, m), 5.77-6.01 (1 H, m), , 4.30 - 4.35 (1 H, m), 4.25 (1 H, d, *J*=12.74 Hz), 3.89 (3 H, s), 3.78 (1 H, d, *J*=12.74 Hz), 1.28 (3 H, d, *J*=6.15 Hz), 1.21 (3 H, d, *J*=6.15 Hz).

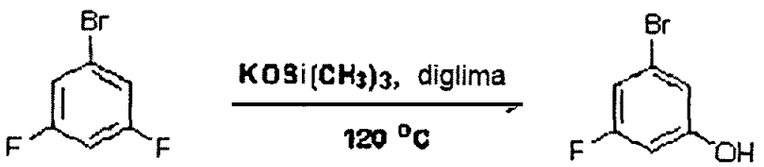



A una solución de 4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)etil)benzoato de (R)-metilo (20 mg, 0.027 mmoles) en THF (2 ml) a -78°C se le agregó una solución de trietilborohidruro de litio (1.0 M en THF, 0.5 ml, 0.5 mmoles). La mezcla de reacción se agitó a -78°C durante 1.5 h. La reacción se apagó por la adición de NaOH 1 N (1 ml) y se diluyó con EtOAc (15 ml). La porción orgánica se lavó con NaCl saturado (2 x 10 ml), se secó sobre sulfato de magnesio, se filtró y se concentró bajo presión reducida. El residuo se purificó por CLAR preparativa (columna YMC Sunfire 5 μ C18 30 x 100mm, eluyendo con 20-90% MeOH/$H_2O$ que contiene TFA 0.1%, 10 min gradiente, relación de flujo 40 ml/min, longitud de onda 220 nm) para producir (R)-

4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-(4-(hidroximatil)fenil)etil)-3-(trifluorometil)benzamida (Ejemplo 348, 13 mg, 78% de rendimiento) como una película incolora. CLEM: TR = 2.17 min [M+H] 704.1 (columna Phenomenex Luna C18 4.6x30mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene TFA 0.1%, 2 min gradiente, relación de flujo 5 ml/min, longitud de onda 220 nm); CLAR: TR = 4.0 min (columna Phenomenex Luna C18 4.6 X 50 mm, eluyendo con 10-90% MeOH/$H_2O$ que contiene 0.2% PPA, relación de flujo 4 ml/min, longitud de onda 220 nm); $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 7.91 (1 H, d, *J*=6.59 Hz), 7.85-7.87 (1 H, m) 7.26 - 7.31 (1 H, m), 7.16 (2 H, d, *J*=7.91 Hz), 6.93-7.05 (4 H, m), 6.68 - 6.73 (3 H, m), 6.60 - 6.66 (2 H, m), 5.75-6.01 (1 H, m), 4.64 (3 H, s), 4.35 (1 H, m), 4.06 (1 H, d, *J*=13.2 Hz), 3.74 (1 H, d, *J*=13.2 Hz), 1.29 (3 H, d, *J*=6.15 Hz), 1.26 (1 H, s), 1.23 (3 H, d, *J*=6.15 Hz).

El Ejemplo 273 se puede también preparar por procedimientos alternativos tales como abajo.

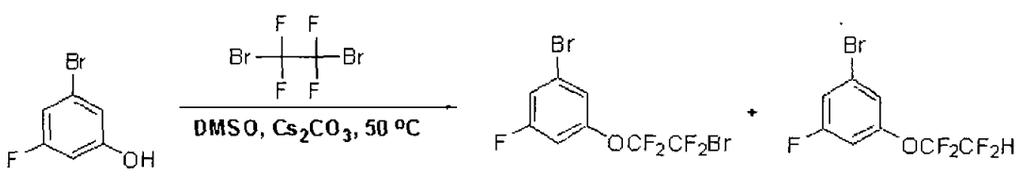
**Procedimiento 178**




A un matraz de cuatro cuellos 2 L, enjuagado con $N_2$ equipado con un agitador mecánico, un condensador, un

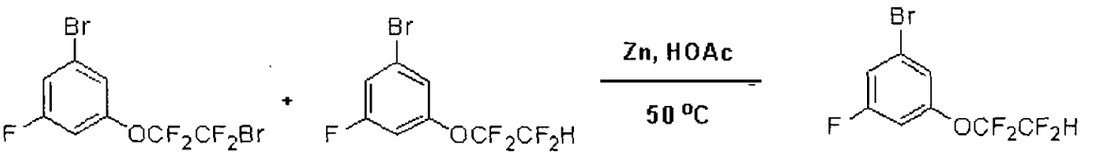
1558

controlador de temperatura y una entrada $N_2$, se le agregó trimetilsilanolato de potasio (225.0 g, 1.75 mol, 90% de pureza tec.), 1-bromo-3,5-difluorobenceno (96.5 g, 0.5 mol) y diglima (300 ml). La mezcla de reacción se calentó a 120°C bajo $N_2$ durante 5 h. Después del enfriamiento hasta temperatura ambiente, el manto de calentamiento se reemplazó con un baño con hielo. La mezcla de reacción se acidificó con una solución HCl 3 N (600 ml) mientras se mantiene la temperatura de reacción bajo 30°C. El éter de butil metilo terciario (1 L) se agregó y la mezcla resultante se agitó bajo 20°C durante 30 min luego se transfiere a un embudo separador 5 L. La capa orgánica se separó y se lavó con agua (3 X 500 ml), NaCl saturado (500 ml), se secó sobre $MgSO_4$, se filtró y se concentró in vacuo para dar el sólido rojo crudo (145.0 g). El material crudo se destiló luego a 52-55°C / 0.1 mm Hg para producir 3-bromo-5-fluorofenol como un aceite ligeramente amarillo (88.0 g, 92% de rendimiento). $^1H$ RMN (300 MHz, $CDCl_3$) $\delta$ 5.34 (s, H), 6.47-6.52 (m, 1H), 6.77-6.83 (m, 2 H).




A un matraz de fondo redondo de tres cuellos, 1 L, secado a la flama equipado con un controlador de temperatura, un agitador mecánico, un condensador y una entrada $N_2$ se le

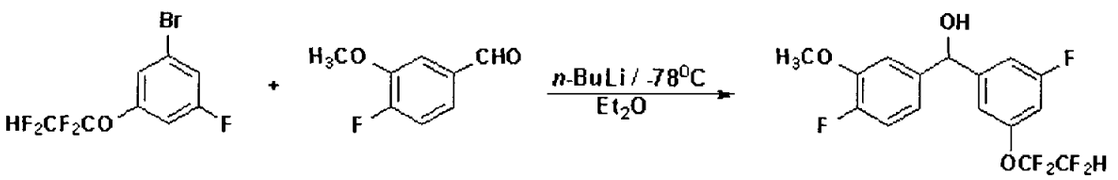
cargó 3-bromo-5-fluorofenol (57.3 g, 300 mmoles), 1,2-dibromo-1,1',2,2'-tetrafluoroetano (156.0 g, 600 mmoles), DMSO seco (300 ml) y $Cs_2CO_3$ (146.6 g, 450 mmoles) bajo $N_2$. La mezcla de reacción se calentó a 50°C durante 5 h. Después del enfriamiento hasta temperatura ambiente, agua (300 ml) y hexano (300 ml) se agregaron. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La fase orgánica se separó y la capa acuosa se extrajo con hexano (300 ml). Los extractos orgánicos combinados se lavaron con agua (500 ml), NaCl saturado (500 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron in vacuo para dar 1-bromo-3-(2-bromo-1,1,2,2-tetrafluoroetoxi)-5-fluorobenceno (104.2 g, 94% de rendimiento) que contiene 5% de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (5.2 g). 1-Bromo-3-(2-bromo-1,1,2,2-tetrafluoroetoxi)-5-fluorobenceno: $^1H$ RMN (300 MHz, $CDCl_3$) δ 6.91-6.94 (m, 1H), 7.18-7.23 (m, 2 H).




A un matraz de fondo redondo de cuatro cuellos 1 L equipado con un controlador de temperatura, un agitador mecánico, y una entrada $N_2$, se le agregó la mezcla cruda de 1-bromo-3-(2-bromo-1,1,2,2,-tetrafluoro-etoxi)-5-fluorobenceno (104.0 g, 281 mmoles) y 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (5.2 g, 18 mmoles), ácido

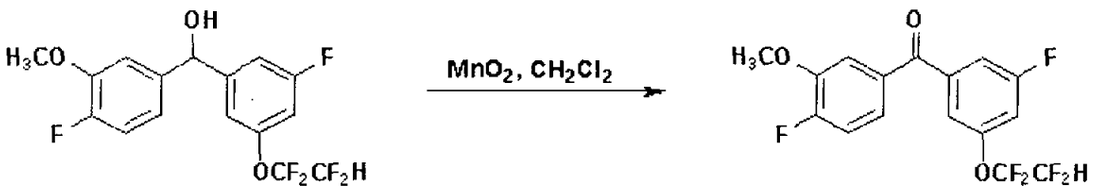
15-60

acético (300 ml). La mezcla de reacción se calentó luego hasta 50°C. El polvo de zinc (91.9 g, 1.405 mol) se agregó en porciones. La mezcla de reacción se agitó a 50°C durante 1 h y se dejó enfriar hasta temperatura ambiente. El agua (300 ml) y hexano (300 ml) se agregaron. La mezcla resultante se agitó a temperatura ambiente durante 30 min. La fase orgánica se separó y la capa acuosa se extrajo con hexano (2 x 300 ml). Los extractos orgánicos combinados se lavaron con agua (500 ml), NaCl saturado (500 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron in vacuo para producir 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno como un líquido ligeramente amarillo (71 g, 87% de rendimiento). $^1H$ RMN (300 MHz, $CDCl_3$) δ ppm 5.87 (tt, J = 52.7 y 2.9 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 7.16-7.18 (m, 2 H). El 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno se puede destilar a 0.6 mm Hg, 47-48°C (baño 77-100°C) a un aceite incoloro.




A una solución de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno, preparada como se describe en el Procedimiento N, (1.00 g, 3.44 mmoles) en éter dietílico en (10 ml) a -72°C se le agregó n-BuLi 2.5 M (1.37 ml, 3.44 mmoles) gota a gota. Una vez que se completa la adición, la mezcla de reacción se agitó durante 15 minutos a -72°C, luego

4-fluoro-3-metoxibenzaldehido (0.53 g, 3.44 mmoles) se agregó mientras la temperatura de la mezcla de reacción se mantuvo bajo -52°C. La mezcla de reacción se agitó durante 3 h a -72°C. La mezcla de reacción se apagó por la adición de HCl 1N y la porción acuosa se extrajo con EtOAc (2 x). Las capas orgánicas combinadas se lavaron con NaCl saturado, se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El residuo se purificó por ISCO al usar un gradiente de 0-50% EtOAc/ hexano como eluyente para producir (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanol (0.83 g, 66% de rendimiento). CLAR: TR = 3.85 min (columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene ácido fosfórico al 0.1% durante un gradiente de 4 minutos, relación de flujo 4 ml/min, observando a 220 nm); $^1H$ RMN ($CDCl_3$): 7.05 - 6.8 (m, 6 H), 5.87 (tt, J=2.8, 52.9Hz), 5.75 (s, 1 H), 3.85 (s, 3 H).

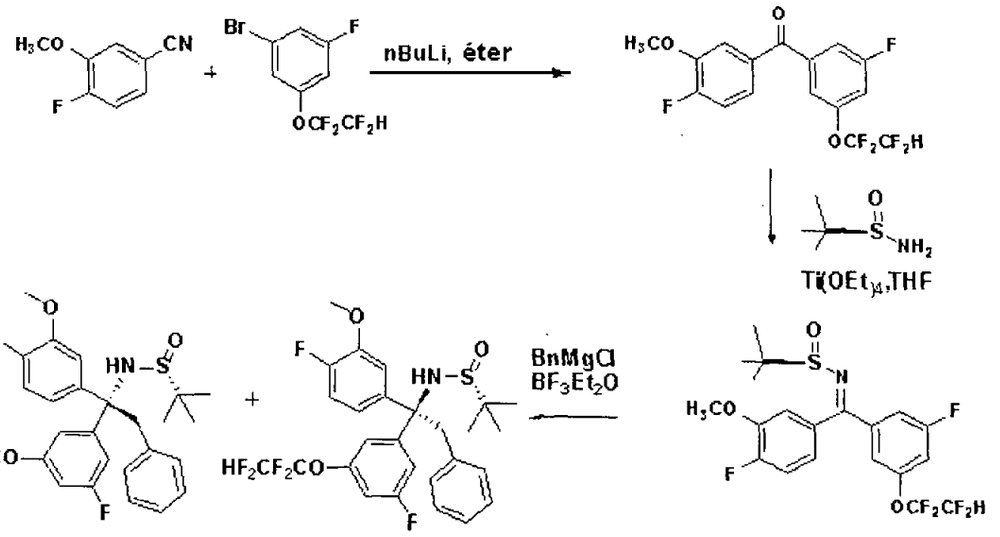



A una solución de (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanol (0.58 g, 1.57 mmoles) en $CH_2Cl_2$ (5 ml) se le agregó dióxido de manganeso activado (0.80 g, 7.86 mmoles). La mezcla de reacción se agitó durante la noche a temperatura ambiente. El dióxido de manganeso adicional (0.80 g, 7.86 mmoles) se agregó y la reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con $CH_2Cl_2$ y se filtró a través de celite y el sólido se lavó con $CH_2Cl_2$. El producto filtrado se concentró

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bajo presión reducida para producir (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (0.56 g, 98% de rendimiento). CLAR: TR = 4.048 minutos (Columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene ácido fosfórico al 0.1% durante un gradiente de 4 minutos, relación de flujo 4 ml/min, observando a 220 nm); CLEM: [M+H] 365.2 (Columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene TFA 0.1% durante un gradiente de 2 minutos, relación de flujo 5 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, $CDCl_3$): 7.5-7.1 (m, 6 H), 5.92 (tt, J=2.2, 53.6Hz, 1 H), 3.93 (s, 3 H).

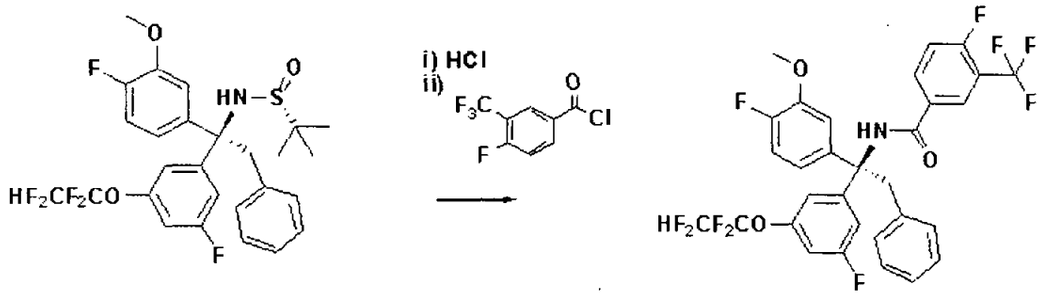
Alternativamente, (4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona se puede preparar por los métodos descritos en el Procedimiento 4 a partir de 4-fluoro-3-metoxibenzonitrilo en 68% de rendimiento.



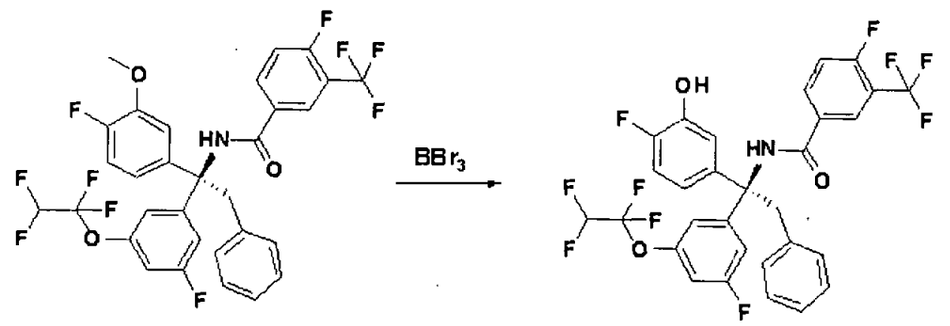

(R)-N-((4-fluoro-3-metoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-

sulfinamida se preparó por los métodos descritos en los Procedimientos 5 proporcionando una mezcla diaestereomérica 3:1 de (R)-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida y (S)-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida en 90% de rendimiento. Los diaestereómeros se separaron por Elución de cromatografía en Columna Chiralcel AD con Heptano IPA (68% de rendimiento). Los datos analíticos y rendimiento para los diaestereómeros están aquí. Isómero A: CLEM: [M+H] 560.2, tiempo de retención = 4.08 min (Columna Phenomenex Luna C18 5µ, eluyendo con 10-90% metanol acuoso que contiene TFA 0.1% durante un gradiente de 4 minutos, relación de flujo 5 ml/min, observando a 220 nm); $^1$H RMN (400 MHz, CLOROFORM-d) δ ppm 1.23 (s, 9 H), 3.63 (d, J = 12 Hz, 1H), 3.73 (s, 3 H), 3.89 (d, J = 12 Hz, 1H), 5.94 (tt, J = 53, 2.4 Hz, 1H), 6.67 - 6.74 (m, 2H), 6.96 - 7.03 (m, 3H), 7.36 - 7.14 (m, 6 H) ppm. CLAR quiral: TR = 8.21 min (Columna Quiral AD 4.6 x 250 mm; 20% Isocrático; Solvente A = Heptano, Solvente B = DEA 0.1% en IPA). Isómero B: CLEM: TR = 4.022 min [M+H] 560.2 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm). $^1$H RMN (400 MHz, $CDCl_3$) δ ppm 1.20 (s, 9 H) 3.56 (d, *J*=12.09 Hz, 1 H) 3.77 (s, 3 H) 3.98 (d, *J*=12.64 Hz, 1 H) 4.20

(s, 1 H) 5.69 - 6.00 (m, 1 H) 6.67 - 6.74 (m, 2 H) 6.80 - 6.89 (m, 2 H) 6.91 (d, *J*=7.70 Hz, 2 H) 7.02 - 7.08 (m, 1 H) 7.10 (s, 1 H) 7.11 - 7.20 (m, 3 H). CLAR quiral: TR = 10.34 min (Columna Quiral AD 4.6 x 250 mm; 20% Isocrático; Solvente A = Heptano, Solvente B = DEA 0.1% en IPA).



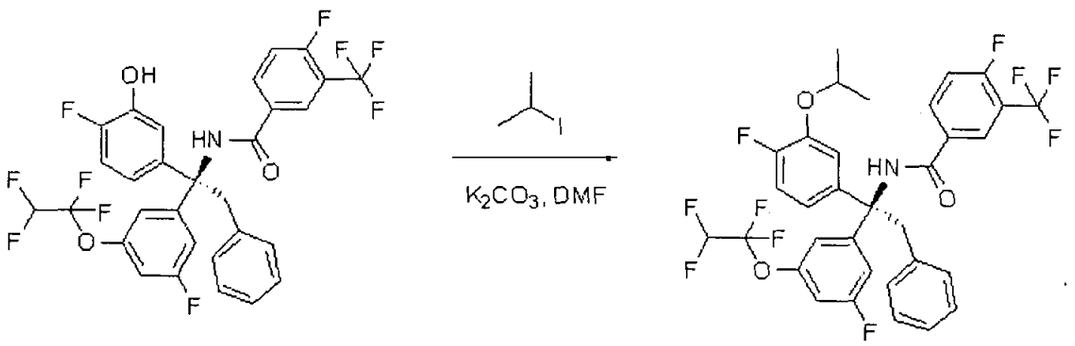

(R)-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se convirtió a (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida por los métodos descritos en el Procedimiento 6 y Procedimiento 7.




A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (2.8 g, 4.43

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mmoles), preparada como se describe en el Procedimiento 5, 6 y 7 (44% de rendimiento), en $CH_2Cl_2$ (15 ml) se agregó $BBr_3$ (12 ml, 12 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 2 h y se apagó por la adición de hielo. La mezcla de reacción se diluyó con EtOAc y se lavó con $NaHCO_3$ saturado, NaCl saturado, se secó sobre $Na_2SO_4$, se filtró y se concentró para resultar (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264) como aceite claro (2.9 g, 100% de rendimiento). CLEM: TR = 4.176 min [M+H] 632.2 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm).



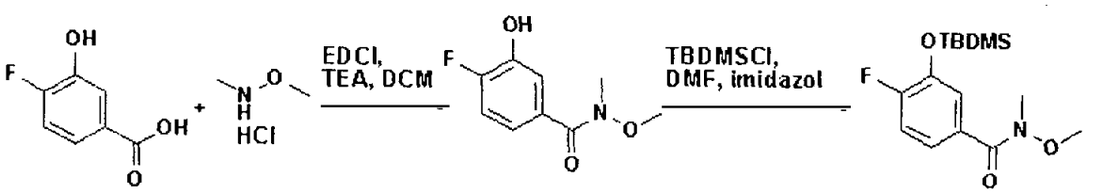

A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2)-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264, 2.70 g, 4.27 mmoles) en DMF (6 ml) se le agregó $K_2CO_3$ (1.47 g, 10.69 mmoles), seguido por yoduro de isopropilo (0.64 ml, 6.40 mmoles). La mezcla de reacción se agitó a 60°C durante 16 h. La mezcla de reacción se filtró y el sólido se lavó con EtOAc. El producto filtrado se lavó con $H_2O$, NaCl

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saturado, se secó sobre $Na_2SO_4$ y se concentró bajo presión reducida. El residuo se purificó por columna de gel de sílice ISCO al usar 0 hasta 50% EtOAc en hexano como solventes de elución para producir (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 273) como un polvo blanco (2.4 g, 83% de rendimiento). CLEM: TR = 4.05 min [M+H] 674.1 (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). $^1H$ RMN (400 MHz, $CD_3OD$) δ ppm 7.95 - 8.00 (2 H, m), 7.42 - 7.47 (1 H, m), 7.19 (1 H, t, J=7.47 Hz), 7.12 (3 H, t, J=7.25 Hz), 6.99 - 7.07 (3 H, m), 6.71 - 6.81 (4 H, m), 6.14 - 6.41 (1 H, m), 4.26 - 4.32 (1 H, m, J=6.15, 6.15, 6.15, 6.15 Hz), 4.12 (1 H, d, J=13.18 Hz), 3.85 (1 H, d, J=12.74 Hz), 1.23 (3 H, d, J=6.15 Hz), 1.17 (3 H, d, J=6.15 Hz).

Alternativamente, (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida se puede preparar por los siguientes Procedimientos:

**Procedimiento 179**




A una solución de ácido 4-fluoro-3-hidroxibenzoico (1.49 g, 9.55 mmoles) en DCM (40 ml) se le agregó TEA (1.2

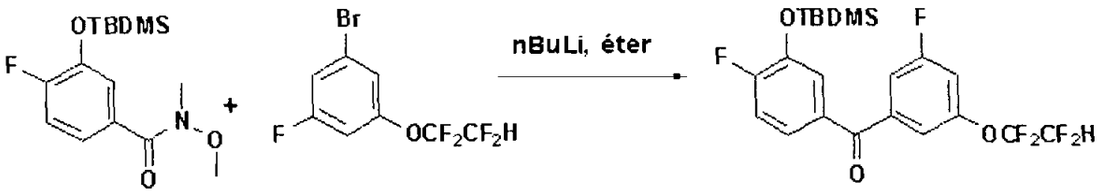
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ml, 8.61 mmoles) seguido por clorohidrato de N,O-dimetilhidroxilamina (1.12 g, 11.5 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se diluyó con DCM, se lavó con agua dos veces, se secó sobre $Na_2SO_4$, se filtró y se concentró para producir 4-fluoro-3-hidroxi-N-metoxi-N-metilbenzamida como un aceite incoloro (1.90 g, 100% de rendimiento). CLEM: TR = 0.89 min [M+H] 200.10 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

A una solución de 4-fluoro-3-hidroxi-N-metoxi-N-metilbenzamida (1.90 g, 9.55 mmoles) en DMF (8 ml) se le agregó imidazol (740 mg, 10.8 mmoles) y TBDMSCl (1.62 g, 10.8 mmoles) a temperatura ambiente. La mezcla de reacción se agitó durante 48 h y se apagó con $NaHCO_3$ saturado. La solución se extrajo con éter (3 x) y las porciones de éter combinadas se lavaron con LiCl (10%), se secaron sobre $Na_2SO_4$, filtraron y se concentraron. El aceite incoloro resultante se purificó por cromatografía ISCO (120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min) para dar 3-(ter-butildimetilsililoxi)-4-fluoro-N-metoxi-N-metilbenzamida (TR = 10-12 minutos) como un aceite incoloro (2.00 g, 67% de rendimiento). CLEM: TR = 2.06 min [M+H] 314.22 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando

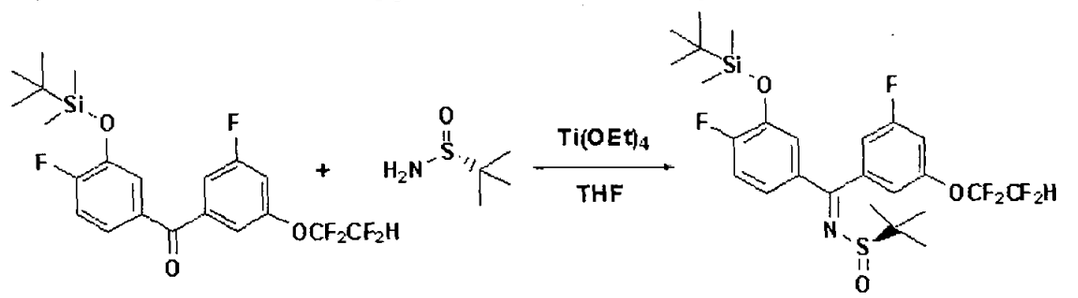
1568

a 220 nm); RMN: 400MHz $^1H$ ($CDCl_3$) 7.26 ppm, 2 H, m; 7.02 ppm, 1 H, m; 3.50 ppm, 3 H, s; 3.31 ppm, 3 H, s; 0.97 ppm, 9 H, s, 0.16 ppm, 6H, s.



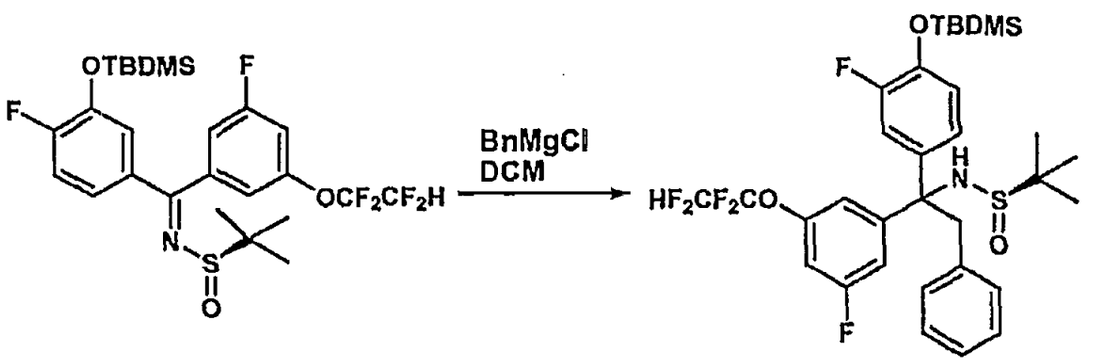

A -78°C bajo argón, a una solución de 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (2.04 g, 7.01 mmoles) en éter anhidro (20 ml) se agregó nBuLi (3.5 ml, 2.0 M en ciclohexano, 7.0 mmoles) gota a gota y la mezcla de reacción se agitó durante 1 h. 3-(Ter-butildimetilsililoxi)-4-fluoro-N-metoxi-N-metilbenzamida (2.00 g, 6.38 mmoles) se agregó en una porción y la mezcla de reacción se agitó a -78°C durante 1.5 h. La solución amarilla pálida se vació dentro de una solución acuosa HCl 1 N (30 ml) y éter (30 ml) se usó para enjuagar el matraz de reacción. La fase acuosa se separó y se extrajo con éter dietílico (20 ml). Las porciones de éter combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El aceite resultante se purificó por cromatografía ISCO (120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min) para dar (3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona a un tiempo de retención de 7 min (2.11 g, 71% de rendimiento). CLEM: TR = 2.41 min [M+H]

465.19 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); RMN: 400 MHz $^1H$ ($CDCl_3$) 7.33 ppm, 3 H, m; 7.28 ppm, 1 H, m; 7.11 ppm, 2 H, m; 5.86 ppm, 1 H, t, J=53.39 Hz; 0.95 ppm, 9 H, s; 0.15 ppm, 6 H, s.




Un matraz de fondo redondo se cargó con (3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (2.09 g, 4.50 mmoles), (R)-2-metilpropano-2-sulfinamida (653 mg, 5.4 mmoles), $Ti(OEt)_4$ (1.54 g, 6.76 mmoles) y THF anhidro (40 ml). La solución resultante se calentó a 75°C bajo argón durante 14 h. Los solventes se retiraron y el residuo se diluyó con éter (50 ml) y NaCl saturado (20 ml). La mezcla resultante se filtró a través de un vidrio fritado y el producto filtrado se transfiere a un embudo de separación. La porción orgánica se separó y la fase acuosa se extrajo con éter dietílico (2 x 20 ml). Las porciones orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El residuo se disolvió en hexano: EtOAc y se purificó por cromatografía ISCO (2 × 120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min)

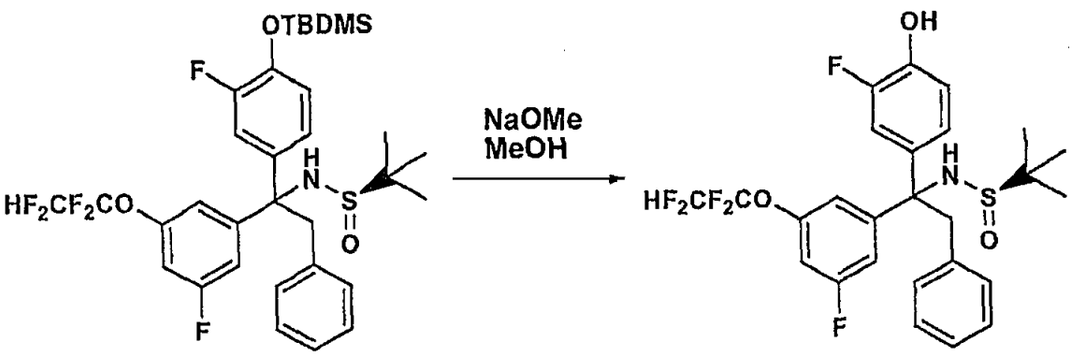
para producir (R)-N-((3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida a un tiempo de retención de 14 min (2.05 g, 80% de rendimiento) CLEM: TR = 2.37 min [M+H] 568.24 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). RMN: 400 MHz $^1H$ ($CDCl_3$) 7.36 ppm, 1 H, m; 7.11 ppm, 5 H, m; 5.90 ppm, 1 H, t, $J$=52.73 Hz; 0.97 ppm, 9 H, s; 0.18 ppm, 6 H, s.




A -78°C a una solución de (R)-N-((3-(ter-butildimetilsililoxi)-4-fluorofenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida (1.0 g, 1.76 mmoles) en DCM (50 ml) se agregó $BF_3 \cdot Et_2O$ (0.77 ml, 3.52 mmoles) por medio de jeringa. Después de 5 min, solución BnMgCl (3.5 ml, solución 1.0 M en éter, 3.5 mmoles) se agregó gota a gota y la mezcla de reacción se agitó a -78°C durante 1 h. Una porción adicional de BnMgCl (3.5 ml, solución 1.0 M en éter, 3.5 mmoles) se agregó gota a gota y

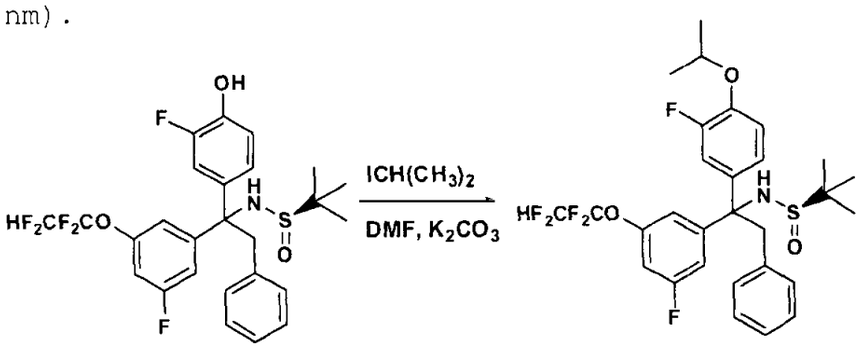
la reacción se agitó durante 1 hora adicional a -78°C. La mezcla de reacción se vació dentro de NaCl saturado (50 ml) y la capa orgánica se separó. La capa acuosa se extrajo con DCM (2 × 20 ml) y las capas orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron. El aceite resultante se purificó por cromatografía ISCO (120 g columna) al usar hexanos/EtOAc (0-100% durante 30 min) para dar una mezcla 4:1 aproximada de (R)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida y (S)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida a un tiempo de retención de 12 min (824 mg, 71% de rendimiento) CLEM: TR = 2.43 min [M+H] 660.39 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm). La relación diaestereomérica del producto se determinó para ser 4:1 por análisis CLAR quiral (Chiralcel® AD, 90:10 heptano: *i*-PrOH, 1 ml / min, 254 nm, TR (menor) = 4.43 min, PA=17%; TR (mayor) = 19.28 min, PA = 71%) y la mezcla diaestereomérica se tomó directamente para la siguiente etapa, Procedimiento 112, o los diaestereómeros se separaron como se describe en el Procedimiento 114. RMN: 400MHz $^1H$ ($CDCl_3$) 7.30 ppm, 2 H, m; 7.06 ppm, 5 H, m; 6.85 ppm, 2 H, m; 6.76 ppm, 1 H, m; 6.62 ppm, 2 H, m; 5.79 ppm, 1

H, m; 4.13 ppm, 1H, s; 3.84 ppm, 1 H, m; 3.47 ppm, 1 H, m; 1.12 ppm, 9 H, s; 0.84 ppm, 9 H, s; 0.01 ppm, 6 H, d, *J*=4.39 Hz.



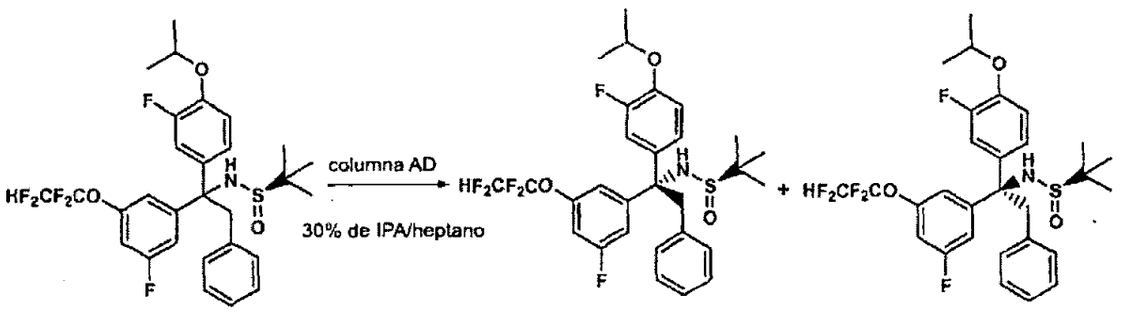

A temperatura ambiente una solución de NaOMe (5 ml, solución 0.5 M en MeOH) se agregó a la mezcla diaestereomérica 4:1 de (R)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (801 mg, 1.22 mmoles). La mezcla de reacción se agitó durante 15 minutos, MeOH se retiró, luego el residuo se disolvió en EtOAc (50 ml) y transfirió a un embudo de separación. HCl (20 ml, solución 1.0 N) se agregó y la capa EtOAc se separó. La capa acuosa se extrajo con EtOAc (2 × 10 ml) y las capas orgánicas combinadas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron para producir (R)-N-(1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma blanca (578 mg, 87% de rendimiento). CLEM: TR = 1.987 min [M+H] 546.35 (columna

Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).




A temperatura ambiente a una solución de mezcla diaestereomérica 4:1 (R)-N-(1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (578 mg, 1.06 mmoles) en DMF (10 ml) se le agregó $K_2CO_3$ (800 mg, 5.80 mmoles) y la solución espesa se agitó vigorosamente. 2-Yodopropano (220 mg, 1.27 mmoles) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con éter (50 ml), se lavó sucesivamente con LiCl 10% (2 × 20 ml) y agua (20 ml). La porción orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró para producir (R)-N-(1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma color naranja pálido (780 mg,

100% de rendimiento).

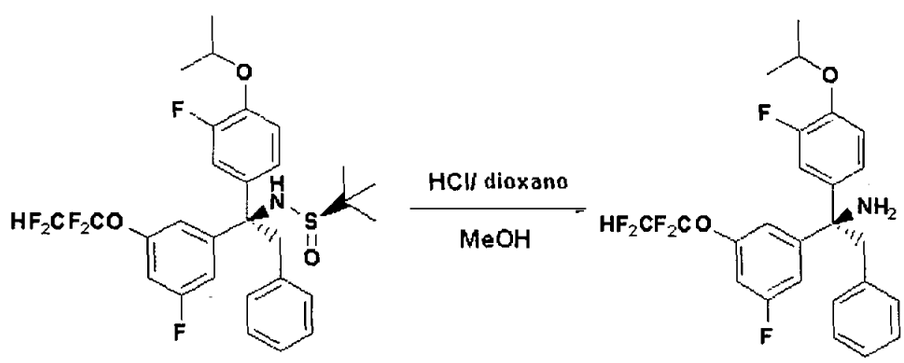



La mezcla diaestereomérica 4:1 de (R)-N-(1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (780 mg, 1.06 mmoles crudo) se separó por CLAR quiral preparativa columna Chiralpak AD 20μ, 5 × 50 cm, eluyendo con 30% IPA/Heptano con relación de flujo 50 ml/min.

La (R)-N-((S)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 17 min y se aisló como un aceite incoloro (101 mg, rendimiento 16%). CLEM: TR = 2.128 min [M+H] 588.38 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); CLAR quiral: TR = 4.35 min, ee 100% (columna Diacel Chiralpak AD 10μ, 4.6 × 250 mm elución isocrática con IPA (20%) y heptano; 1 ml/min, observando a 254 nm).

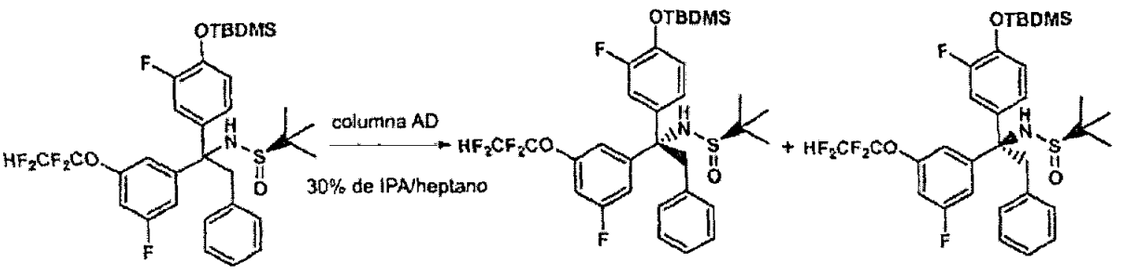
(R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención

de 39 min y se aisló como un aceite incoloro (398 mg, rendimiento 64%). CLEM: TR = 2.138 min [M+H] 588.38 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); CLAR quiral: TR = 9.98 min, ee 100% (columna Diacel Chiralpak AD 10 µ, 4.6 × 250 mm elución isocrática con IPA (20%) y heptano; 1 ml/min, observando a 254 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.08 ppm, 5 H, m; 6.84 ppm, 2 H, d, *J*=7.47 Hz; 6.77 ppm, 2 H, d, *J*=7.47 Hz; 6.63 ppm, 2 H, m; 5.79 ppm, 1 H, t, *J*=52.95 Hz; 4.33 ppm, 1 H, m; 4.15 ppm, 1 H, s; 3.92 ppm, 1 H, d, *J*=12.30 Hz; 3.48 ppm, 1 H, d, *J*=12.30 Hz; 1.22 ppm, 3 H, d, *J*=6.15 Hz; 1.18 ppm, 3 H, d, *J*=5.71 Hz; 1.14 ppm, 9 H, s.




A una solución de (R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (398 mg, 0.678 mmoles) en MeOH (1.5 ml) se agregó HCl (1.5 ml, solución 4 M en dioxano) y la mezcla de reacción se agitó durante 30 min. La mezcla de reacción se diluyó con

por los métodos descritos en el Procedimiento 113.

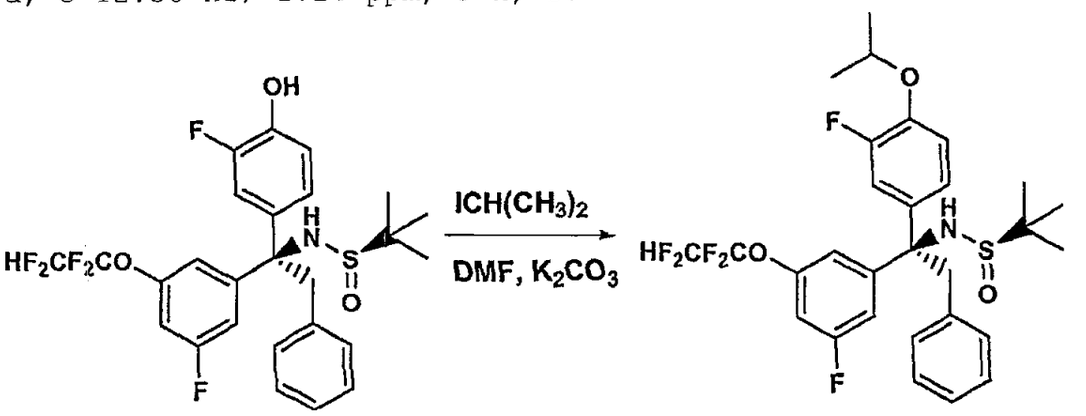



La mezcla de diaestereómeros de (R)-N-(1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (1.14 g, 1.73 mmoles) se separó por CLAR quiral preparativa columna Chiralpak AD 20µ, 5 × 50 cm, eluyendo con 30% IPA/Heptano con relación de flujo 50 ml/min.

(R)-N-((S)-1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 19 min (114 mg, rendimiento 10%). CLEM: TR = 2.45 min [M+H] 660.41 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm).

(R)-N-((R)-1-(4-(ter-butildimetilsililoxi)-3-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se eluyó a un tiempo de retención de 36 min (634 mg, rendimiento 56%). CLEM: TR = 2.41 min [M+H] 660.39 (columna Phenomenex Luna

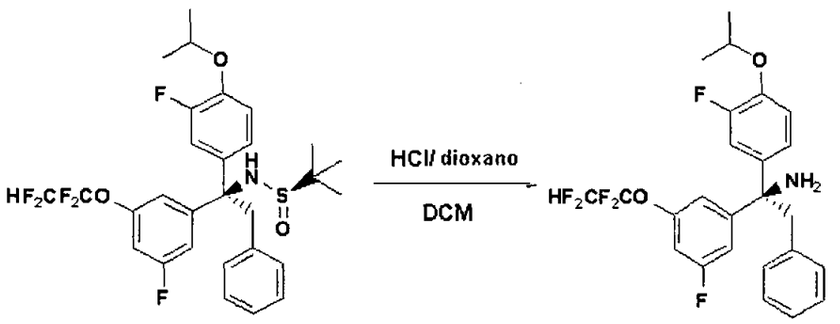
observando a 220 nm). CLAR: TR = 3.83 min, Pureza 98% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.61 ppm, 1 H, s; 7.40 ppm, 1 H, dd, *J*=8.13, 1.98 Hz; 7.13 ppm, 3 H, m; 6.99 ppm, 1 H, dd, *J*=10.33, 8.57 Hz; 6.84 ppm, 3 H, m; 6.68 ppm, 2 H, m; 6.61 ppm, 1 H, m; 5.85 ppm, 1 H, tt, *J*=52.95, 2.64 Hz; 4.30 ppm, 1 H, s; 4.02 ppm, 1 H, d, *J*=12.30 Hz; 3.50 ppm, 1 H, d, *J*=12.30 Hz; 1.24 ppm, 9 H, s.




(R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se preparó a partir de (R)-N-(1-(3-fluoro-4-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como se describe en el Procedimiento 6 en 78% de rendimiento. CLEM: TR = 2.17 min [M+H] 588.17 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm) CLAR: TR = 4.20 min, Pureza 95% (columna Phenomenex

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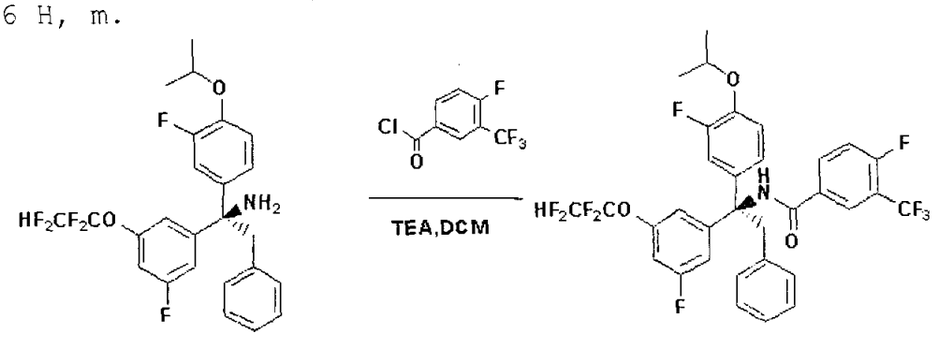
Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.10 ppm, 2 H, m; 6.87 ppm, 4 H, m; 6.70 ppm, 2 H, m; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 4.31 ppm, 1 H, s; 3.98 ppm, 1 H, d, *J*=12.74 Hz; 3.56 ppm, 1 H, d, *J*=12.74 Hz; 1.30 ppm, 3 H, d, *J*=5.71 Hz; 1.25 ppm, 3 H, d, *J*=6.15 Hz; 1.22 ppm, 9 H, s.




(R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina se preparó a partir de (R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como se describe en el Procedimiento 6 en 97% de rendimiento. CLEM: TR = 1.83 min [M-$NH_2$] 467.24 (columna Phenomenex Luna C18, 4.6 × 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 ml/min, observando a 220 nm); CLAR: TR = 3.17 min, Pureza 100% (columna Phenomenex Luna C18, 4.6 × 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene 0.2% PPA; 4 ml/min, observando a 220 nm) RMN: 400MHz $^1H$ ($CDCl_3$) 7.16 ppm, 3 H, m; 7.01 ppm, 3 H, m; 6.92 ppm, 2 H, m;

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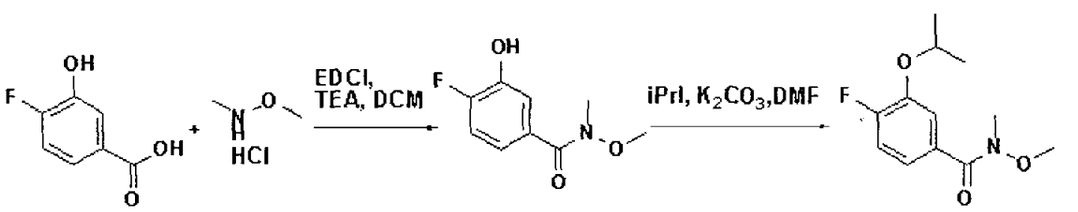
6.84 ppm, 1 H, d, *J*=8.79 Hz; 6.74 ppm, 2 H, d, *J*=7.03 Hz; 5.86 ppm, 1 H, m; 4.41 ppm, 1 H, m; 3.49 ppm, 2 H, s; 1.25 ppm, 6 H, m.




(R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida se puede preparar a partir de (R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletanamina por los métodos descritos en el Procedimiento 7.

Alternativamente, (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida se puede preparar por los siguientes Procedimientos:

**Procedimiento 180**



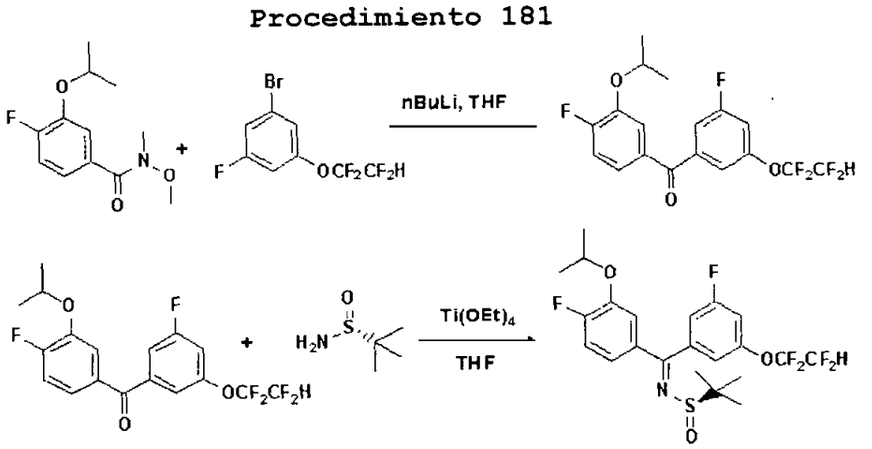

A un matraz de fondo redondo de cuatro cuellos 5 L se agregó ácido 3-hidroxi-4-fluorobenzoico (100 g, 0.64 mol) y $CH_2Cl_2$ (2.3 L). Trietilamina (107 ml, 0.768 moles) luego se

agregó a la suspensión. La solución se enfrió a -78°C, y EDCI (184.2 g, 0.961 mol) se agregó en porciones seguido por la adición de clorohidrato de N,O-dimetilhidroxiamina (93.6 g, 0.96 mol). La mezcla de reacción se agitó a -78°C durante 1 h y luego se permitió entibiar hasta 0°C durante un periodo de 2 h. La mezcla de reacción se transfirió a un embudo de separación y se lavó agua (2 X 1.2 L). La porción orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró in vacuo para dar 4-fluoro-3-hidroxi-N-metoxi-N-metilbenzamida como un sólido blanco (94.4 g, 74%).

Un matraz de fondo redondo 2 L equipado con un agitador mecánico, una entrada $N_2$, un condensador y un controlador de temperatura, se cargó 4-fluoro-3-hidroxi-N-metoxi-N-metilbenzamida (99.6 g, 0.5 mol), yoduro de isopropilo (110.5 g, 0.65 mol) y $Cs_2CO_3$ (195.5 g) y DMF (300 ml). La mezcla de reacción se calentó a 50°C durante 3 h. Yoduro de isopropilo (17.0 g, 0.1 mol) se agregó y la reacción se calentó a 50°C durante 12 h. La mezcla de reacción se permitió enfriar hasta temperatura ambiente y agua (1 L) y $CH_2Cl_2$ (500 ml) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante 0.5 h, y la fase orgánica se separó. La capa acuosa se extrajo con $CH_2Cl_2$ (3 X 500 ml). Los extractos orgánicos combinados se lavaron con agua (2 X 1 L), salmuera (1 L), se secó sobre $MgSO_4$, se filtró y se concentró in vacuo a 40°C durante 18 h para dar

4-fluoro-3-isopropoxi-N-metoxi-N-methlbenzamida como un sólido blanco apagado (120.0 g, 100%).

**Procedimiento 181**



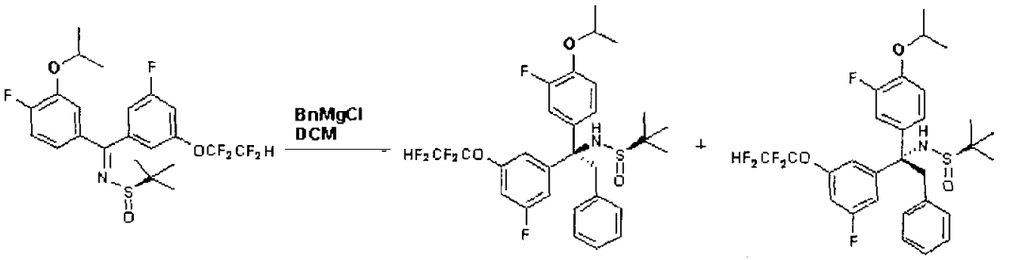

Un matraz de fondo redondo de cuatro cuellos 3 litros (secado a la flama) se cargó con 1-bromo-3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)benceno (72.88 g, 0.25 mol), 4-fluoro-3-isopropoxi-N-metoxi-N-metilbenzamida (60.39 g, 0.25 mol) y THF seco (700 ml) bajo $N_2$. La solución se enfrió a -76°C, y una solución de n-BuLi en hexano (2.5M, 100 ml, 0.25 mol) se administró gota a gota manteniendo la temperatura de la mezcla de reacción bajo -70°C durante un periodo de 40 min. La mezcla de reacción se agitó a -76°C durante 1.5 h luego se apagó con HCl 1N (500 ml). La mezcla se concentró in vacuo a la mitad del volumen y se dividió entre EtOAc y $H_2O$ (v/v 1:0.3, 1L). La fase orgánica se separó y la capa acuosa se extrajo con EtOAc (500 ml). Los extractos orgánicos combinados se lavaron con salmuera y luego se concentraron in vacuo para dar un aceite amarillo el cual se purificó por

cromatografía de columna al usar $CH_2Cl_2$ en hexanos (0% hasta 20%) para dar (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona como un aceite incoloro contaminado con un sub-producto (49.0 g, 50%). CL-EM (10-90% MeOH en $H_2O$ con TFA 0.1% en un gradiente de 2 min) 393.2 (M+H), tiempo de retención = 2.15 min.

Una solución de (4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metanona (49.0 g, 0.125 mol), (R)-(+)-2-metilpropano-2-sulfinamida (30.2 g, 0.25 mol), y $Ti(Oet)_4$ (51.9 ml, 0.25 mol) en THF seco se calentó a reflujo bajo $N_2$ durante 20 h. Después de permitir enfriar hasta temperatura ambiente, la mezcla de reacción se vació dentro de agua con hielo (800 ml) con agitación. El matraz de reacción se lavó con cantidad pequeña de EtOAc. La suspensión amarilla se filtró luego a través de una almohadilla de Celite y la almohadilla se enjuaga con EtOAc (ca. 500 ml). El producto filtrado se concentró in vacuo para remover más de THF (<30°C). El filtrado restante se dividió entre EtOAc y $H_2O$ (1:1, 1L). La fase orgánica se separó y se lavó con salmuera (1 L). Después de la concentración in vacuo, el residuo aceitoso naranja se disolvió en $CH_2Cl_2$ (ca. 100 ml). La solución se purificó por columna instantánea de gel de sílice al usar EtOAc en Hexano (0-20%) para dar (*R,Z/E*)-N-((4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida

(24.4 g). Las fracciones mezcladas se sometieron a una columna instantánea de gel de sílice adicional para dar 9.9 g adicionales de (*R,Z/E*)-N-((4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida. La fracción mezclada residual (ca. 9.7 g) se disolvió en EtOAc en hexano (25%, 80mL) y se sometió a una columna de Cromatografía de vaporización instantánea de gel de sílice adicional para dar (*R,Z/E*)-N-((4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida (6.90 g). Rendimiento total: 41.2 g (67%). CL-EM (10-90% MeOH en $H_2O$ con TFA 0.1% en un gradiente de 4 min) 496.1 (M+H), tiempo de retención = 4.23 min.

**Procedimiento 182**




Un matraz de fondo redondo 3L secado a la flama equipado con un agitador mecánico, un termómetro, una entrada $N_2$ y un embudo de goteo, se cargó con una solución de (*R,Z/E*)-N-((4-fluoro-3-isopropoxifenil)(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)metileno)-2-metilpropano-2-sulfinamida (40.5 g, 81.7 mol) en $CH_2Cl_2$ seco (1 L). La solución se enfrió a -76°C y $BF_3{\cdot}Et_2O$ (12.3 ml, 90.0 mol, 1.2 eq) se agregó en

una porción. La mezcla de reacción se agitó a -76°C durante 15 min, y una solución de cloruro de fenil magnesio (1.0 M en éter, 105.7 ml, 105.7 mol) se agregó gota a gota bajo -70°C durante un periodo de 1 h antes de que la mezcla de reacción se apagó con salmuera (800 ml). La solución resultante se agitó durante 10 min, luego se transfirió un embudo separador de 2 L. La fase orgánica se separó y la capa acuosa se extrajo con $CH_2Cl_2$ (500 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$. La solución se filtró y se concentró a ca. 100 ml. El residuo se purificó luego por cromatografía de columna de gel de sílice al usar 0-20% de EtOAc en hexanos para dar un aceite amarillo (48.5 g, 100%). CL-EM (10-90% MeOH en $H_2O$ con TFA 0.1% en un gradiente de 4 min) 588.3 (M+H), tiempo de retención = 4.36 min. CLAR Quiral Analítica (columna AD, 25% IPA en heptano con DEA 0.01%, isocrático), $t_{R1}$ = 4.16 min para (R)-N-((S)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida, $t_{R2}$ = 8.60 min para (*R*)-N-((*R*)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida. 48.5 g de la mezcla diaestereomérica compuesto (4/1 ratio) se separó por SFC en el sistema Thar 350. Un total de 33.5 g de (*R*)-N-((*R*)-1-(3-

fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (rendimiento: 69.3%) se obtuvo. Las condiciones de Quiral preparativa se enlistan aquí.

**Preparación Muestra:**

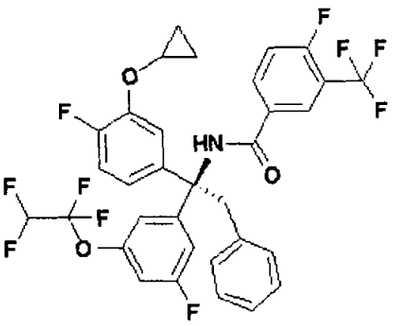
La muestra se disuelve en IPA a una concentración de 110 mg/ml. a una concentración de 50 mg/ml. La muestra se disuelve rápidamente.

**Condiciones Preparativas en Thar SFC-350**

| | | |
|---|---|---|
| columna | Chiralcel AD-H | 5x25 cm |
| Fase móvil | IPA 20% en $CO_2$ | |
| Presión (baria) | 100 | |
| Relación de flujo (ml/ min) | 240 | |
| Concentración de solución (mg/ml) | 110 | |
| Cantidad de inyección (ml) | 10 | |
| Tiempo de ciclo (min/iny) | 6.5 | |
| Temperatura (°C) | 35 | |
| rendimiento total (g/ hr) | 10 | |
| Detector de longitud de onda (nm) | 254 | |

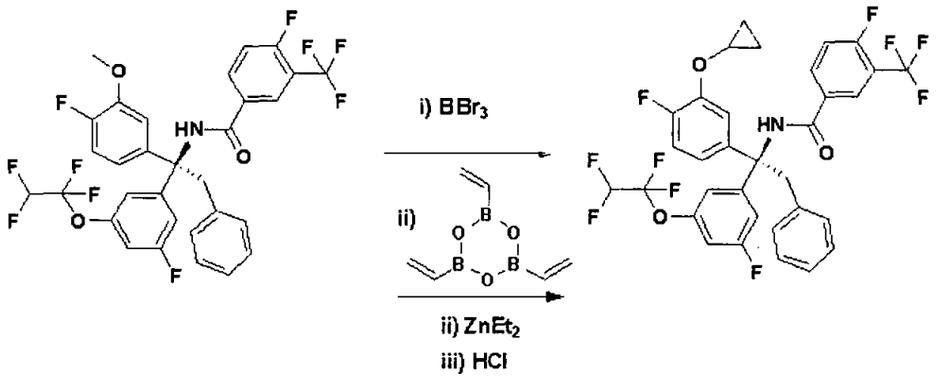
(R)-N-((R)-1-(3-fluoro-4-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se convirtió a (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5(1,1,2,2-tetrafluoro etoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida como se describe en 114.

**EJEMPLO 349A**



**(R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida**

**Procedimiento 183**



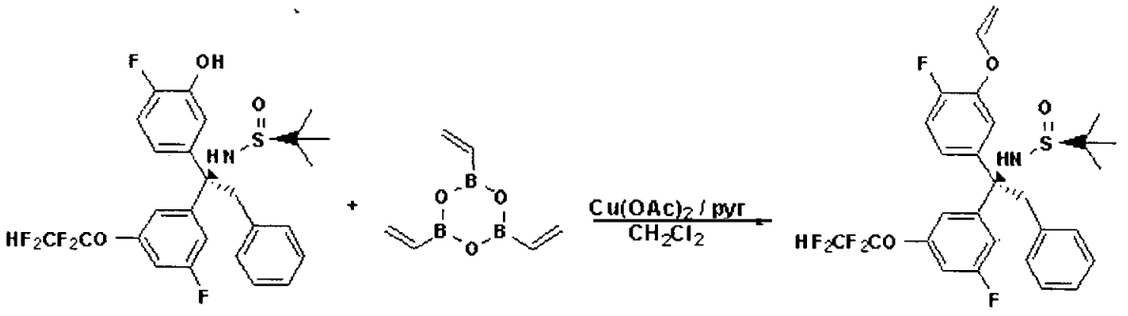

(R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 273) se convirtió a (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida como se describe en el Procedimiento 59. (R)-4-fluoro-N-(1-(4-fluoro-3-

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hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida se convirtió posteriormente a (R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida por los métodos descritos en el Procedimiento 161.

Alternativamente, (R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida se puede preparar por los siguientes Procedimientos:

**Procedimiento 184**

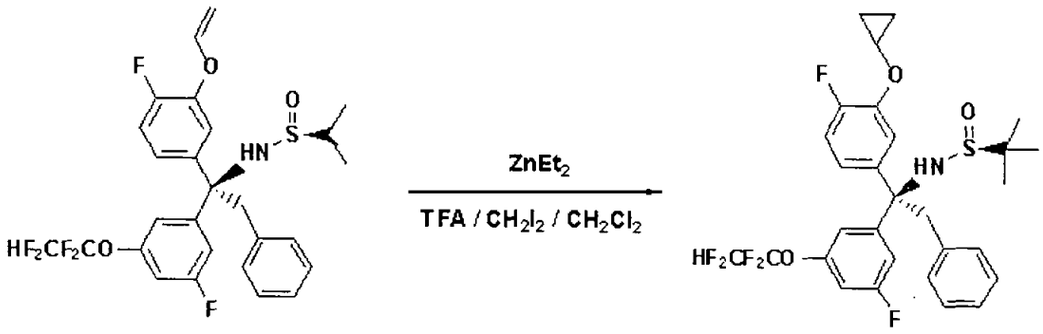



A una solución de (S)-N-((R)-1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida preparada como se describe en el Procedimiento 3, 4, 5, 6 y 59 (0.545 g , 1 mmoles) en $CH_2Cl_2$ (10 ml) se agregó $Cu(OAc)_2$ (0.182 g, 1 mmoles), seguido por piridina (0.79 g, 10 mmoles) y 2,4,6-trivinil-1,3,5,2,4,6-trioxatriborinano (0.159 g, 0.66 mmoles). La mezcla de reacción se agitó durante la noche bajo aire ambiente y se filtró a través de un tapón de celite y

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alúmina neutral. El sólido se lavó con acetato de etilo y el producto filtrado se concentró bajo presión reducida para producir (S)-N-((R)-1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma blanca apagada (0.495 g, 87% de rendimiento). CLEM: TR = 3.653 min [M+H] 572.2 (columna Phenomenex Luna C18 5 µ, eluyendo con 10-90% acetonitrilo acuoso que contiene ácido trifluoroacético 0.1% durante un gradiente de 4 minutos, observando a 220 nM). $^1$H RMN ($CDCl_3$) ppm 7.2-7.1 (m, 5 H), 7.02 (d, J=6.2 Hz, 1 H), 6.89 (d, J=6.2 Hz, 2 H), 6.82 (d, J=8.8 Hz, 1H), 6.68 (br, 2 H), 6.54 (dd, J=6.2 Hz, 13.6Hz, 1 H), 5.84 (t, J=52.7 Hz, 1 H), 4.62 (dd, J=2.2 Hz, 13.6 Hz, 1 H), 4.40 (dd, J=2.2Hz, 5.7 Hz, 1 H), 4.21 (s, 1 H), 3.95 (d, J=12.8 Hz, 1H), 3.55 (d, J=12.7 Hz, 1 H), 1.19 (s, 9 H).

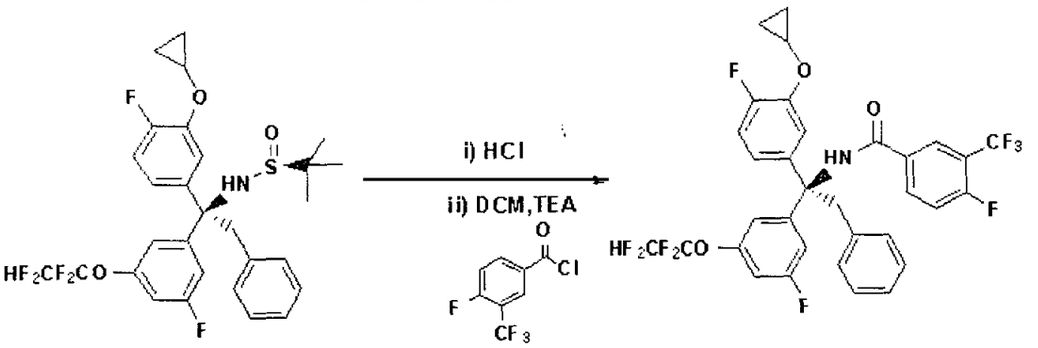
**Procedimiento 185**




A un matraz RB 25 ml de 3 cuellos secado al horno bajo nitrógeno se le agregó $CH_2Cl_2$ (3.5 ml) y solución dietilzinc 1 M en hexano (3.43 ml, 3.43 mmoles). El matraz se enfrió en un baño de hielo y una solución de ácido

trifluoroacético (0.391 g, 3.43 mmoles) en $CH_2Cl_2$ (1 ml) se agregó gota a gota por medio de jeringa. Después de agitar durante 15 min, una solución de diyodometano (0.918 g, 3.43 mmoles) en $CH_2Cl_2$ (1 ml) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 15 min, seguido por la adición de (S)-N-((R)-1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida (0.495 g, 0.87 mmoles) en $CH_2Cl_2$ (1 ml). La mezcla de reacción se permitió entibiar hasta temperatura ambiente y se agitó durante 4 h. La mezcla de reacción se diluyó con $CH_2Cl_2$ y se lavó sucesivamente con bicarbonato de sodio saturado, agua, NaCl saturado, se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se purificó por ISCO al usar un gradiente de 5-70% EtOAc/hexano como eluyente para producir (S)-N-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida como una espuma blanca (0.347 g, 71% de rendimiento). CLAR: TR = 3.668 min [M+H] 586.3 (Columna Phenomenex Luna C18 5µ, eluyendo con acetonitrilo acuoso 10-90% que contiene ácido trifluoroacético 0.1% durante un gradiente de 4 minutos, observando a 220 nm). $^1H$ RMN ($CDCl_3$) ppm 7.2-7.05 (m, 6 H), 6.91 (d, J=6.6 Hz, 2H), 6.83 (d, J=8.4 Hz, 1 H), 6.71 (m, 2 H), 5.84 (t, J=53.1 Hz, 1 H), 4.21 (s, 1 H), 3.99 (d, J=12.3 Hz, 1 H), 3.62 (m, 1 H), 3.56 (d, J=12.8 Hz, 1 H), 1.22 ( s, 9 H), 0.72-0.65 (m, 4 H).

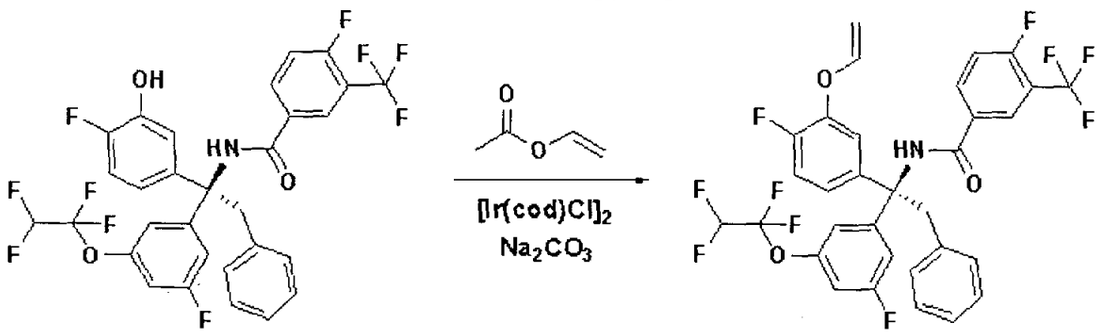
**Procedimiento 186**




(S)-N-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-2-metilpropano-2-sulfinamida se convirtió a (R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida por los métodos descritos en los Procedimientos 6 y 7.

Alternativamente, R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida se puede preparar a partir de (R)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida por los siguientes métodos:

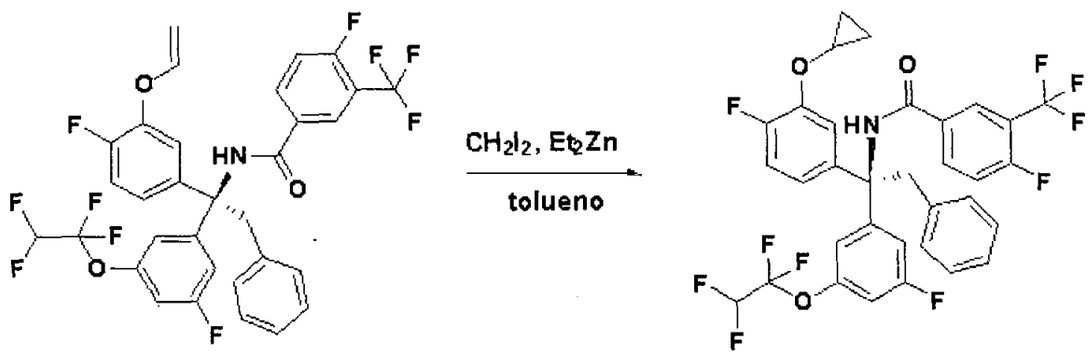
**Procedimiento 187**




A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-

hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (Ejemplo 264, 100 mg, 0.158 mmoles) en tolueno (0.2 ml) se le agregó $Na_2CO_3$ (25 mg, 0.235 mmoles) y cantidad catalítica de $[Ir(cod)Cl]_2$ (2 mg), seguido por acetato de vinilo (68 mg, 0.79 mmoles). La mezcla de reacción se agitó a 100°C durante 16 h. La mezcla resultante se filtró y el sólido se lavó con $CH_2Cl_2$. La capa $CH_2Cl_2$ se lavó con NaOH 1 N, $H_2O$ y la porción orgánica se secó sobre $Na_2SO_4$ y se filtró. El solvente se evaporó bajo presión reducida y el residuo se purificó por columna de gel de sílice al usar 0 hasta 60% EtOAc en hexano para resultar (R)-4-fluoro-N-(1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil)benzamida eluyendo a 20% EtOAc en hexano como un aceite incoloro (80 mg, 77%). CLEM: TR = 2.237 min [M+H] 658.3 (2 min Columna Phenomenex Luna C18, 4.6 X 30 mm eluyendo con 10-90% MeOH/$H_2O$ durante 2 minutos que contiene TFA 0.1%; 5 Ml/min, observando a 220 nm. RMN: 400MHz $^1H$ ($CD_3OD$) ppm 3.87 (d, *J*=12.74 Hz, 1 H), 4.05 - 4.15 (m, 1 H), 4.35 (dd, *J*=5.93, 1.98 Hz, 1 H), 4.55 (dd, *J*=13.84, 1.98 Hz, 1 H), 6.12-6.41 (m, 1 H), 6.48 (dd, *J*=13.62, 6.15 Hz, 1 H), 6.72 (d, *J*=7.03 Hz, 2 H), 6.87-7.24 (m, 9 H), 7.37-7.51 (m, 1 H), 7.88-8.04 (m, 2 H).

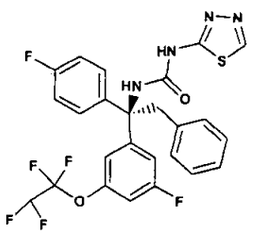
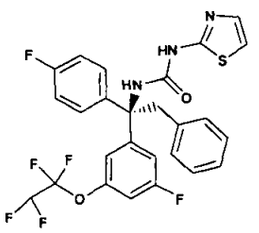
**Procedimiento 188**



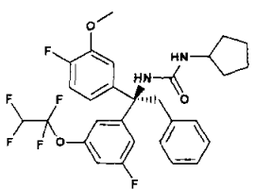
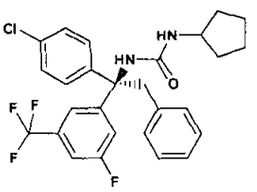
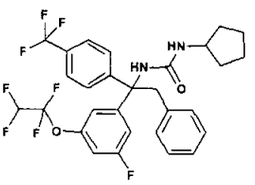
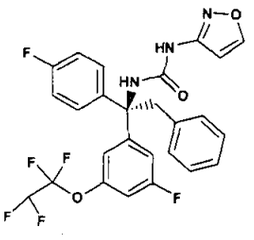

A una solución de (R)-4-fluoro-N-(1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(trifluorometil)benzamida (66 mg, 0.10 mmoles) en tolueno 0.5 ml se le agregó $Et_2Zn$ (1 N, 0.2 ml, 0.2 mmoles), seguido por $CH_2I_2$ (16 ml, 0.2 mmoles). La mezcla de reacción se agitó a 120°C durante 3 h. La mezcla de reacción se apagó por la adición de HCl 1 N y la capa acuosa se extrajo con $CH_2Cl_2$. La capa orgánica se lavó con $NaHCO_3$ saturado y se concentró bajo presión reducida. El residuo resultante se purificó por columna de gel de sílice ISCO al usar 0 hasta 50% a EtOAc en hexano como solventes de elución y CLAR preparativa (columna phenomenex AXIA Luna 75X30 mm, 5u eluyendo con 10-90% ACN/$H_2O$ durante 10 minutos que contiene TFA 0.1%; 40 ml/min, observando a 220 nm) para resultar (R)-N-(1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida (Ejemplo 305) como liofilato blanco

(36 mg, 52% de rendimiento). CLEM: TR = 4.268 min [M+H] 672.3 (4 min Columna Phenomenex Luna C18, 4.6 X 50 mm eluyendo con 10-90% MeOH/$H_2O$ durante 4 minutos que contiene TFA 0.1%; 4 ml/min, observando a 220 nm. RMN: 400 MHz $^1H$ ($CDCl_3$) ppm 0.45 - 0.73 (m, 4 H), 3.51 - 3.59 (m, 1 H), 3.76 (d, J=13.18 Hz, 1 H), 4.22 (d, J=12.74 Hz, 1 H), 6.13 - 6.44 (m, 1 H), 6.66 - 6.76 (m, 3 H), 6.97 - 7.08 (m, 3 H), 7.10 - 7.23 (m, 5 H), 7.42 - 7.50 (m, 1 H), 7.95 - 8.03 (m, 2 H).

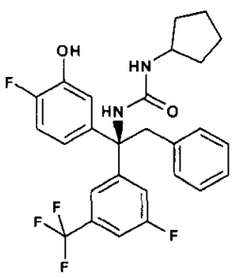
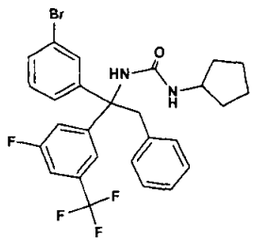
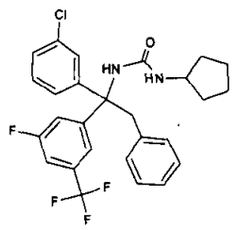
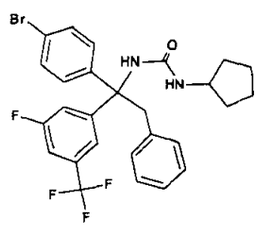
**TABLA 9**

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 349B |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1,3,4-thiadiazol-2-il)urea | 4.02 CL(1) 553.27 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 350 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(tiazol-2-il)urea | 4.12 CL(1) 552.28 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |

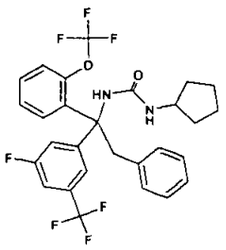
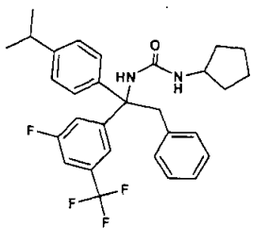
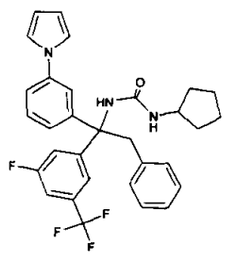
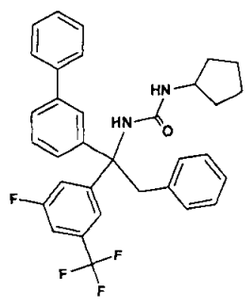
1595

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 351 |  | (R)-1-ciclopentil-3-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.524 CL(1) 567.01 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 352 |  | (R)-1-(1-(4-clorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 3.803 CL(1) 505.37 $[M+H]^+$ | Procedimientos 4, 5, 6 y 2 |
| 353 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometil) fenil)etil) urea | 3.845 CL(1) 587.11 $[M+H]^+$ | Procedimientos 3, 1, 2 y 23 |
| 354 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(isoxazol-3-il)urea | 4.11 CL(1) 536.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |

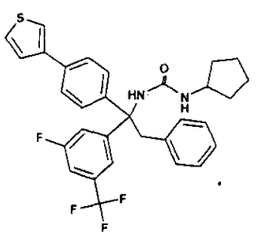
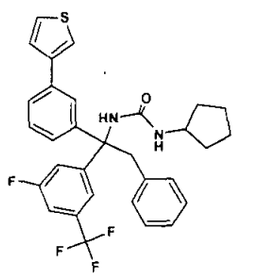
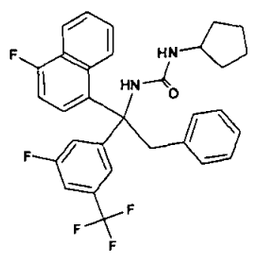
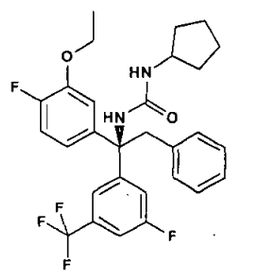
1596

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 355 |  | (R)-1-ciclopentil-3-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 3.176 CL(1) 505.22 $[M+H]^+$ | Procedimientos 4, 5, 6, 2 y 59 |
| 356 |  | 1-(1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.25 CL(4) 549.21 $[M+H]^+$ | Procedimientos 1 y 2 |
| 357 |  | 1-(1-(3-clorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.23 CL(4) 505.26 $[M+H]^+$ | Procedimientos 1 y 2 |
| 358 |  | 1-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.29 CL(4) 549.16 $[M+H]^+$ | Procedimientos 1 y 2 |

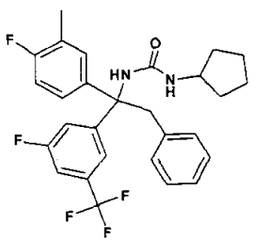
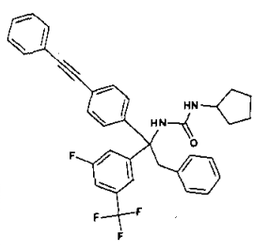
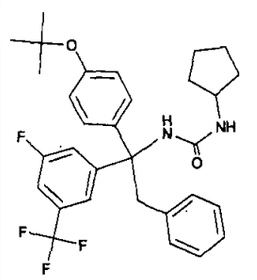
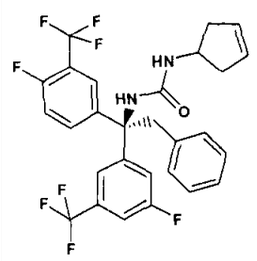
1592

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 359 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(2-(trifluorometoxi) fenil)etil)urea | 4.21 CL(4) 555.21 $[M+H]^+$ | Procedimientos 1 y 2 |
| 360 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-isopropilfenil)-2-feniletil)urea | 4.40 CL(4) 513.32 $[M+H]^+$ | Procedimientos 1 y 2 |
| 361 |  | 1-(1-(3-(1H-pirrol-1-il)fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.26 CL(4) 536.28 $[M+H]^+$ | Procedimientos 1 y 2 |
| 362 |  | 1-ciclopentil-3-(1-(bifenil-3-il)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.40 CL(4) 547.28 $[M+H]^+$ | Procedimientos 1 y 2 |

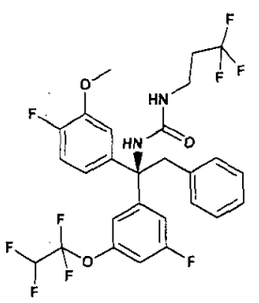
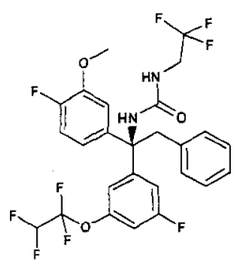
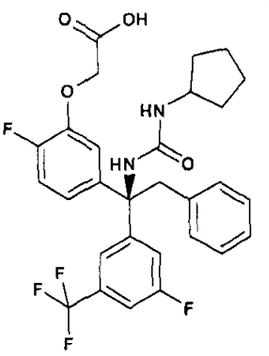
1598

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 363 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(4-(tiofen-3-il)fenil)etil) urea | 4.33 CL(4) 553.23 $[M+H]^+$ | Procedimientos 1 y 2 |
| 364 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(tiofen-3-il)fenil)etil)urea | 4.33 CL(4) 553.26 $[M+H]^+$ | Procedimientos 1 y 2 |
| 365 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluoronaftalen-1-il)-2-feniletil)urea | 4.29 CL(4) 539.27 $[M+H]^+$ | Procedimientos 1 y 2 |
| 366 |  | (R)-1-ciclopentil-3-(1-(3-etoxi-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 3.683 CL(1) 533.36 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59 y 68 |

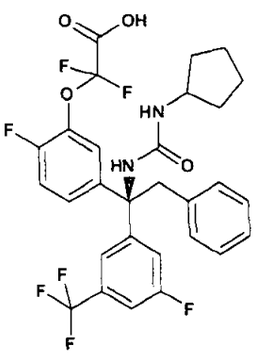
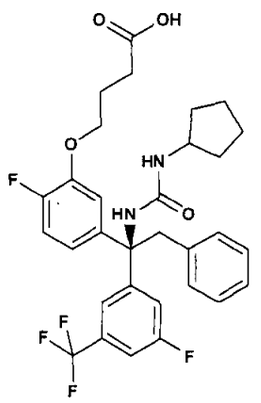
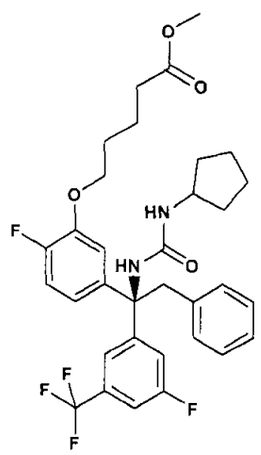
1599

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 367 |  | 1-ciclopentil-3-(1-(4-fluoro-3-metilfenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.23 CL(4) 503.31 $[M+H]^+$ | Procedimientos 1 y 2 |
| 368 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(4-(2-feniletinil) fenil)etil)urea | 4.49 CL(4) 571.28 $[M+H]^+$ | Procedimientos 1 y 2 |
| 369 |  | 1-(1-(4-ter-butoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.29 CL(4) 543.34 $[M+H]^+$ | Procedimientos 1 y 2 |
| 370 |  | (R)-1-(ciclopent-3-enil)-3-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.24 CL(1) 555.23 $[M+H]^+$ | Procedimientos 4, 5, 6 y 10 |

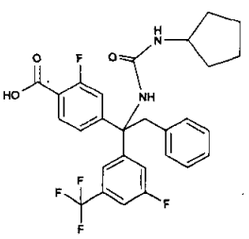
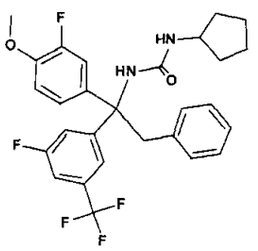
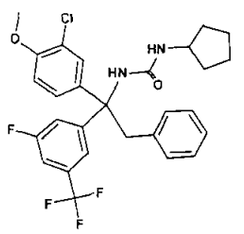
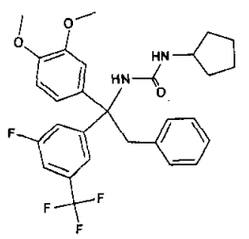
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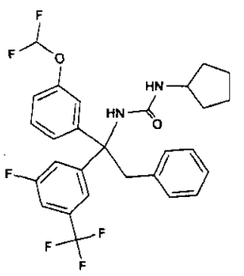
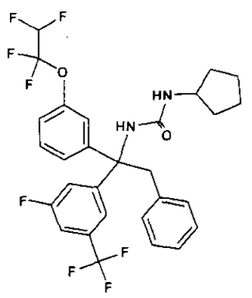
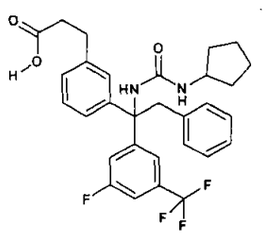
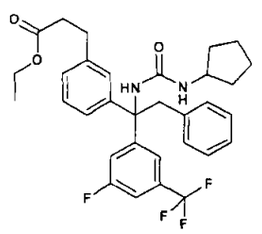
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 371 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(3,3,3-trifluoropropil) urea | 3.39 CL(1) 595.63 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 372 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.391 CL(1) 581.15 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 373 |  | ácido (R)-2-(5-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) acético | 3.210 CL(1) 563.29 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59, 68 y 23 |

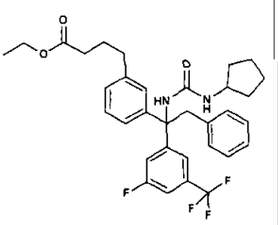
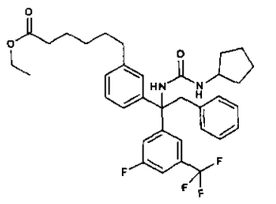
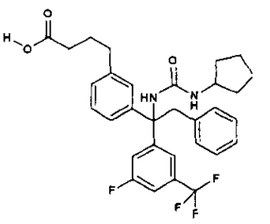
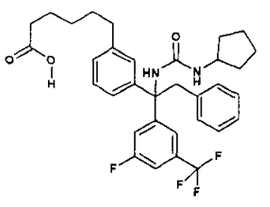
1601

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 374 |  | ácido (R)-2-(5-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi)-2,2-difluoroacético | 3.131 CL(1) 599.27 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59, 68 y 23 |
| 375 |  | ácido (R)-4-(5-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) butanoico | 3.068 CL(1) 591.31 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59, 68 y 23 |
| 376 |  | (R)-metil 5-(5-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) pentanoato | 3.715 CL(1) 619.33 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59 y 68 |

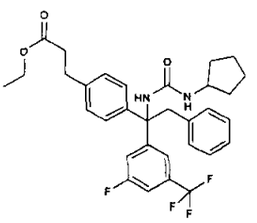
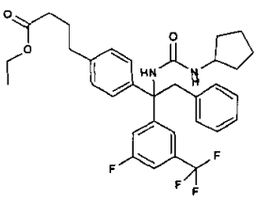
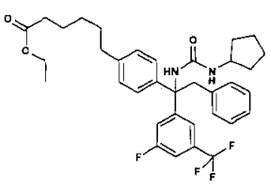
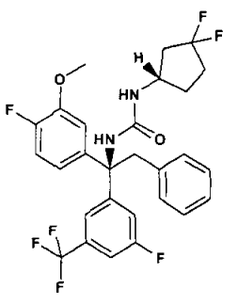
1602

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 377 |  | ácido 4-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-2-fluorobenzoico | 3.46 CL(5) 533.24 $[M+H]^+$ | Procedimientos 1 y 2 |
| 378 |  | 1-ciclopentil-3-(1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea | 4.08 CL(4) 519.22 $[M+H]^+$ | Procedimientos 1 y 2 |
| 379 |  | 1-(1-(3-cloro-4-metoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-ciclopentilurea | 4.15 CL(4) 535.20 $[M+H]^+$ | Procedimientos 1 y 2 |
| 380 |  | 1-ciclopentil-3-(1-(3,4-dimetoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea | 3.99 CL(4) 531.27 $[M+H]^+$ | Procedimientos 1 y 2 |

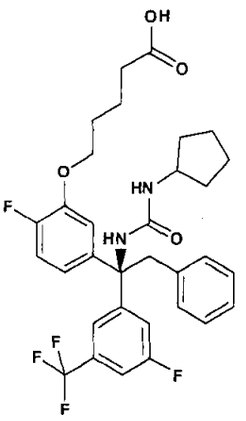
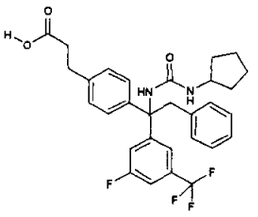
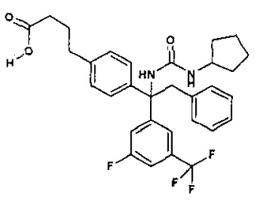
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 381 |  | 1-ciclopentil-3-(1-(3-(difluorometoxi) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.10 CL(4) 537.20 $[M+H]^+$ | Procedimientos 1 y 2 |
| 382 |  | 1-ciclopentil-3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(1,1,2,2-tetrafluoroetoxi) fenil)etil) urea | 4.15 CL(4) 587.17 $[M+H]^+$ | Procedimientos 1 y 2 |
| 383 |  | ácido 3-(3-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)fenil) propanoico | 4.251 CL(4) 554.2 $[M+H]^+$ | Procedimientos 1, 2, 24 y 23 |
| 384 |  | 3-(3-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) fenil)propanoato de etilo | 4.285 CL(4) 571.3 $[M+H]^+$ | Procedimientos 1, 2 y 24 |

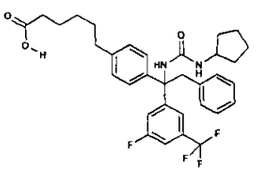
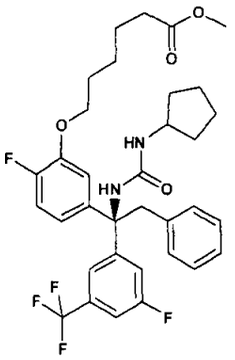
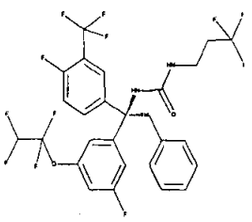
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 385 |  | 4-(3-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)butanoato de etilo | 4.376 CL(4) 585.3 $[M+H]^+$ | Procedimientos 1, 2 y 24 |
| 386 |  | 6-(3-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)hexanoato de etilo | 4.536 CL(4) 613.4 $[M+H]^+$ | Procedimientos 1, 2 y 24 |
| 387 |  | ácido 4-(3-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)butanoico | 4.135 CL(4) 557.3 $[M+H]^+$ | Procedimientos 1, 2, 24 y 23 |
| 388 |  | ácido 6-(3-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)hexanoico | 4.288 CL(4) 585.3 $[M+H]^+$ | Procedimientos 1, 2, 24 y 23 |

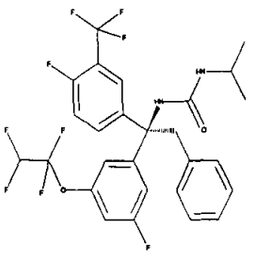
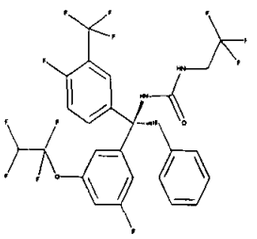
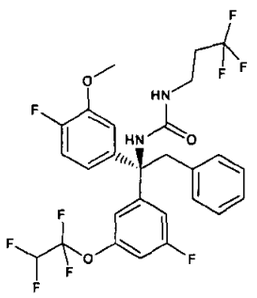
1605

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 389 |  | 3-(4-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)propanoato de etilo | 4.286 CL(4) 571.3 $[M+H]^+$ | Procedimientos 1, 2 y 24 |
| 390 |  | 4-(4-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)butanoato de etilo | 4.391 CL(4) 585.3 $[M+H]^+$ | Procedimientos 1, 2 y 24 |
| 391 |  | 6-(4-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)hexanoato de etilo | 4.54 CL(4) 613.3 $[M+H]^+$ | Procedimientos 1, 2 y 24 |
| 392 |  | 1-((S)-3,3-difluorociclopentil)-3-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)urea | 3.456 CL(1) 555.27 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |

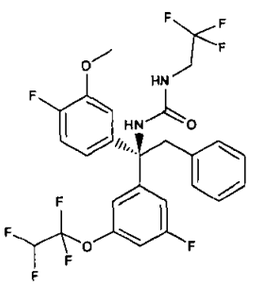
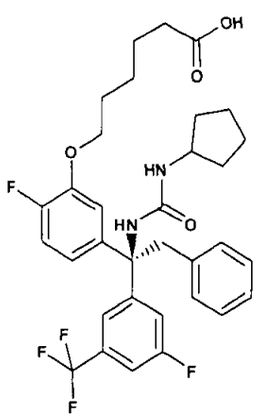
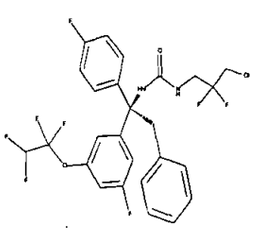
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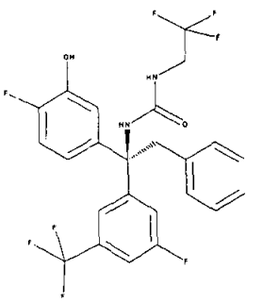
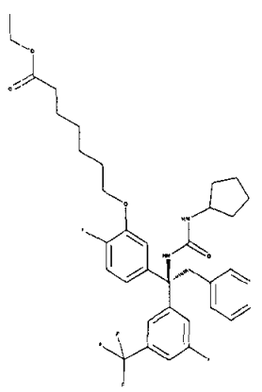
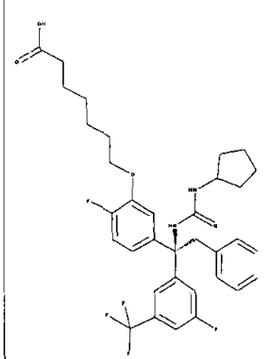
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 393 |  | ácido (R)-5-(5-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-2-fluorofenoxi)pentanoico | 3.265 CL(1) 605.15 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59, 68 y 23 |
| 394 |  | ácido 3-(4-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)propanoico | 4.045 CL(4) 543.3 $[M+H]^+$ | Procedimientos 1, 2, 24 y 23 |
| 395 |  | ácido 4-(4-(1-(3-ciclopentilureido)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)fenil)butanoico | 4.098 CL(4) 557.2 $[M+H]^+$ | Procedimientos 1, 2, 24 y 23 |

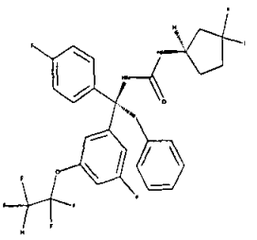
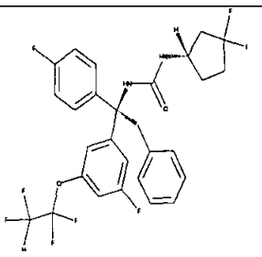
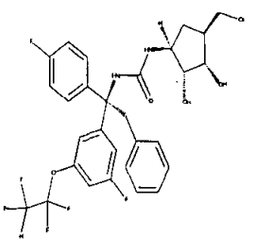
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 396 |  | ácido 6-(4-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)fenil) hexanoico | 4.275 CL(4) 585.2 $[M+H]^+$ | Procedimientos 1, 24 y 23 |
| 397 |  | 6-(5-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) hexanoato de (R)-metilo | 3.818 CL(1) 633.45 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59, 68 y 23 |
| 398 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(3,3,3-trifluoropropil) urea | 3.653 CL(1) 633.14 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 399 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-isopropilurea | 3.59 CL(1) 579.03 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 400 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.06 CL(1) 619.64 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 401 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(3,3,3-trifluoropropil) urea | 3.39 CL(1) 595.63 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |

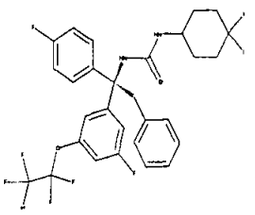
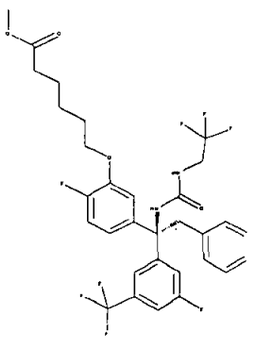
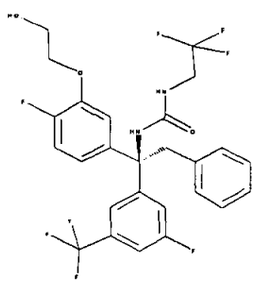
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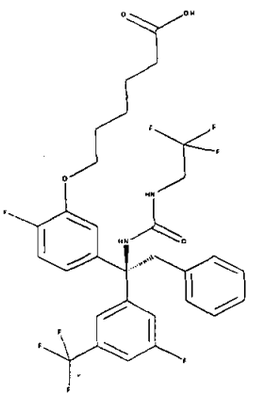
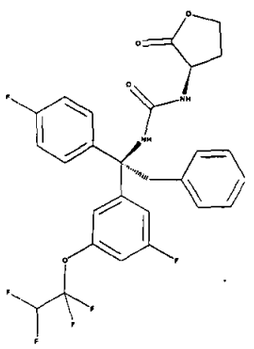
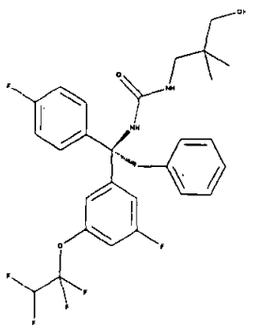
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 402 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.4 CL(1) 581.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 403 |  | ácido (R)-6-(5-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) hexanoico | 3.37 CL(1) 619.39 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59, 68 y 23 |
| 404 |  | (R)-1-(2,2-difluoro-3-hidroxipropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.82 CL(1) 563.16 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |

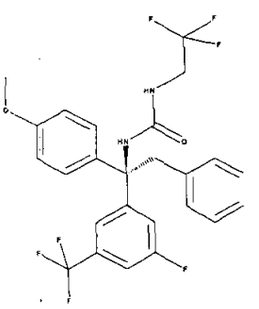
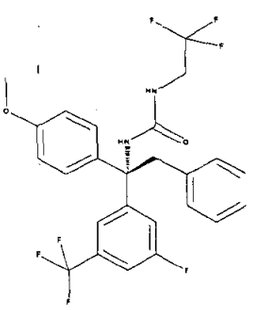
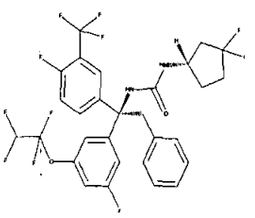
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 405 |  | (R)-1-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.07 CL(1) 519.14 $[M+H]^+$ | Procedimientos 4, 5, 6, 10 y 59 |
| 406 |  | (R)-etil 7-(5-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) heptanoato | 4.09 CL(1) 661.37 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59 y 68 |
| 407 |  | ácido (R)-7-(5-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2-fluorofenoxi) heptanoico | 3.48 CL(1) 633.21 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 59 68 y 23 |

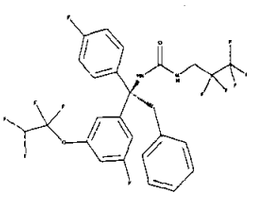
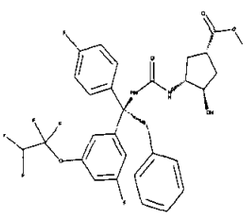
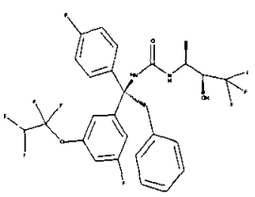
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 408 |  | 1-((R)-3,3-difluorociclopentil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 4.011 CL(3) 573.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 409 |  | 1-((S)-3,3-difluorociclopentil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.455 CL(3) 573.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 410 |  | 1-((1S,2R,3S,4S)-2,3-dihidroxi-4-(hidroximetil) ciclo pentil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.736 CL(3) 599.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

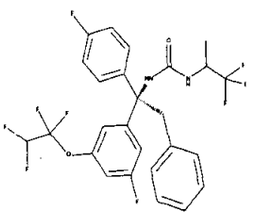
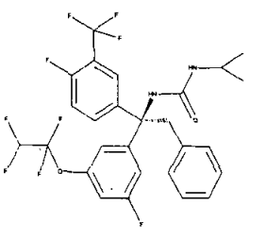
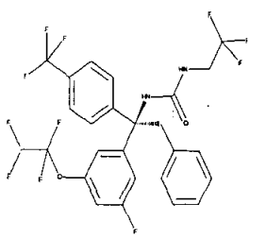
1612

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 411 |  | (R)-1-(4,4-difluorociclohexil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 4.046 CL(3) 585.3 $[M-H]^-$ | Procedimientos 3, 4, 5, 6, 130 y 12 |
| 412 |  | 6-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenoxi)hexanoato de (R)-metilo | 3.69 CL(1) 647.11 $[M+H]^+$ | Procedimientos 4, 5, 6, 10, 59 y 68 |
| 413 |  | (R)-1-(1-(4-fluoro-3-(2-hidroxietoxi) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.03 CL(1) 563.17 $[M+H]^+$ | Procedimientos 4, 5, 6, 10, 59 y 68 |

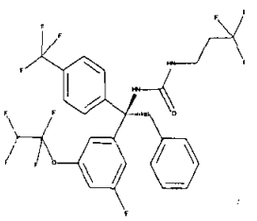
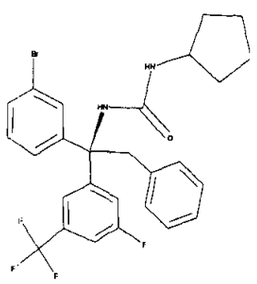
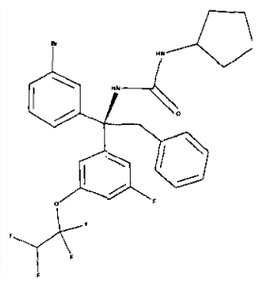
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 414 |  | ácido (R)-6-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenoxi)hexanoico | 3.28 CL(1) 633.17 $[M+H]^+$ | Procedimientos 4, 5, 6, 10, 59, 68 y 23 |
| 415 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-((R)-2-oxotetrahidrofuran -3-il)urea | 3.85 CL(1) 553.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 416 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(3-hidroxi-2,2-dimetilpropil) urea | 3.97 CL(1) 555.14 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

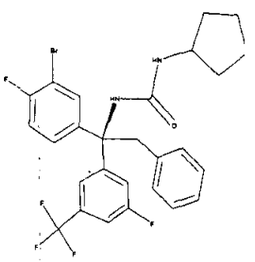
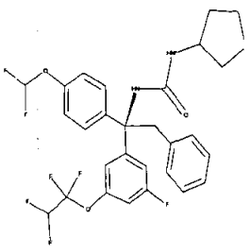
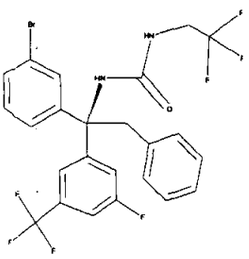
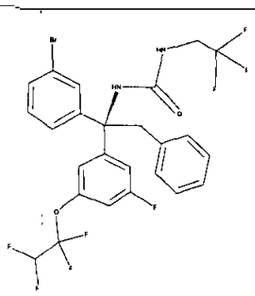
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 417 |  | (R)-1-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metoxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.438 CL(1) 515.10 $[M+H]^+$ | Procedimientos 4, 5, 6 y 10 |
| 418 |  | (S)-1-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-metoxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.436 CL(1) 515.11 $[M+H]^+$ | Procedimientos 4, 5, 6 y 10 |
| 419 |  | 1-((S)-3,3-difluorociclopentil)-3-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.66 CL(1) 641.68 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

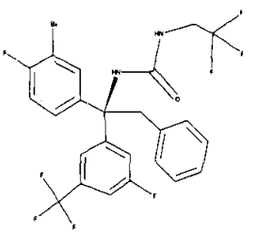
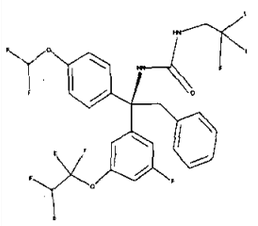
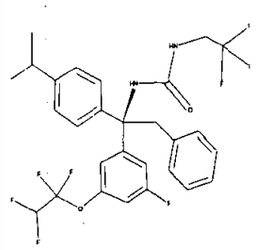
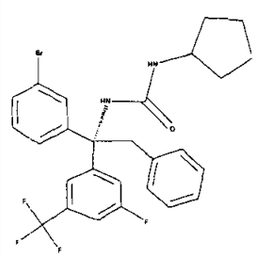
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 420 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(2,2,3,3,3-pentafluoropropil) urea | 4.06 CL(1) 601.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 421 |  | 3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-4-hidroxiciclopentano carboxilato de (1S,3R,4R)-metilo | 3.87 CL(3) 611.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 422 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-((2S,3S)-4,4,4-trifluoro-3-hidroxibutan-2-il)urea | 3.99 CL(1) 595.12 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |

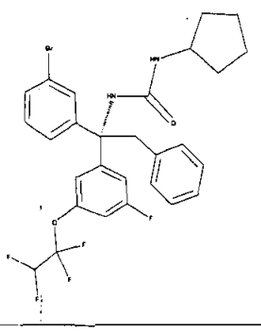
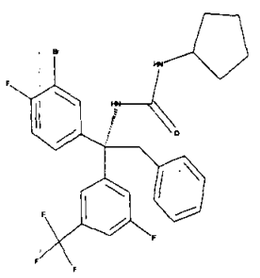
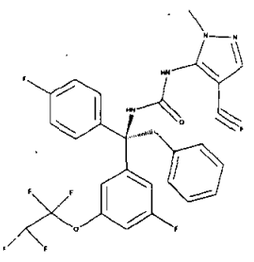
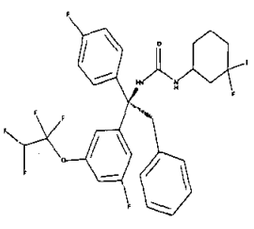
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 423 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1,1,1-trifluoropropan-2-il)urea | 4.05 CL(1) 565.65 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 424 |  | (R)-1-ciclopropil-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea | 3.46 CL(1) 577.03 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 425 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-fenil-1-(4-(trifluorometil)fenil)etil)-3-(2,2,2-trifluoroetil)urea | 3.62 CL(1) 600.98 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 2 y 9 |

1617

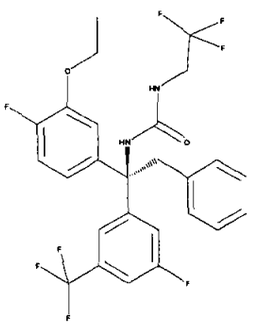
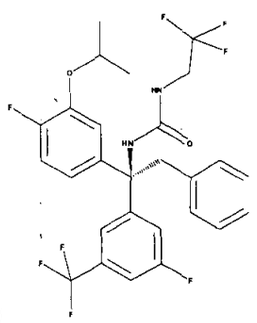
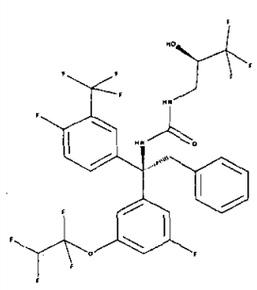
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 426 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometil) fenil)etil)-3-(3,3,3-trifluoropropil)urea | 3.64 CL(1) 615.65 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 2 y 9 |
| 427 |  | (S)-1-(1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.30 CL(4) 549.13 $[M+H]^+$ | Procedimientos 4, 5, 6 y 2 |
| 428 |  | (S)-1-(1-(3-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 4.23 CL(4) 597.15 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |

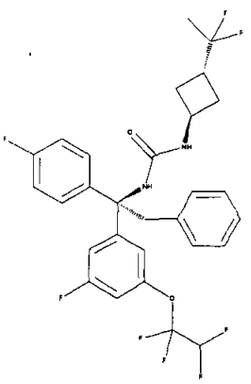
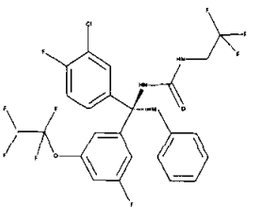
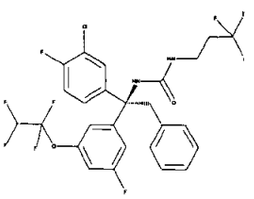
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 429 |  | (S)-1-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.30 CL(4) 567.14 $[M+H]^+$ | Procedimientos 62, 5, 6 y 2 |
| 430 |  | (R)-1-ciclopentil-3-(1-(4-(difluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 4.10 CL(4) 585.20 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 431 |  | (S)-1-(1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.21 CL(4) 563.07 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 432 |  | (S)-1-(1-(3-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.13 CL(4) 611.06 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 433 |  | (S)-1-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.19 CL(4) 581.04 $[M+H]^+$ | Procedimientos 62, 5, 6 y 12 |
| 434 |  | (R)-1-(1-(4-(difluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.01 CL(4) 599.15 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 435 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-isopropilfenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.27 CL(4) 575.23 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 436 |  | (R)-1-(1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.30 CL(4) 549.13 $[M+H]^+$ | Procedimientos 4, 5, 6 y 2 |

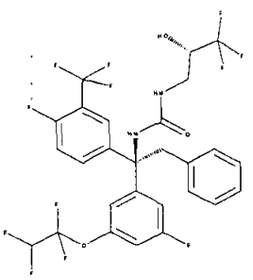
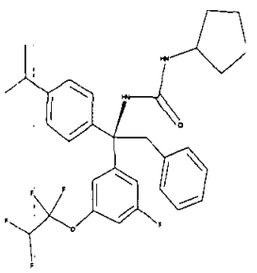
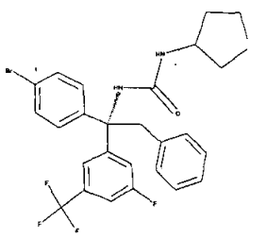
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 437 |  | (R)-1-(1-(3-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 4.22 CL(4) 597.12 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 438 |  | (R)-1-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.30 CL(4) 567.11 $[M+H]^+$ | Procedimientos 62, 5, 6 y 2 |
| 439 |  | (R)-1-(4-ciano-1-metil-1H-pirazol-5-il)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.91 CL(3) 574.67 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 440 |  | 1-(3,3-difluorociclohexil )-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 4.048 CL(3) 587.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 130 y 12 |

1621

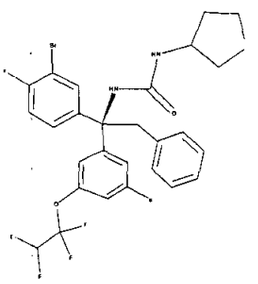
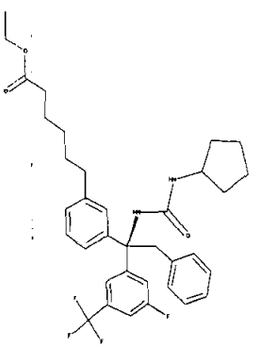
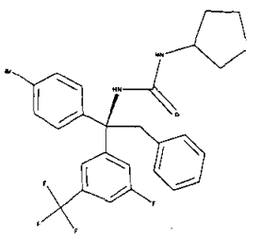
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 441 |  | (R)-1-(1-(3-etoxi-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.57 CL(1) 547.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 9, 59 y 68 |
| 442 |  | (R)-1-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.68 CL(1) 561.1 $[M+H]^+$ | Procedimientos 4, 5, 6, 2, 9, 59 y 68 |
| 443 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-((R)-3,3,3-trifluoro-2-hidroxipropil)urea | 3.81 CL(1) 649.66 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 28 y 10 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 444 |  | 1-((1r,3R)-3-(1,1-difluoroetil)ciclobutil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)urea | 4.10 CL(3) 587.13 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 445 |  | (S)-1-(1-(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.558 CL(1) 585.01 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 2 y 9 |
| 446 |  | (S)-1-(1-(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(3,3,3-trifluoropropil)urea | 3.593 CL(1) 599.04 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 2 y 9 |

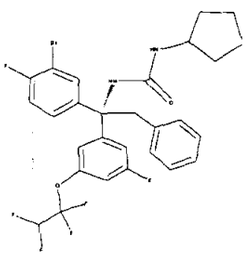
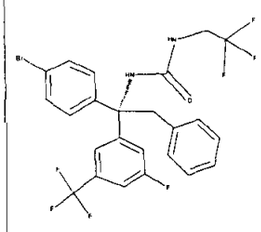
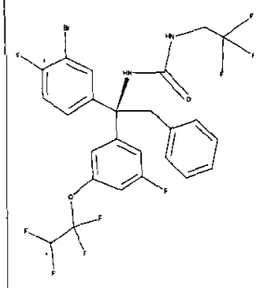
1623

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 447 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-((S)-3,3,3-trifluoro-2-hidroxipropil)urea | 3.445 CL(1) 649.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 28 y 10 |
| 448 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-isopropilfenil)-2-feniletil)urea | 4.35 CL(4) 561.36 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 449 |  | (S)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.32 CL(4) 549.25 $[M+H]^+$ | Procedimientos 4, 5, 6 y 2 |

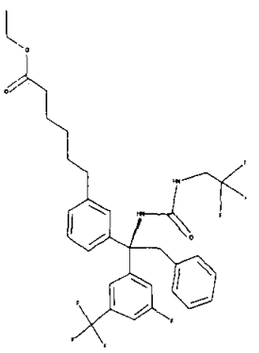
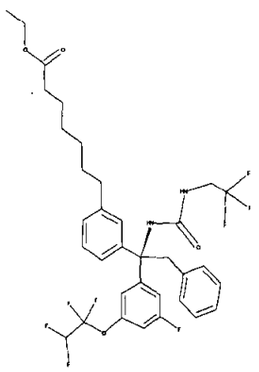
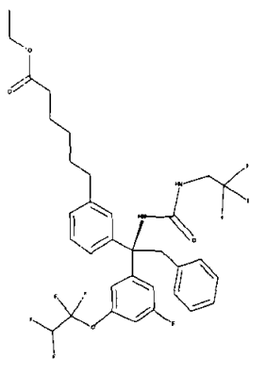
1624

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 450 |  | (S)-1-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 4.23 CL(4) 615.24 $[M+H]^+$ | Procedimientos 62, 3, 5, 6 y 2 |
| 451 |  | 6-(3-(1-(3-ciclopentilureido) -1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)fenil) hexanoato de (R)-etilo | 4.48 CL(4) 613.43 $[M+H]^+$ | Procedimientos 4, 5, 6, 24 y 2 |
| 452 |  | (R)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-ciclopentilurea | 4.33 CL(4) 549.21 $[M+H]^+$ | Procedimientos 4, 5, 6 y 2 |

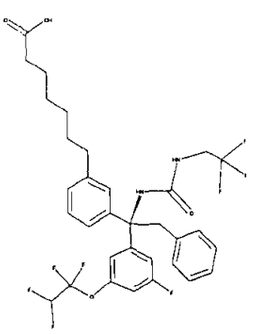
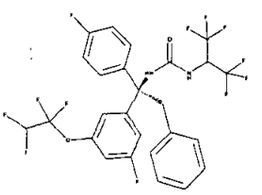
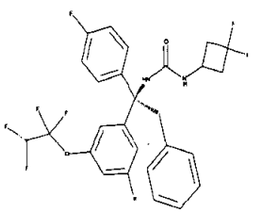
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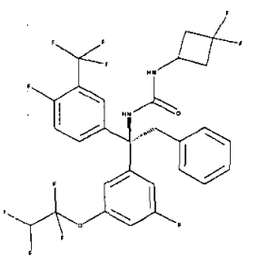
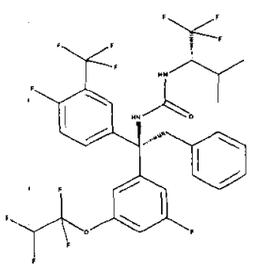
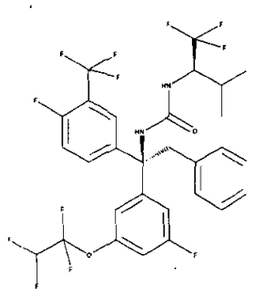
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 453 |  | (R)-1-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 4.23 CL(4) 615.26 $[M+H]^+$ | Procedimientos 62, 3, 5, 6 y 2 |
| 454 |  | (S)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.22 CL(4) 563.16 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 455 |  | (S)-1-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.14 CL(4) 629.11 $[M+H]^+$ | Procedimientos 62, 3, 5, 6 y 12 |

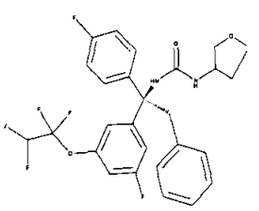
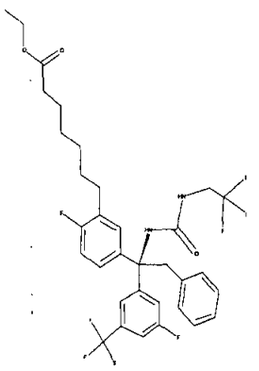
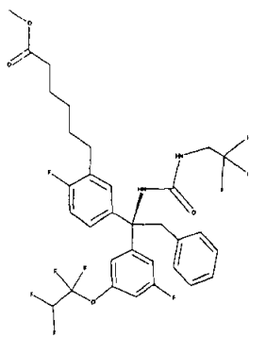
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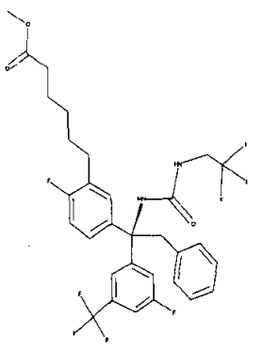
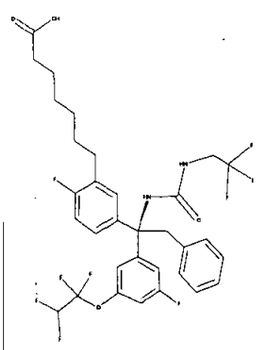
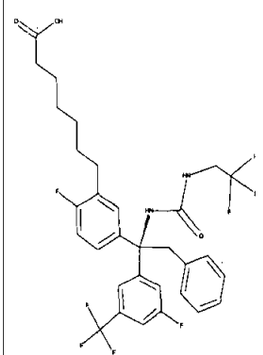
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 456 |  | (R)-etil 6-(3-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil)fenil) hexanoato | 4.36 CL(4) 627.31 $[M+H]^+$ | Procedimientos 4, 5, 6, 12 y 22 |
| 457 |  | 7-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)heptanoato de (R)-etilo | 4.36 CL(4) 689.31 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 12 y 22 |
| 458 |  | 6-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)hexanoato de (R)-etilo | 4.29 CL(4) 675.31 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 12 y 22 |

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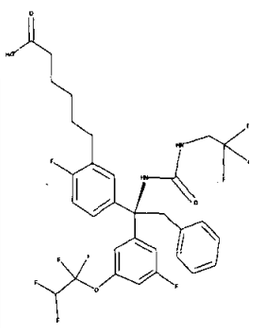
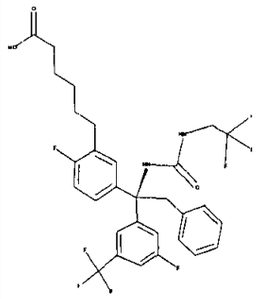
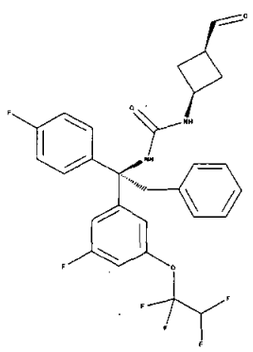
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 459 |  | ácido (R)-7-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil)fenil) heptanoico | 4.17 CL(4) 661.31 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 12, 22 y 23 |
| 460 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1,1,1,3,3,3-hexafluoropropan-2-il)urea | 4.23 CL(1) 619.04 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 461 |  | (R)-1-(3,3-difluorociclobutil )-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.383 CL(3) 559.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 116, 117, 118, 119, 120 y 25 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 462 |  | (R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea | 3.611 CL(3) 627.15 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 116, 117, 118, 119, 120 y 10 |
| 463 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-((S)-1,1,1-trifluoro-3-metilbutan-2-il)urea | 3.891 CL(1) 661.11 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |
| 464 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-((R)-1,1,1-trifluoro-3-metilbutan-2-il)urea | 3.885 CL(1) 661.12 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 10 |

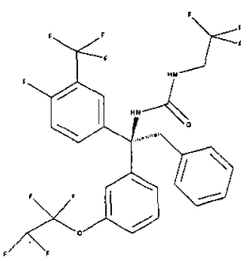
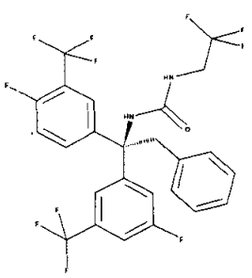
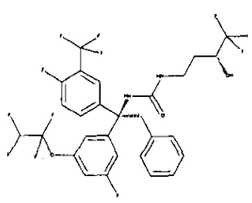
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 465 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(tetrahidrofuran-3-il)urea | 3.97 CL(1) 539.09 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 466 |  | 7-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)heptanoato de (R)-etilo | 4.45 CL(4) 659.46 $[M+H]^+$ | Procedimientos 62, 3, 5, 6, 12 y 22 |
| 467 |  | 6-(2-fluoro-5-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)hexanoato de (R)-metilo | 4.24 CL(4) 679.45 $[M+H]^+$ | Procedimientos 62, 3, 5, 6, 12 y 22 |

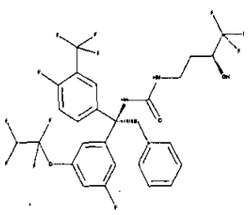
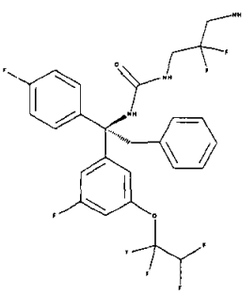
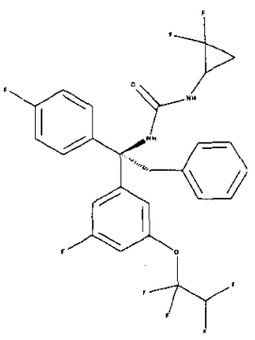
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 468 |  | 6-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)hexanoato de (R)-metilo | 4.30 CL(4) 631.41 $[M+H]^+$ | Procedimientos 62, 5, 6, 12 y 22 |
| 469 |  | Acido (R)-7-(2-fluoro-5-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)heptanoico | 4.18 CL(4) 679.43 $[M+H]^+$ | Procedimientos 62, 3, 5, 6, 12, 22 y 23 |
| 470 |  | Acido (R)-7-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil)fenil) heptanoico | 4.23 CL(4) 631.42 $[M+H]^+$ | Procedimientos 62, 3, 5, 6, 12, 22 y 23 |

1631

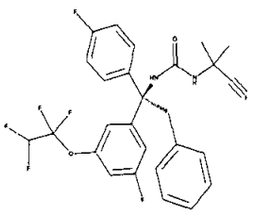
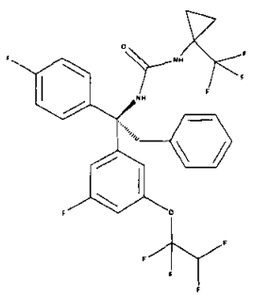
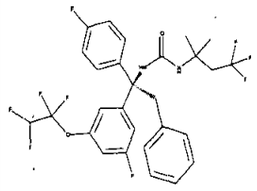
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 471 |  | ácido (R)-6-(2-fluoro-5-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) fenil)hexanoico | 4.11 CL(4) 665.40 $[M+H]^+$ | Procedimientos 62, 3, 5, 6, 12, 22 y 23 |
| 472 |  | ácido (R)-6-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil)fenil) hexanoico | 4.17 CL(4) 617.37 $[M+H]^+$ | Procedimientos 62, 3, 5, 6, 12, 22 y 23 |
| 473 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-((1s,3S)-3-formilciclobutil) urea | 2.01 CL(3) 550.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 39, 40 y 41 |

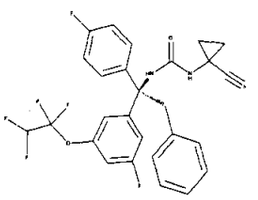
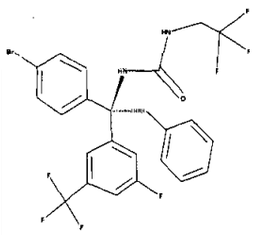
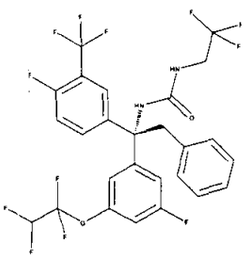
1632

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 474 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-2-fenil-1-(3-(1,1,2,2-tetrafluoroetoxi) fenil)etil)-3-(2,2,2-trifluoroetil)urea | 4.13 CL(1) 601.9 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 2 y 9 |
| 475 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 4.21 CL(1) 571.08 $[M+H]^+$ | Procedimientos 4, 5, 6, 2 y 9 |
| 476 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-((R)-4,4,4-trifluoro-3-hidroxibutil)urea | 3.486 CL(1) 663.15 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 28 y 10 |

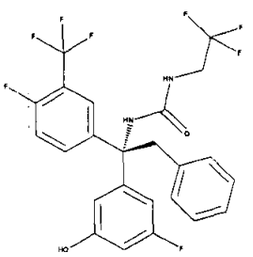
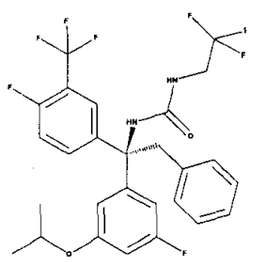
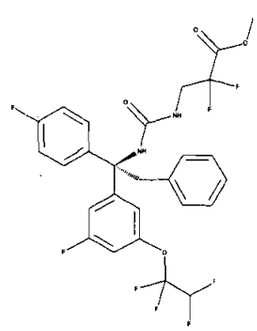
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 477 |  | 1-((R)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-((S)-4,4,4-trifluoro-3-hidroxibutil)urea | 3.486 CL(1) 663.16 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 28 y 25 |
| 478 |  | (R)-1-(3-amino-2,2-difluoropropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 1.86 CL(2) 562.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25 y 39 |
| 479 |  | 1-(2,2-difluorociclopropil)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 2.05 CL(2) 545.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |

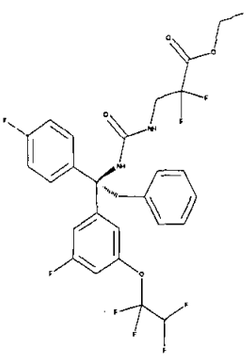
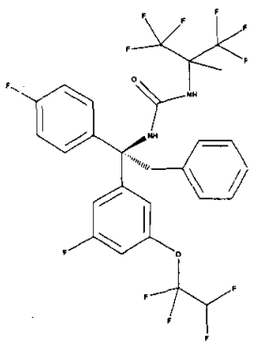
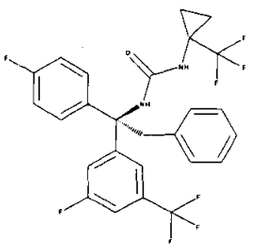
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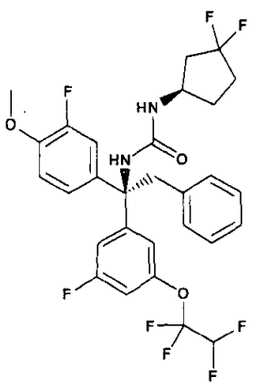
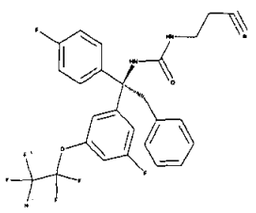
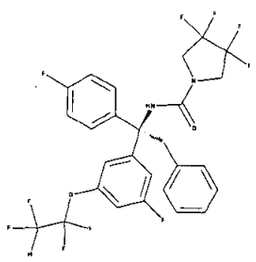
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 480 |  | (R)-1-(2-cianopropan-2-il)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.93 CL(1) 536.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 481 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil)urea | 2.08 CL(2) 577.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 30 |
| 482 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(4,4,4-trifluoro-2-metilbutan-2-il)urea | 2.16 CL(2) 593.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 30 |

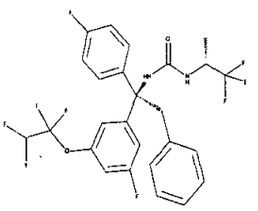
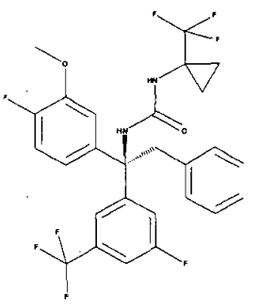
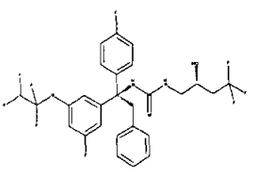
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 483 |  | (R)-1-(1-cianociclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 1.97 CL(2) 534.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 30 |
| 484 |  | (R)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.68 CL(4) 561.1 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 485 |  | (S)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 2.16 CL(2) 619.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 2 y 9 |

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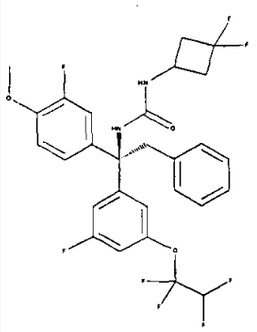
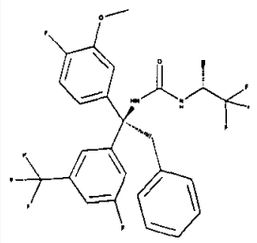
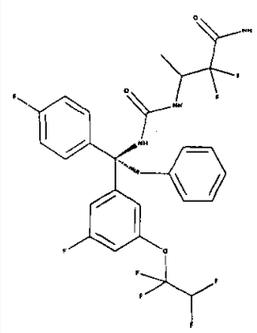
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 486 |  | (S)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-hidroxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 2.0 CL(2) 519.1 $[M+H]^+$ | Procedimientos 49 y 10 |
| 487 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-isopropoxifenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 2.20 CL(2) 561.2 $[M+H]^+$ | Procedimientos 49, 10 y 68 |
| 488 |  | 2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) ureido)propanoato de (R)-metilo | 4.01 CL(1) 591.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 46, 25 y 127 |

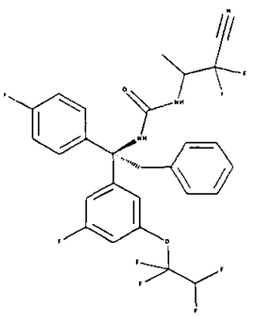
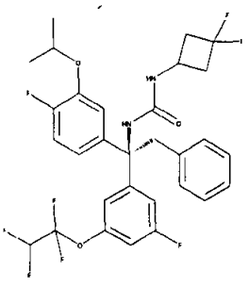
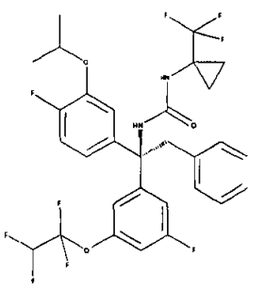
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 489 |  | 2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) ureido)propanoato de (R)-etilo | 4.06 CL(1) 605.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 46, 25 y 127 |
| 490 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1,1,1,3,3,3-hexafluoro-2-metilpropan-2-il)urea | 2.19 CL(2) 633.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 30 |
| 491 |  | (R)-1-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil) urea | 2.12 CL(2) 529.31 $[M+H]^+$ | Procedimientos 4, 5, 6 y 30 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 492 |  | 1-((R)-3,3-difluorociclopentil)-3-((R)-1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 10.11 CL(7) 603 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 493 |  | (R)-1-(2-cianoetil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.075 CL(3) 522.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 494 |  | (R)-3,3,4,4-tetrafluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) pirrolidin-1-carboxamida | 3.603 CL(3) 595.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

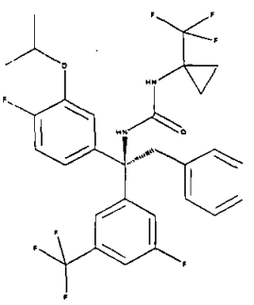
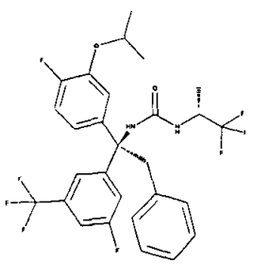
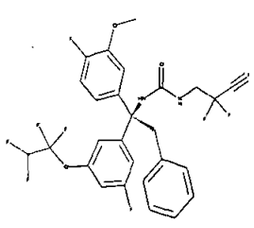
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 495 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-((R)-1,1,1-trifluoropropan-2-il)urea | 2.12 CL(2) 565.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 496 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil) urea | 3.50 CL(1) 559.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 30 |
| 497 |  | 1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-((R)-4,4,4-trifluoro-2-hidroxibutil)urea | 4.271 CL(1) 595.27 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 28 y 25 |

1640

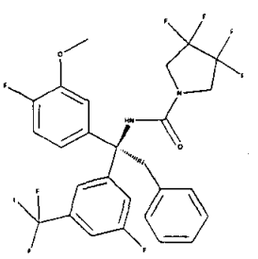
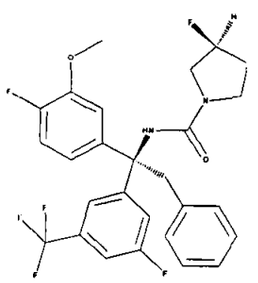
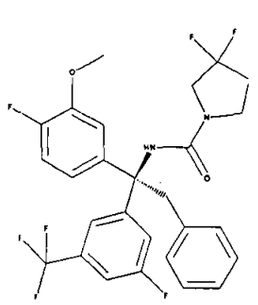
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 498 |  | (R)-1-(3,3-difluorociclobutil)-3-(1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea | 9.97 CL(7) 589 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 116, 117, 118, 119, 120 y 10 |
| 499 |  | 1-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil)fenil)-2-feniletil)-3-((R)-1,1,1-trifluoropropan-2-il)urea | 2.10 CL(2) 547.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 25 |
| 500 |  | 2,2-difluoro-3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-1-(4-fluorofenil)-2-feniletil)ureido)butanamida | 2.00 CL(2) 590.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 46 y 47 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 501 |  | 1-(1-ciano-1,1-difluoropropan-2-il)-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 2.10 CL(2) 572.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 46, 47 y 48 |
| 502 |  | (R)-1-(3,3-difluorociclobutil )-3-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.72 CL(1) 617.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 116, 117, 118, 119, 120, 59, 68 y 10 |
| 503 |  | (R)-1-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil) urea | 3.60 CL(1) 635.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68 y 30 |

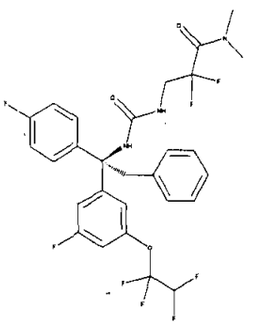
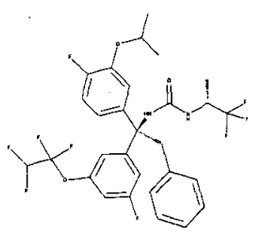
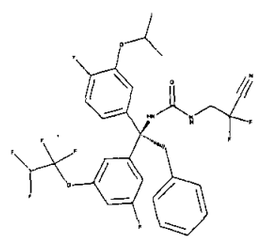
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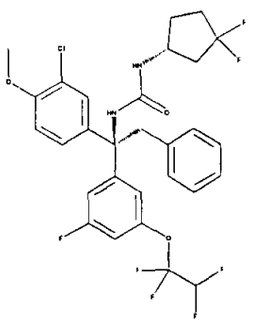
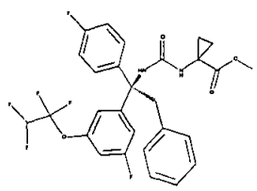
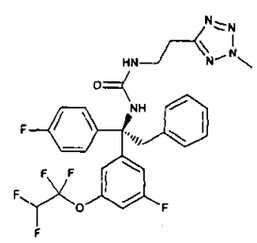
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 504 |  | (R)-1-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil) urea | 3.745 CL(1) 587.4 $[M+H]^+$ | Procedimientos 4, 5, 6, 59, 68 y 30 |
| 505 |  | 1-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-((R)-1,1,1-trifluoropropan-2-il)urea | 2.20 CL(2) 575.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68 y 25 |
| 506 |  | (R)-1-(2-ciano-2,2-difluoroetil)-3-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.96 CL(1) 588.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 46, 47 y 48 |

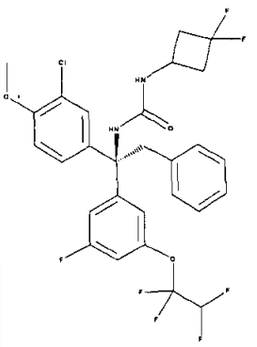
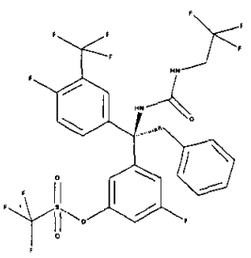
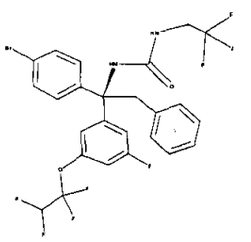
1643

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 507 |  | (R)-3,3,4,4-tetrafluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-1-carboxamida | 3.596 CL(3) 577.2 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 508 |  | (S)-3-fluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidina-1-carboxamida | 3.233 CL(3) 523.2 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 509 |  | (R)-3,3-difluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidina-1-carboxamida | 3.403 CL(3) 541.2 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |

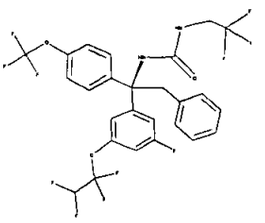
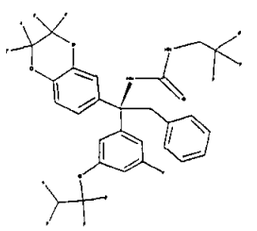
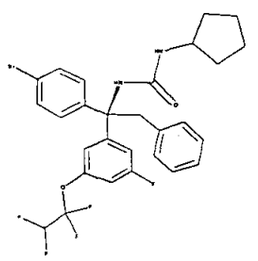
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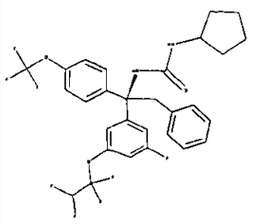
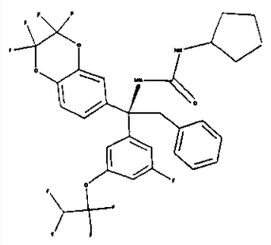
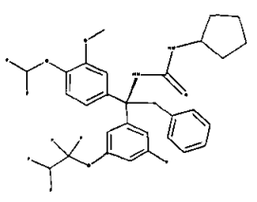
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 510 |  | (R)-2,2-difluoro-3-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)ureido)-N,N-dimetilpropanamida | 3.21 CL(1) 604.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25 y 127 |
| 511 |  | 1-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-((R)-1,1,1-trifluoropropan-2-il)urea | 3.66 CL(1) 623.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68 y 25 |
| 512 |  | (R)-1-(2-ciano-2,2-difluoroetil)-3-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 2.26 CL(2) 616.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68, 46, 25, 47 y 48 |

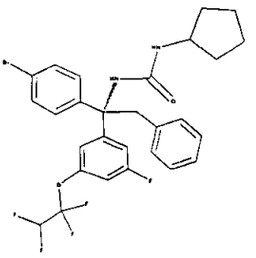
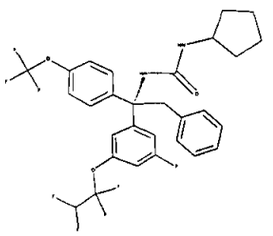
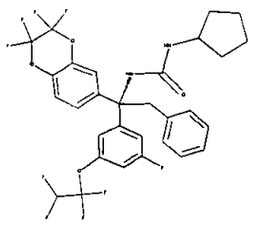
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 513 |  | 1-((S)-1-(3-cloro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-((R)-3,3-difluorociclopentil) urea | 10.28 CL(7) 619 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 514 |  | 1-(3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)ureido) ciclopropano carboxilato de (R)-metilo | 3.89 CL(1) 567.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 515 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(2-(2-metil-2H-tetrazol-5-il)etil)urea | 3.005 CL(3) 579.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 12 y 55 |

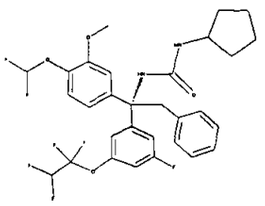
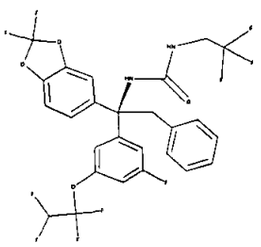
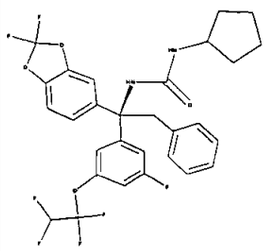
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 516 |  | (S)-1-(1-(3-cloro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(3,3-difluorociclobutil) urea | 10.16 CL(7) 606 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 116, 117, 118, 119, 120 y 25 |
| 517 |  | (R)-3-fluoro-5-(1-(4-fluoro-3-(trifluorometil) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil)fenil trifluorometan sulfonato | 2.34 CL(2) 651.4 $[M+H]^+$ | Procedimientos 49 y 66 |
| 518 |  | (R)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.76 CL(4) 611.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

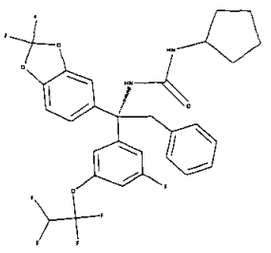
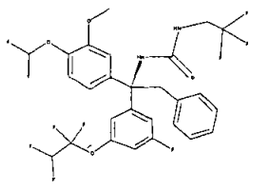
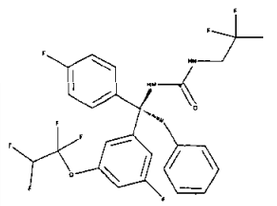
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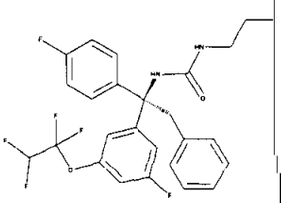
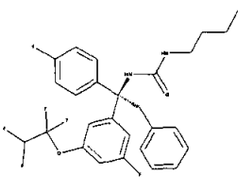
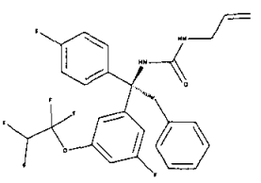
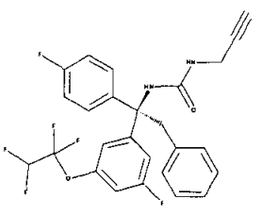
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 519 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometoxi) fenil)etil)-3-(2,2,2-trifluoroetil)urea | 3.79 CL(4) 617.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 520 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(2,2,3,3-tetrafluoro-2,3-dihidrobenzo[b][1,4]dioxin-6-il)etil)-3-(2,2,2-trifluoroetil) urea | 3.88 CL(4) 663.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 521 |  | (R)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 3.87 CL(4) 597.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |

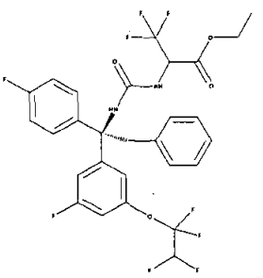
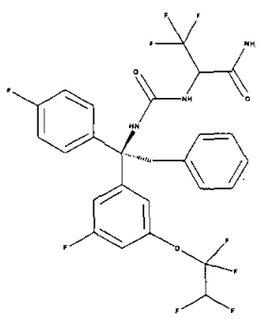
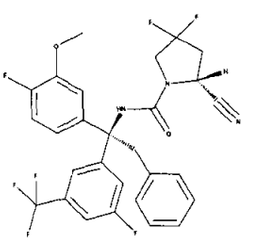
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 522 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometoxi) fenil)etil)urea | 3.90 CL(4) 603.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 523 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(2,2,3,3-tetrafluoro-2,3-dihidrobenzo[b] [1,4]dioxin-6-il)etil)urea | 4.02 CL(4) 649.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 524 |  | (R)-1-ciclopentil-3-(1-(4-(difluorometoxi)-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.68 CL(4) 615.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |

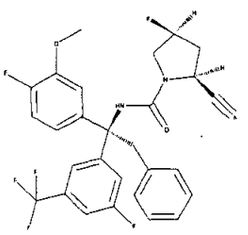
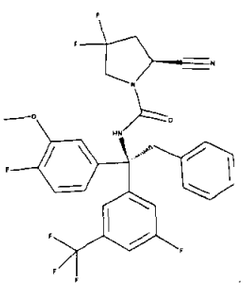
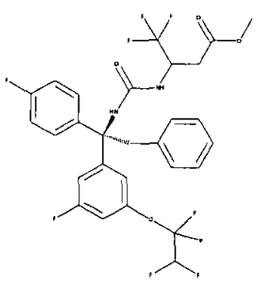
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 525 |  | (S)-1-(1-(4-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-ciclopentilurea | 3.87 CL(4) 597.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 526 |  | (S)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometoxi) fenil)etil) urea | 3.90 CL(4) 603.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 527 |  | (S)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(2,2,3,3-tetrafluoro-2,3-dihidrobenzo[b] [1,4]dioxin-6-il)etil)urea | 4.02 CL(4) 649.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |

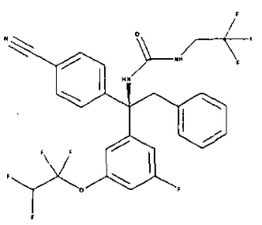
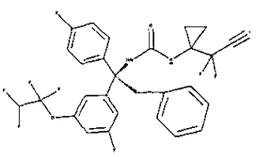
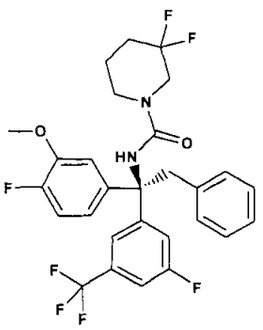
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 528 |  | (S)-1-ciclopentil-3-(1-(4-(difluorometoxi)-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.68 CL(4) 615.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 529 |  | (R)-1-(1-(2,2-difluorobenzo[d] [1,3]dioxol-5-il)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.74 CL(4) 613.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 530 |  | (R)-1-ciclopentil-3-(1-(2,2-difluorobenzo[d][1 ,3]dioxol-5-il)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.85 CL(4) 599.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |

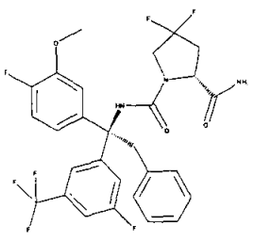
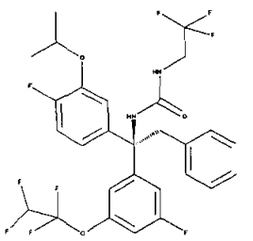
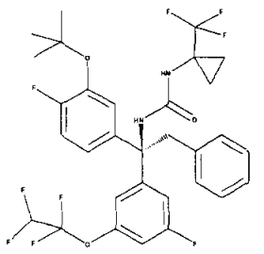
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 531 |  | (S)-1-ciclopentil-3-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-il)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.85 CL(4) 599.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 532 |  | (R)-1-(1-(4-(difluorometoxi)-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.59 CL(4) 629.09 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 2 |
| 533 |  | (R)-1-(2,2-difluoropropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.955 CL(3) 547.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

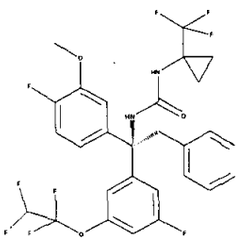
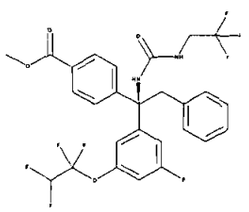
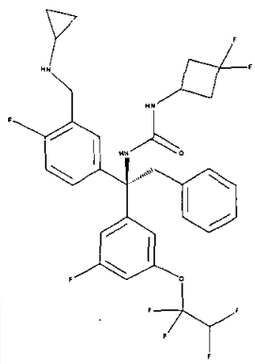
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 534 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-propilurea | 3.985 CL(3) 511.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 535 |  | (R)-1-butil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 4.063 CL(3) 525.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 536 |  | (R)-1-alil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.948 CL(3) 509.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |
| 537 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(prop-2-inil)urea | 3. 866 CL(3) 507.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 12 |

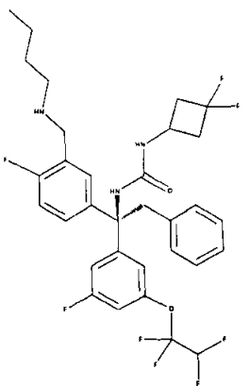
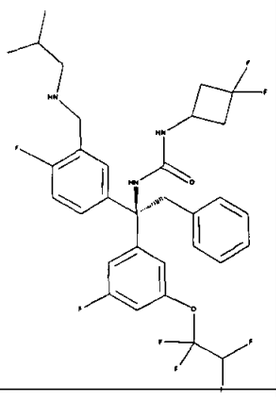
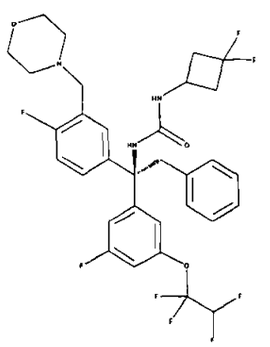
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 538 |  | 3,3,3-trifluoro-2-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) ureido)propanoato de etilo | 2.15 CL(2) 623.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 539 |  | 3,3,3-trifluoro-2-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) ureido)propanamida | 3.04 CL(8) 594.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 23 y 47 |
| 540 |  | (R)-2-ciano-4,4-difluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-1-carboxamida | 3.895 CL(3) 566.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 12 y 48 |

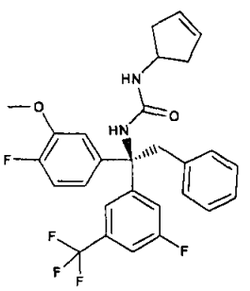
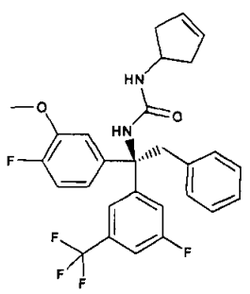
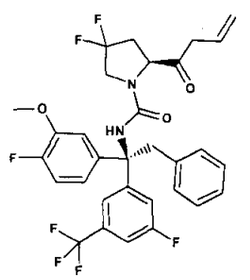
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 541 |  | (2S,4S)-2-ciano-4-fluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-1-carboxamida | 3.82 CL(3) 548.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 12 y 48 |
| 542 |  | (S)-2-ciano-4,4-difluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-1-carboxamida | 3.925 CL(3) 566.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 12 y 48 |
| 543 |  | 4,4,4-trifluoro-3-(3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) ureido)butanoato de metilo | 4.0 CL(1) 623.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 544 |  | (R)-1-(1-(4-cianofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 1.12 CL(9) 558 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 56 y 25 |
| 545 |  | (R)-1-(1-(cianodifluorometil) ciclopropil)-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)urea | 3.44 CL(8) 584.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 34, 35, 47 y 48 |
| 546 |  | (R)-3,3-difluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) piperidin-1-carboxamida | 4.023 CL(3) 555.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 547 |  | (R)-4,4-difluoro-N1-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-1,2-dicarboxamida | 3.901 CL(3) 584.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 548 |  | (R)-1-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 3.633 CL(1) 609.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 10, 59 y 68 |
| 549 |  | (R)-1-(1-(3-ter-butoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil) urea | 3.798 CL(1) 649.6 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 30, 59 y 108 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 550 |  | (R)-1-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(1-(trifluorometil) ciclopropil)urea | 3.46 CL(1) 607.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 30 |
| 551 |  | 4-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(3-(2,2,2-trifluoroetil) ureido)etil) benzoato de (R)-metilo | 1.19 CL(12) 591 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 56 y 57 |
| 552 |  | (R)-1-(1-(3-((ciclopropilamino) metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(3,3-difluorociclobutil) urea | 3.331 CL(15) 628 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 116-120, 12, 147 y 148 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 553 |  | (R)-1-(1-(3-((butilamino)metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-3-(3,3-difluorociclobutil)urea | 3.488 CL(15) 644 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 116-120, 12, 147 y 148 |
| 554 |  | (R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-((isobutilamino)metil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea | 3.458 CL(15) 644 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 116-120, 12, 147 y 148 |
| 555 |  | (R)-1-(3,3-difluorociclobutil)-3-(1-(4-fluoro-3-(morfolinometil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)urea | 3.636 CL(15) 658 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 116-120, 12, 147 y 148 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 556 |  | (R)-1-(ciclopent-3-enil)-3-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)urea | 4.068 CL(3) 517.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 557 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-2,5-dihidro-1H-pirrol-1-carboxamida | 3.986 CL(3) 503.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 12 |
| 558 |  | (S)-2-but-3-enoil-4,4-difluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-1-carboxamida | 4.09 CL(3) 609.3 $[M+H]^+$ | Procedimiento 4, 5, 6 y 12 |

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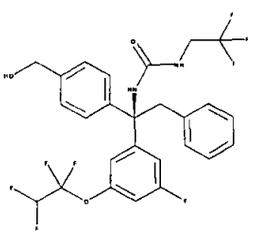
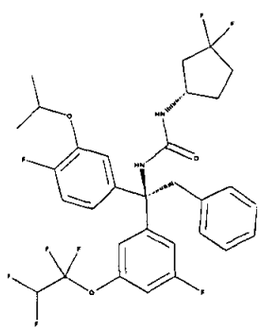
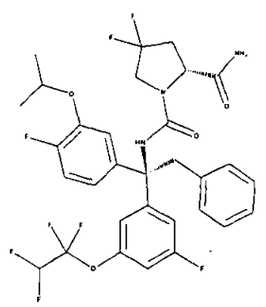
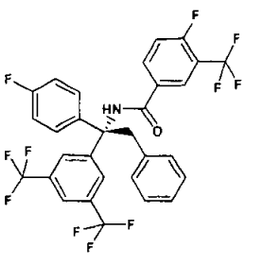
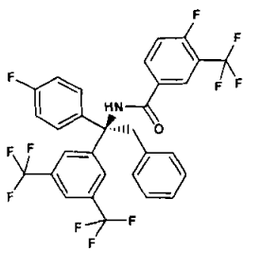
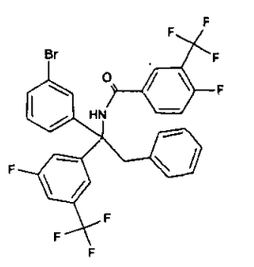
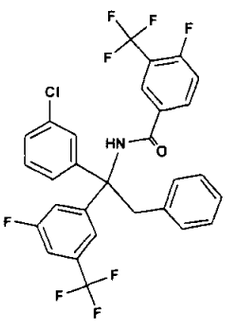
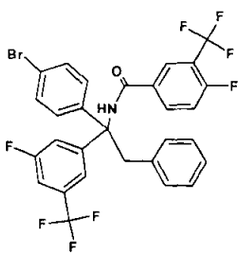
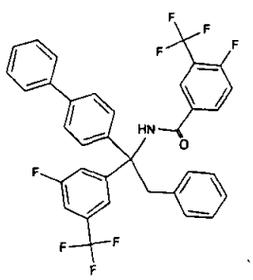
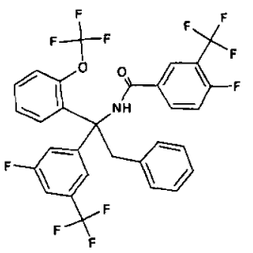
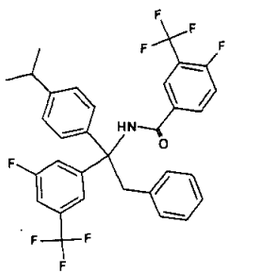
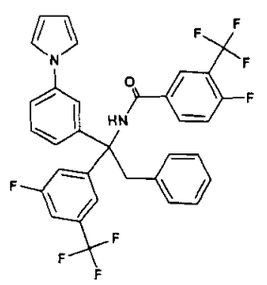
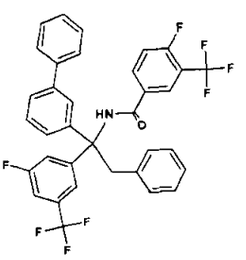
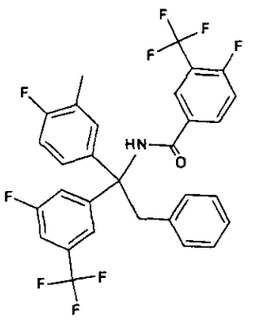
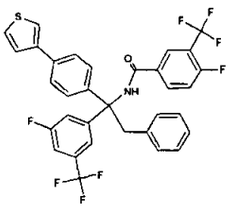
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 559 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-(hidroximetil) fenil)-2-feniletil)-3-(2,2,2-trifluoroetil)urea | 1.78 CL(9) 563 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 56, 57 y 100 |
| 560 |  | 1-((S)-3,3-difluorociclopentil)-3-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)urea | 3.633 CL(3) 661.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 12, 59 y 68 |
| 561 |  | (R)-4,4-difluoro-N1-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) pirrolidin-1,2-dicarboxamida | 3.221 CL(3) 660.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 12, 59 y 68 |

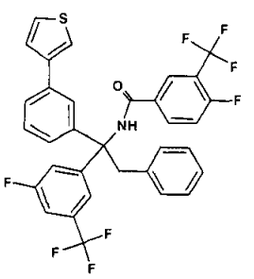
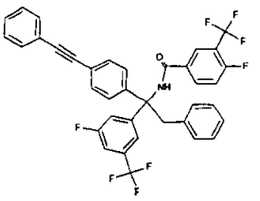
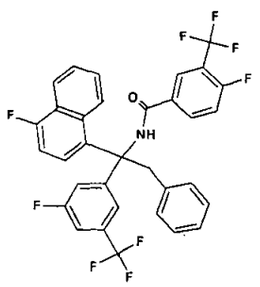
**TABLA 10**

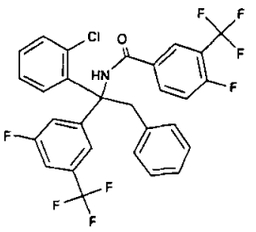
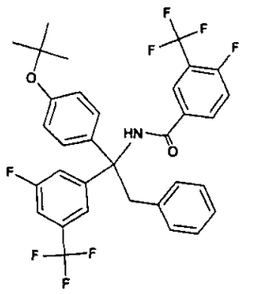
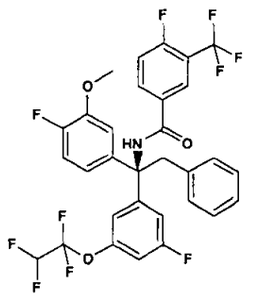
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 562 |  | (S)-N-(1-(3,5-bis(trifluoro metil)fenil)-1-(4-fluorofenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.120 CL(1) 617.97 $[M+H]^+$ | Procedimientos 4, 5, 6 y 7 |
| 563 |  | (R)-N-(1-(3,5-bis(trifluoro metil)fenil)-1-(4-fluorofenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.528 CL(1) 617.97 $[M+H]^+$ | Procedimientos 4, 5, 6 y 7 |
| 564 |  | N-(1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.33 CL(4) 628.12 $[M+H]^+$ | Procedimientos 1 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 565 |  | N-(1-(3-clorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.31 CL(4) 584.15 $[M+H]^+$ | Procedimientos 1 y 7 |
| 566 |  | N-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.37 CL(4) 628.10 $[M+H]^+$ | Procedimientos 1 y 7 |
| 567 |  | N-(1-(bifenil-4-il)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.50 CL(4) 626.26 $[M+H]^+$ | Procedimientos 1 y 7 |

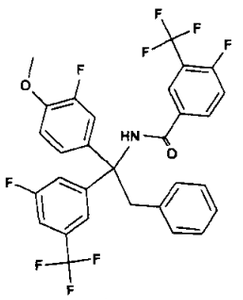
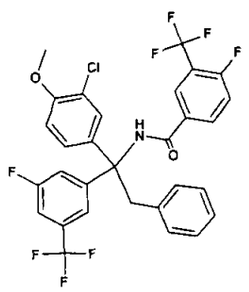
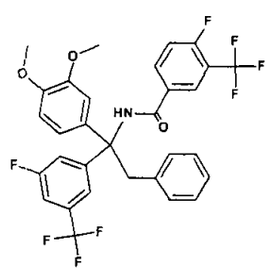
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 568 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(2-(trifluorometoxi) fenil)etil)-3-(trifluorometil) benzamida | 4.32 CL(4) 634.18 $[M+H]^+$ | Procedimientos 1 y 7 |
| 569 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-isopropilfenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.50 CL(4) 592.23 $[M+H]^+$ | Procedimientos 1 y 7 |
| 570 |  | N-(1-(3-(1H-pirrol-1-il)fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.34 CL(4) 615.24 $[M+H]^+$ | Procedimientos 1 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 571 |  | N-(1-(bifenil-3-il)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.48 CL(4) 626.25 $[M+H]^+$ | Procedimientos 1 y 7 |
| 572 |  | 4-fluoro-N-(1-(4-fluoro-3-metilfenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.33 CL(4) 582.22 $[M+H]^+$ | Procedimientos 1 y 7 |
| 573 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(4-(tiofen-3-il)fenil)etil)-3-(trifluorometil) benzamida | 4.41 CL(4) 632.16 $[M+H]^+$ | Procedimientos 1 y 7 |

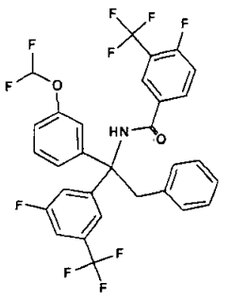
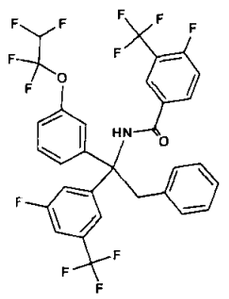
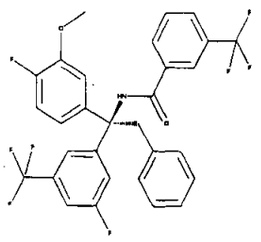
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 574 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(tiofen-3-il)fenil)etil)-3-(trifluorometil) benzamida | 4.43 CL(4) 632.18 $[M+H]^+$ | Procedimientos 1 y 7 |
| 575 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(4-(2-feniletinil) fenil)etil)-3-(trifluorometil) benzamida | 4.59 CL(4) 650.20 $[M+H]^+$ | Procedimientos 1 y 7 |
| 576 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluoronaftalen-1-il)-2-feniletil)-3-(trifluorometil) benzamida | 4.40 CL(4) 618.20 $[M+H]^+$ | Procedimientos 1 y 7 |

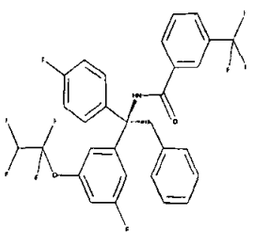
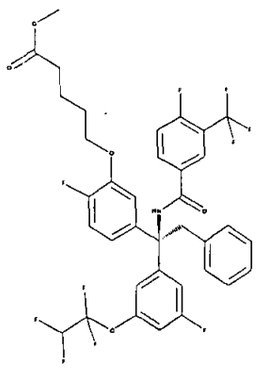
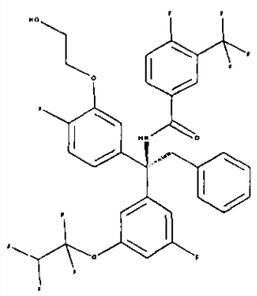
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 577 |  | N-(1-(2-clorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.33 CL(4) 584.19 $[M+H]^+$ | Procedimientos 1 y 7 |
| 578 |  | N-(1-(4-ter-butoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.40 CL(4) 622.28 $[M+H]^+$ | Procedimientos 1 y 7 |
| 579 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.833 CL(1) 646.14 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

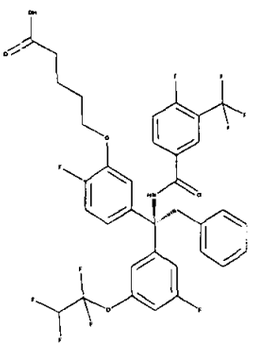
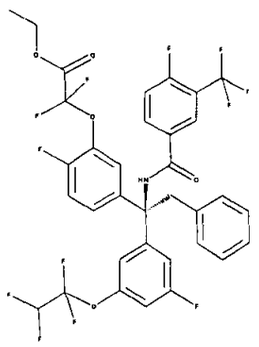
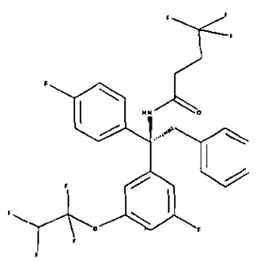
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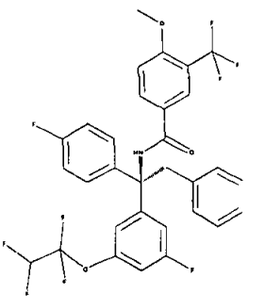
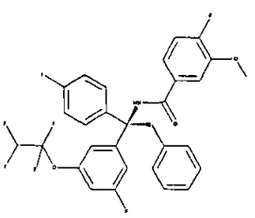
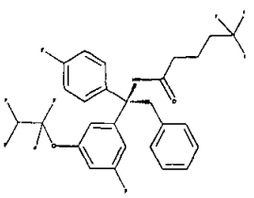
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 580 |  | 4-fluoro-N-(1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.20 CL(4) 598.10 $[M+H]^+$ | Procedimientos 1 y 7 |
| 581 |  | N-(1-(3-cloro-4-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.26 CL(4) 614.07 $[M+H]^+$ | Procedimientos 1 y 7 |
| 582 |  | N-(1-(3,4-dimetoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.15 CL(4) 610.13 $[M+H]^+$ | Procedimientos 1 y 7 |

1668

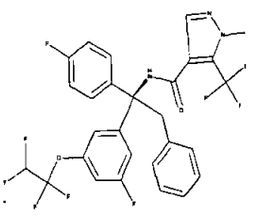
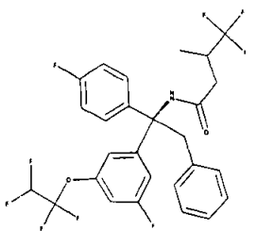
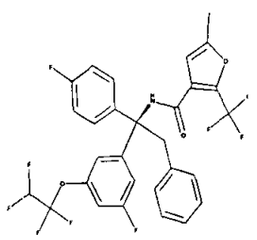
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 583 |  | N-(1-(3-(difluorometoxi) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.21 CL(4) 616.10 $[M+H]^+$ | Procedimientos 1 y 7 |
| 584 |  | 4-fluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(1,1,2,2-tetrafluoroetoxi) fenil)etil)-3-(trifluorometil) benzamida | 4.24 CL(4) 666.13 $[M+H]^+$ | Procedimientos 1 y 7 |
| 585 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.92 CL(1) 580.1 $[M+H]^+$ | Procedimientos 4, 5, 6 y 7 |

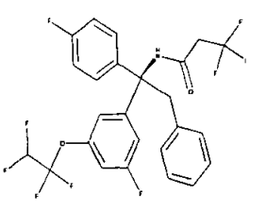
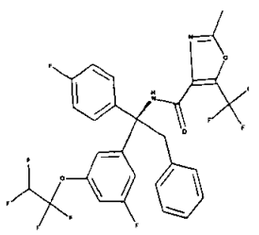
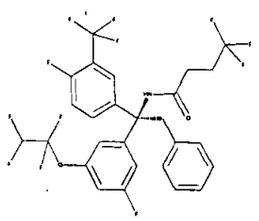
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 586 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.84 CL(1) 598.15 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 587 |  | (R)-metil 5-(2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) fenoxi)pentanoato | 3.95 CL(1) 746.12 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 588 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(2-hidroxietoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.48 CL(1) 676.10 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 589 |  | Ácido (R)-5-(2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) fenoxi)pentanoico | 3.59 CL(1) 732.08 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 68 y 23 |
| 590 |  | 2,2-difluoro-2-(2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)fenoxi) acetato de (R)-etilo | 3.92 CL(1) 754.30 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 591 |  | (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) butanamida | 3.60 CL(1) 550.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

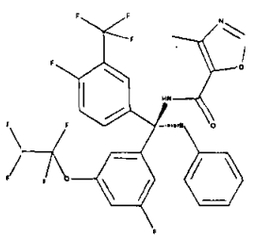
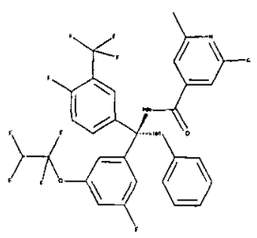
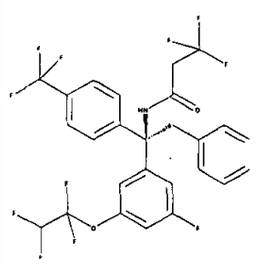
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 592 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-4-metoxi-3-(trifluorometil) benzamida | 3.81 CL(1) 628.21 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 593 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-metoxibenzamida | 3.68 CL(1) 578.12 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 594 |  | (R)-5,5,5-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) pentanamida | 3.65 CL(1) 564.09 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

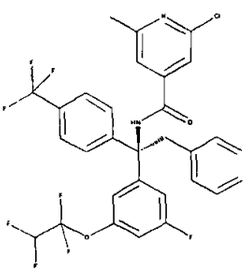
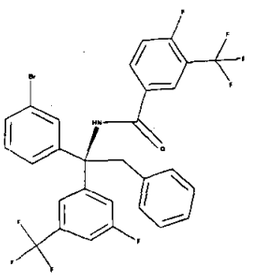
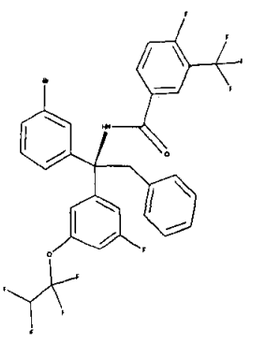
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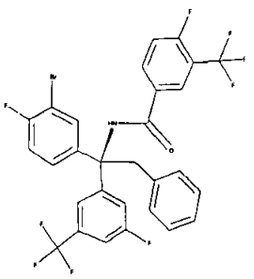
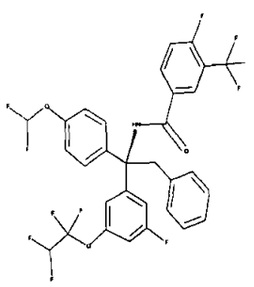
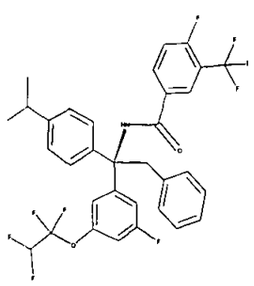
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 595 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-1-metil-5-(trifluorometil)-1H-pirazol-4-carboxamida | 4.01 CL(4) 602.17 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 127 |
| 596 |  | 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-metilbutanamida | 4.14 CL(4) 564.21 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 127 |
| 597 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-5-metil-2-(trifluorometil) furan-3-carboxamida | 4.12 CL(4) 602.17 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 127 |

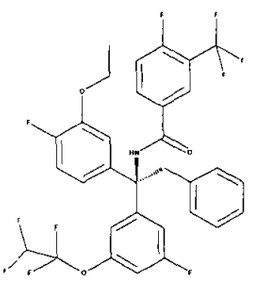
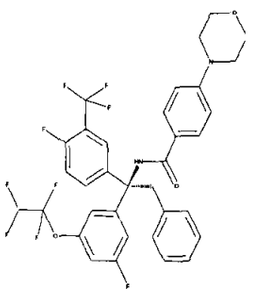
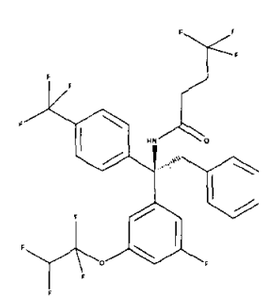
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 598 |  | (R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) propanamida | 3.99 CL(4) 535.21 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 127 |
| 599 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-2-metil-5-(trifluorometil) oxazol-4-carboxamida | 4.15 CL(4) 603.14 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 127 |
| 600 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) butanamida | 3.751 CL(1) 617.96 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

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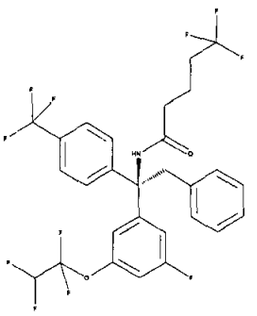
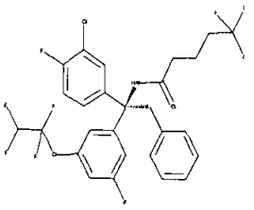
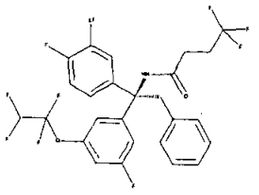
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 601 |  | (R)-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-metiloxazol-5-carboxamida | 3.513 CL(1) 603.69 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 602 |  | (R)-2-cloro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-6-metilisonicotinamida | 3.836 CL(1) 647.69 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 603 |  | (R)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometil) fenil)etil) propanamida | 3.61 CL(1) 586.67 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 604 |  | (R)-2-cloro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometil) fenil)etil)-6-metilisonicotinamida | 3.72 CL(1) 629.70 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 605 |  | (S)-N-(1-(3-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.41 CL(4) 628.08 $[M+H]^+$ | Procedimientos 4, 5, 6 y 7 |
| 606 |  | (S)-N-(1-(3-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.32 CL(4) 676.06 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

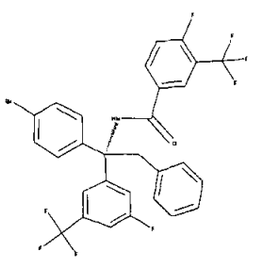
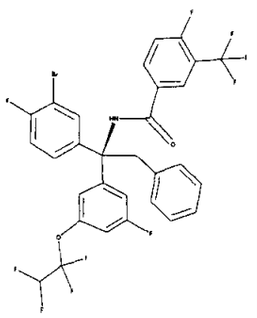
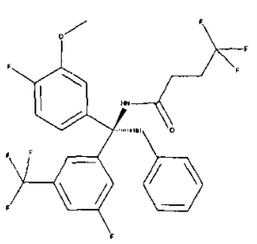
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 607 |  | (S)-N-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.43 CL(4) 646.05 $[M+H]^+$ | Procedimientos 62, 5, 6 y 7 |
| 608 |  | (R)-N-(1-(4-(difluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.22 CL(4) 664.14 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 609 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-isopropilfenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.47 CL(4) 640.20 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

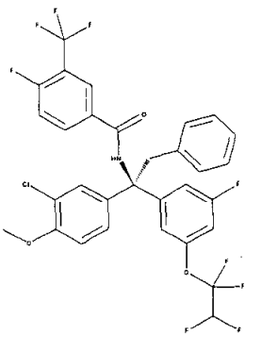
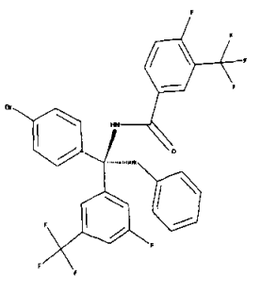
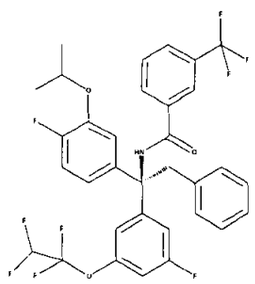
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 610 |  | (R)-N-(1-(3-etoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 3.606 CL(1) 660.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 611 |  | (R)-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-morfolinobenzamida | 3.66 CL(1) 683.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 612 |  | (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometil) fenil)etil) butanamida | 3.455 CL(1) 600.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

1678

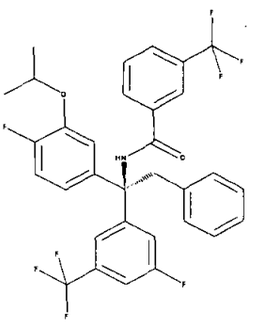
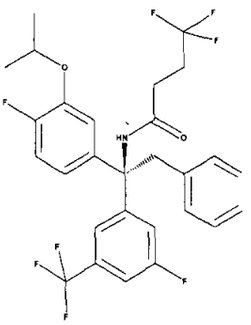
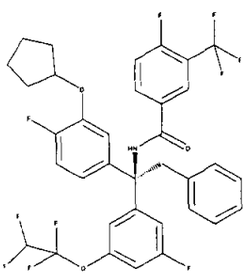
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 613 |  | (R)-5,5,5-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometil) fenil)etil) pentanamida | 3.773 CL(1) 614.66 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 614 |  | (S)-N-(1-(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-5,5,5-trifluoropentan amida | 3.76 CL(1) 598.05 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 615 |  | (S)-N-(1-(3-cloro-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4,4,4-trifluorobutan amida | 3.73 CL(1) 587.04 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

1679

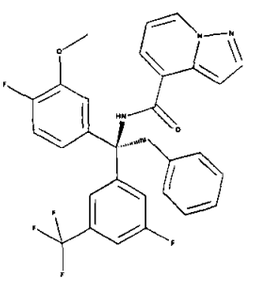
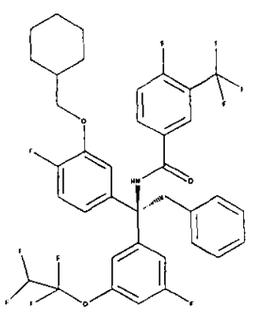
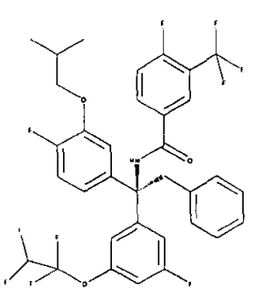
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 616 |  | (S)-N-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.44 CL(4) 628.19 $[M+H]^+$ | Procedimientos 4, 5, 6 y 7 |
| 617 |  | (S)-N-(1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.33 CL(4) 694.21 $[M+H]^+$ | Procedimientos 62, 3, 5, 6 y 7 |
| 618 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) butanamida | 3.628 CL(1) 532.15 $[M+H]^+$ | Procedimientos 4, 5, 6 y 128 |

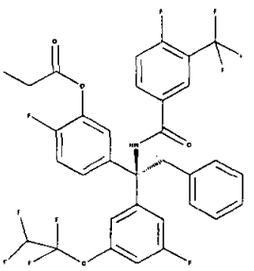
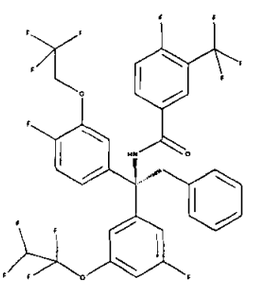
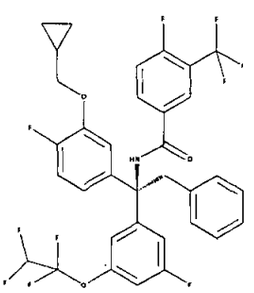
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 619 |  | (S)-N-(1-(3-cloro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 10.93 CL(7) 662.0 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 620 |  | (R)-N-(1-(4-bromofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.43 CL(4) 628.30 $[M+H]^+$ | Procedimientos 4, 5, 6 y 7 |
| 621 |  | (R)-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.00 CL(1) 656.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

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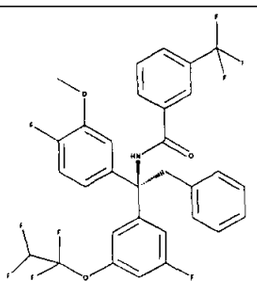
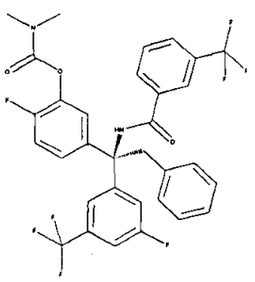
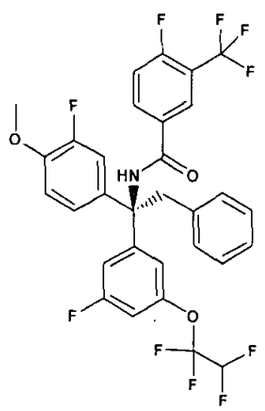
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 622 |  | (R)-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.10 CL(1) 608.4 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |
| 623 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) butanamida | 3.85 CL(1) 560.2 $[M+H]^+$ | Procedimientos 4, 5, 6, 128, 59 y 68 |
| 624 |  | (R)-N-(1-(3-(ciclopentiloxi)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.24 CL(1) 700.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

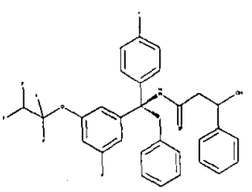
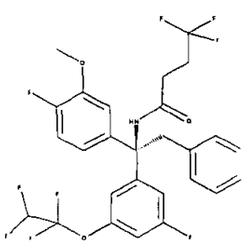
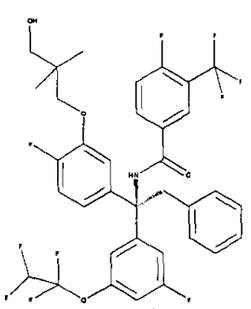
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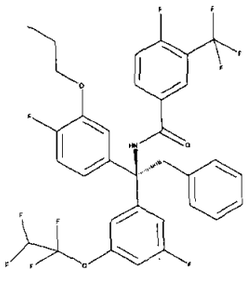
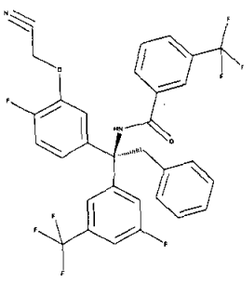
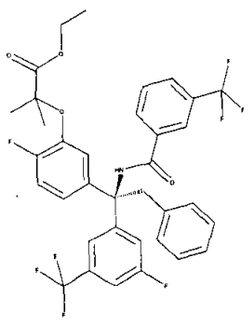
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 625 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)pirazolo [1,5-a]piridina-4-carboxamida | 2.12 CL(1) 552.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 127 |
| 626 |  | (R)-N-(1-(3-(ciclohexilmetoxi) -4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.51 CL(1) 729.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 627 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isobutoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.23 CL(1) 688.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

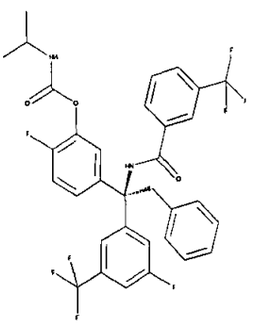
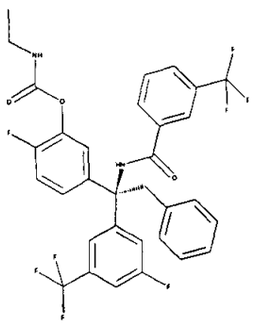
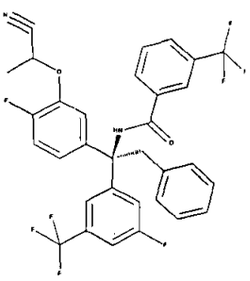
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 628 |  | propionato de (R)-2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)fenilo | 3.905 CL(1) 688.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 629 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(2,2,2-trifluoroetoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.95 CL(1) 714.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 630 |  | (R)-N-(1-(3-(ciclopropil metoxi)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.04 CL(1) 686.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

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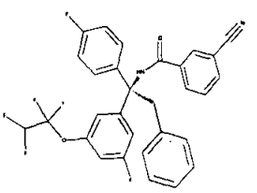
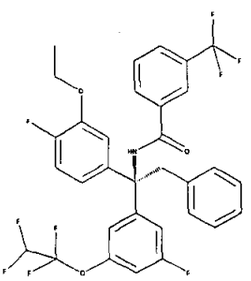
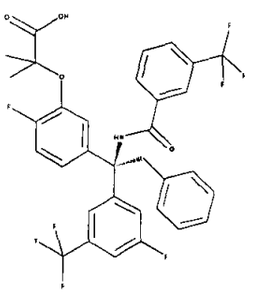
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 631 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.88 CL(1) 628.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 632 |  | dimetilcarbamato de (R)-2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) benzamido)etil) fenilo | 2.21 CL(2) 637.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 633 |  | (R)-4-fluoro-N-(1-(3-fluoro-4-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 645.487 | Procedimientos 3, 4, 5, 6 y 7 |

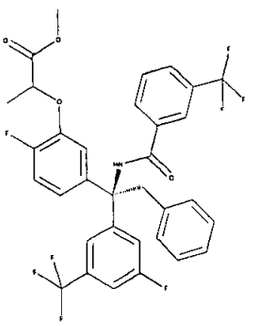
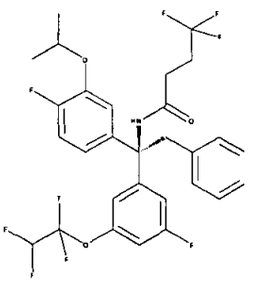
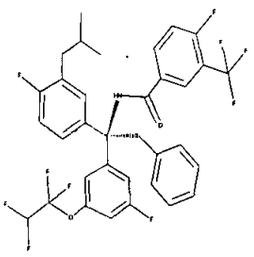
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 634 |  | N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-fenilpropanamida | 4.28 CL(11) 574.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 60 y 23 |
| 635 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) butanamida | 3.56 CL(1) 580.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 636 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(3-hidroxi-2,2-dimetilpropoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.833 CL(1) 718.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 637 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-propoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.08 CL(1) 674.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 638 |  | (R)-N-(1-(3-(cianometoxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.24 CL(1) 605.2 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |
| 639 |  | 2-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) benzamido) etil)fenoxi)-2-metilpropanoato de (R)-etilo | 4.44 CL(1) 680.2 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |

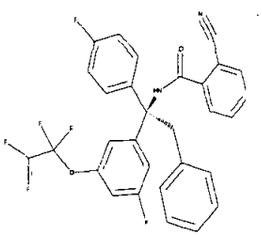
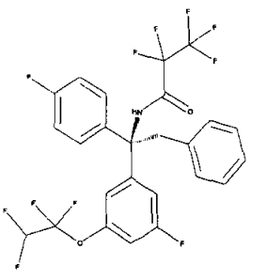
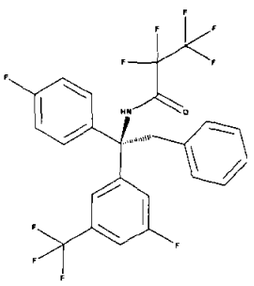
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 640 |  | isopropilcarbamato de (R)-2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) benzamido)etil) fenilo | 2.20 CL(2) 651.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |
| 641 |  | (R)-2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) benzamido)etil) fenil etilcarbamato | 2.15 CL(2) 637.2 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |
| 642 |  | N-((1R)-1-(3-(1-cianoetoxi)-4-fluorofenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 2.18 CL(2) 619.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |

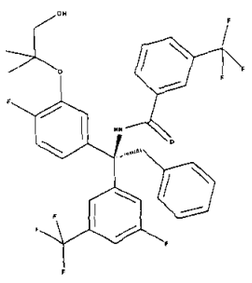
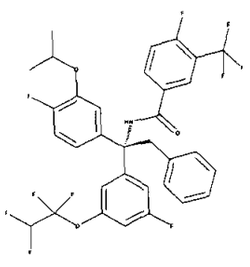
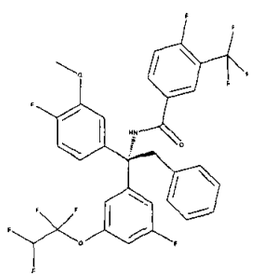
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| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 643 |  | (R)-3-ciano-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) Benzamida | 2.07 CL(2) 555.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 644 |  | (R)-N-(1-(3-etoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.91 CL(1) 642.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 645 |  | Ácido (R)-2-(2-fluoro-5-(1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) benzamido)etil) fenoxi)-2-metilpropanoico | 2.23 CL(2) 652.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59, 68 y 23 |

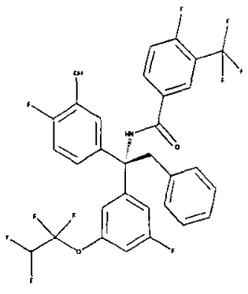
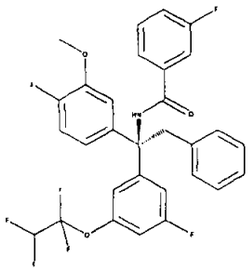
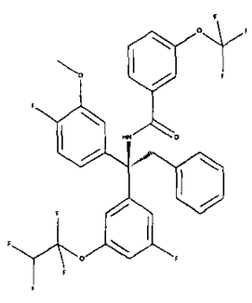
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 646 |  | metil 2-(2-fluoro-5-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-2-fenil-1-(3-(trifluorometil) benzamido) etil)fenoxi) propanoato | 2.24 CL(2) 652.4 $[M+H]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |
| 647 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Butanamida | 3.79 CL(1) 608.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68 y 128 |
| 648 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isobutilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.54 CL(4) 672.40 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 122 y 7 |

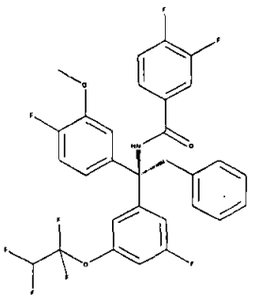
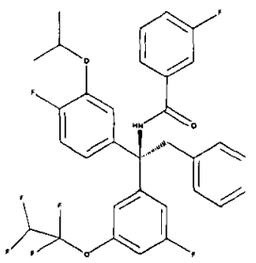
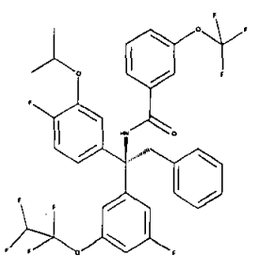
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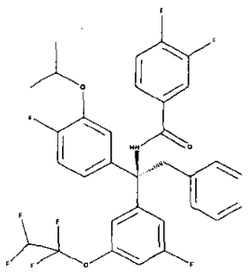
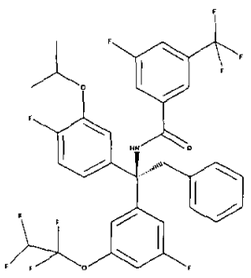
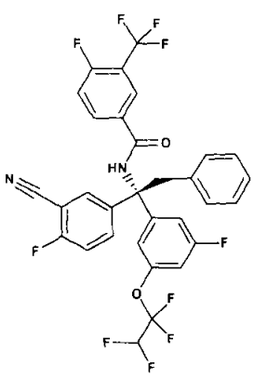
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 649 |  | (R)-2-ciano-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) Benzamida | 2.14 CL(2) 577.4 $[M+Na]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 650 |  | (R)-2,2,3,3,3-pentafluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) Propanamida | 2.11 CL(2) 409.2 [M-amida] | Procedimientos 3, 109, 110, 111, 112, 113, 114 y 115 |
| 651 |  | (R)-2,2,3,3,3-pentafluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil) propanamida | 2.15 CL(2) pico no ionizable | Procedimientos 4, 5, 6 y 115 |

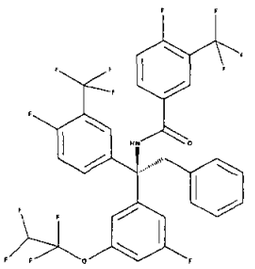
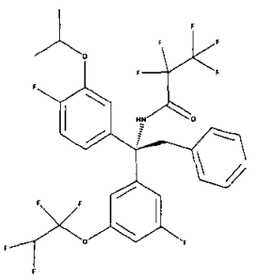
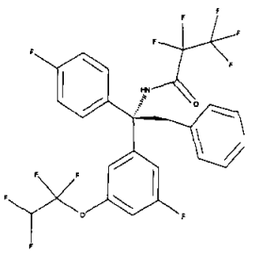
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 652 |  | (R)-N-(1-(4-fluoro-3-(1-hidroxi-2-metilpropan-2-iloxi)fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 2.33 CL(2) 660.5 $[M+Na]^+$ | Procedimientos 4, 5, 6, 7, 59 y 68 |
| 653 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.35 CL(4) 674.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 654 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.21 CL(1) 645.14 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

1692

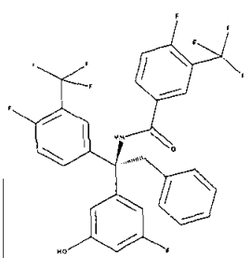
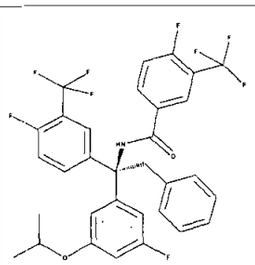
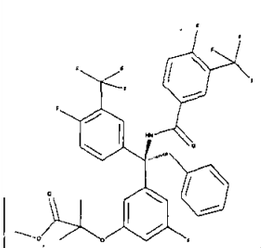
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 655 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-hidroxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.06 CL(1) 632.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7 y 59 |
| 656 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) benzamida | 3.63 CL(1) 578.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 657 |  | (R)-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometoxi) benzamida | 3.87 CL(1) 644.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

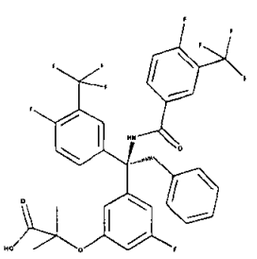
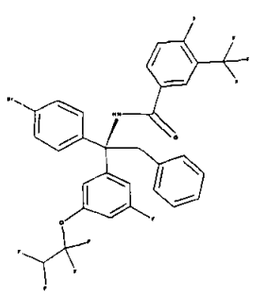
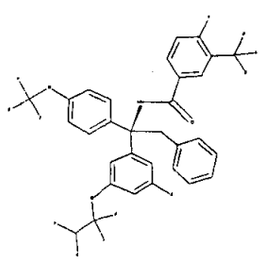
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 658 |  | (R)-3,4-difluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Benzamida | 3.701 CL(1) 596.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 659 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Benzamida | 3.85 CL(1) 606.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 660 |  | (R)-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometoxi) benzamida | 4.06 CL(1) 672.6 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 661 |  | (R)-3,4-difluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Benzamida | 3.91 CL(1) 624.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 662 |  | (R)-3-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-5-(trifluorometil) benzamida | 4.08 CL(1) 674.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 663 |  | N-(1-(3-ciano-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 2.335 CL(2) 641.3 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7 y 56 |

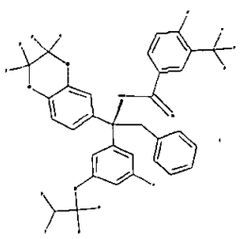
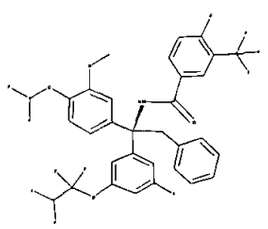
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 664 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.30 CL(1) 684.46 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 665 |  | (S)-2,2,3,3,3-pentafluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Propanamida | 2.22 CL(2) pico no ionizable | Procedimientos 3, 109, 110, 111, 112, 113, 114 y 115 |
| 666 |  | (S)-2,2,3,3,3-pentafluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) propanamida | 2.14 CL(2) pico no ionizable | Procedimientos 3, 4, 5, 6 y 115 |

1696

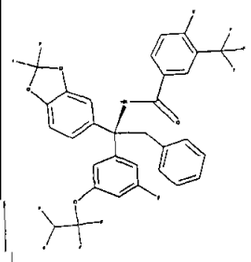
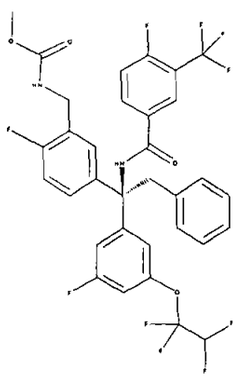
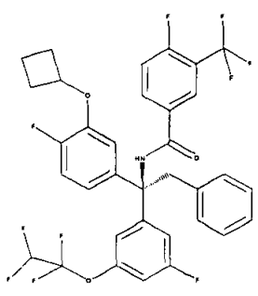
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 667 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-hidroxifenil)-2-feniletil)-3-(trifluorometil) benzamida | 2.19 CL(2) 584.4 $[M+H]^+$ | Procedimientos 49 y 7 |
| 668 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-isopropoxifenil)-2-feniletil)-3-(trifluorometil) benzamida | 2.34 CL(2) 626.5 $[M+H]^+$ | Procedimientos 49, 7 y 68 |
| 669 |  | 2-(3-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(4-fluoro-3-(trifluorometil) fenil)-2-feniletil)fenoxi)-2-metilpropanoato de (R)-metilo | 2.26 CL(2) 684.6 $[M+H]^+$ | Procedimientos 49, 7 y 68 |

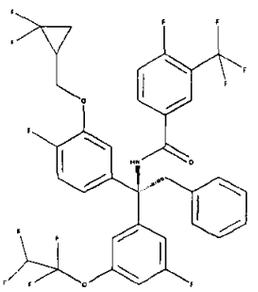
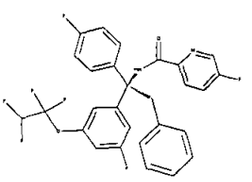
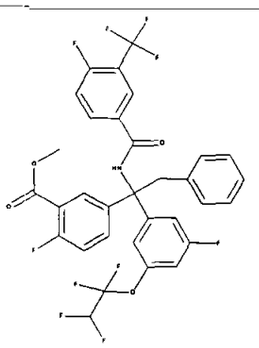
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 670 |  | Ácido (R)-2-(3-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(4-fluoro-3-(trifluorometil) fenil)-2-feniletil)fenoxi)-2-metilpropanoico | 2.25 CL(2) 670.6 $[M+H]^+$ | Procedimientos 49, 7, 68 y 23 |
| 671 |  | (R)-N-(1-(4-bromofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.13 CL(4) 676.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 672 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(4-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.13 CL(4) 682.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

1698

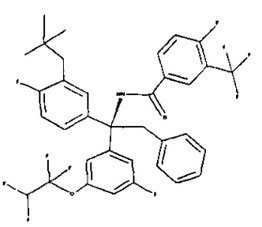
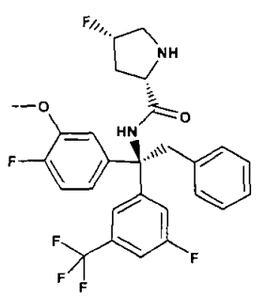
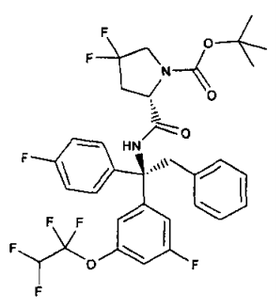
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 673 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-(2,2,3,3-tetrafluoro-2,3-dihidrobenzo[b][1,4]dioxin-6-il)etil)-3-(trifluorometil) benzamida | 4.21 CL(4) 728.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 674 |  | (R)-N-(1-(4-(difluorometoxi)-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 3.95 CL(4) 694.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

1699

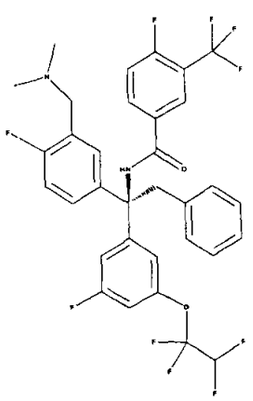
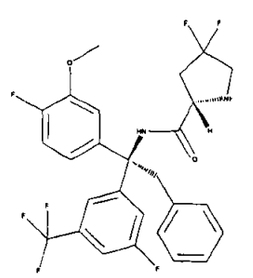
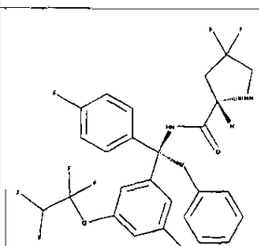
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 675 |  | (R)-N-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-il)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida | 4.10 CL(4) 678.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 676 |  | (R)-metil 2-fluoro-5-(1-(4-fluoro-3-(trifluorometil)benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)bencilcarbamato | 10.26 CL(7) 703.1 $[M+H]^+$ | Procedimientos 3, 62, 63, 7, 64 y 82 |
| 677 |  | (R)-N-(1-(3-ciclobutoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletil)-4-fluoro-3-(trifluorometil)benzamida | 4.12 CL(1) 686.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 678 |  | N-((1R)-1-(3-((2,2-difluorociclopropil) metoxi)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 3.94 CL(1) 722.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 679 |  | (R)-5-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) picolinamida | 4.13 CL(1) 549 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 71 |
| 680 |  | 2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) benzoato de metilo | 2.38 CL(9) 674 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7, 56 y 57 |

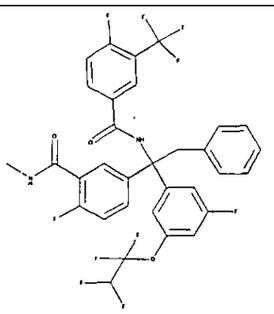
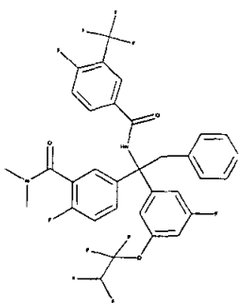
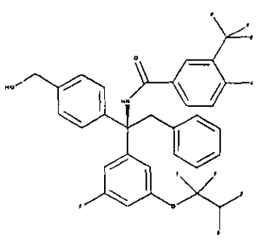
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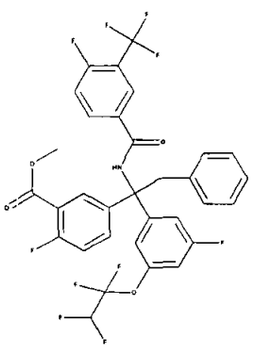
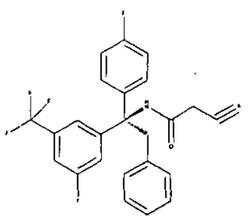
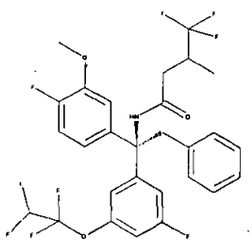
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 681 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-neopentilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.60 CL(4) 686.43 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 122 y 7 |
| 682 |  | (2S,4S)-4-fluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-2-carboxamida | 3.94 CL(3) 523.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 71 y 39 |
| 683 |  | 4,4-difluoro-2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil carbamoil) pirrolidin-1-carboxilato de (S)-ter-butilo | 4.218 CL(3) 659.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 71 |

1702

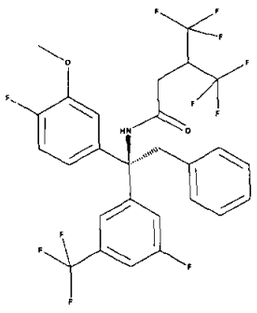
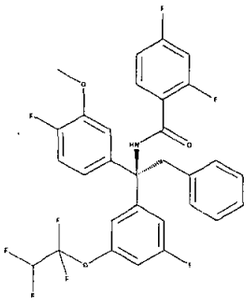
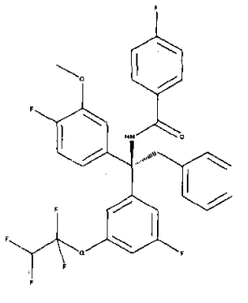
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 684 |  | (R)-N-(1-(3-((dimetilamino) metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.48 CL(1) 632.4 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7, 56, 57, 100 y 102 |
| 685 |  | (S)-4,4-difluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil) pirrolidin-2-carboxamida | 4.008 CL(3) 541.2 $[M+H]^+$ | Procedimientos 4, 5, 6, 71 y 39 |
| 686 |  | (S)-4,4-difluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)pirrolidin-2-carboxamida | 3.963 CL(3) 559.3 $[M+H]^+$ | Procedimientos 4, 5, 6, 71 y 39 |

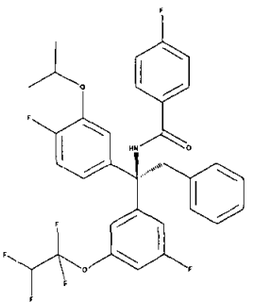
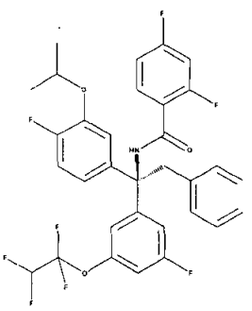
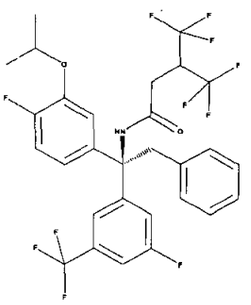
1703

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 687 |  | 2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-N-metilbenzamida | 2.28 CL(9) 673 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 56, 57, 23 y 103 |
| 688 |  | 2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-N,N-dimetilbenzamida | 4.213 CL(11) 687 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 56, 57, 23 y 103 |
| 689 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-(hidroximetil) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 1.90 CL(12) 628 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 56, 57 y 100 |

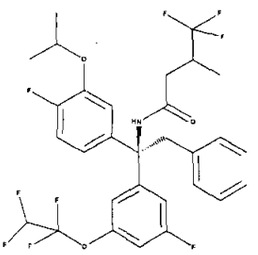
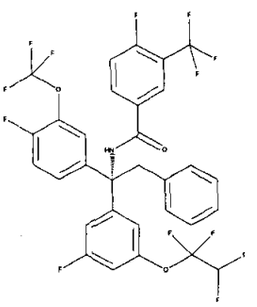
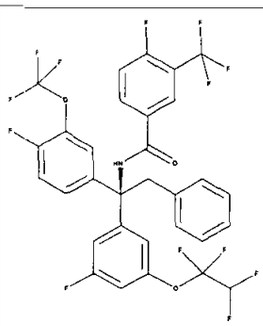
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 690 |  | 2-fluoro-5-(1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) benzoato de metilo | 2.353 CL(2) 674.0 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 56 y 57 |
| 691 |  | (R)-2-ciano-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil) acetamida | 2.163 CL(1) 654.3 $[M+H]^+$ | Procedimientos 4, 5, 6 y 127 |
| 692 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-metilbutanamida | 3.67 CL(1) 594.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |

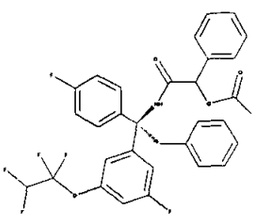
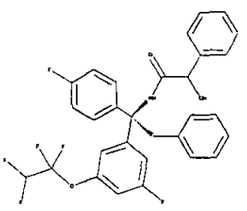
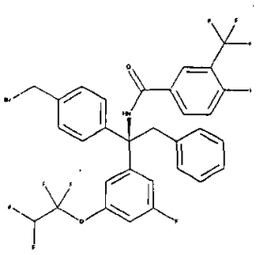
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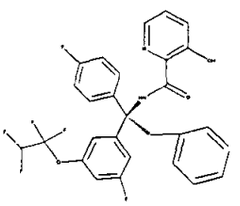
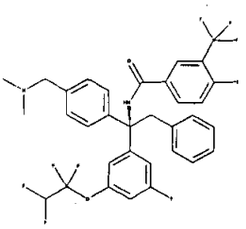
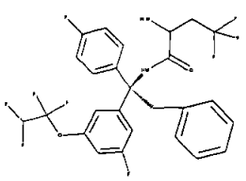
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 693 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) butanamida | 4.09 CL(1) 600.0 $[M+H]^+$ | Procedimientos 4, 5, 6 y 128 |
| 694 |  | (R)-2,4-difluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Benzamida | 3.67 CL(1) 596.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 695 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) benzamida | 3.61 CL(1) 578.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

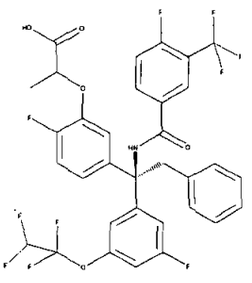
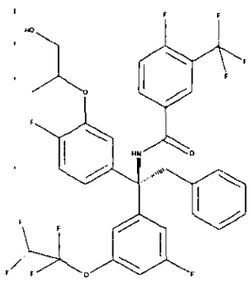
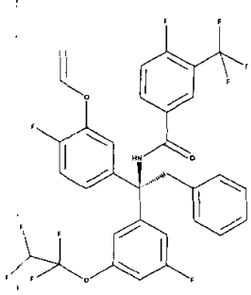
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 696 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Benzamida | 3.836 CL(1) 606.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 697 |  | (R)-2,4-difluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) Benzamida | 3.91 CL(1) 624.5 $[M+H]^+$ | Procedimientos 4, 5, 6, 128, 59 y 68 |
| 698 |  | (R)-4,4,4-trifluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)-3-(trifluorometil) butanamida | 4.05 CL(1) 628.5 $[M+H]^+$ | Procedimientos 4, 5, 6, 128, 59 y 68 |

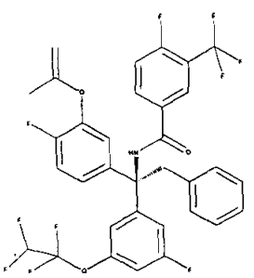
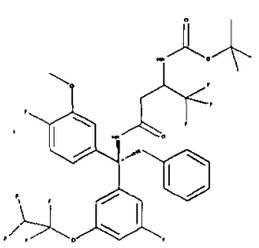
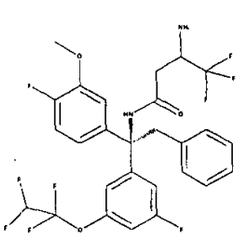
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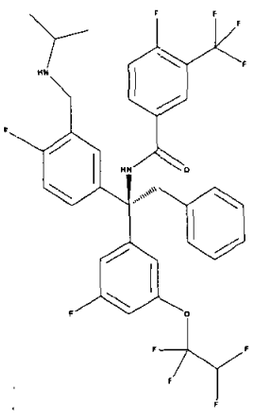
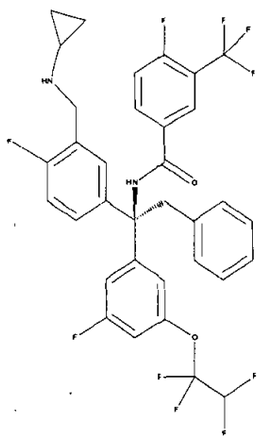
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 699 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-metilbutanamida | 3.911 CL(1) 622.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 128, 59 y 68 |
| 700 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.36 CL(4) 700.32 $[M+H]^+$ | Procedimientos 3, 62, 5, 6 y 7 |
| 701 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.36 CL(4) 700.26 $[M+H]^+$ | Procedimientos 3, 62, 5, 6 y 7 |

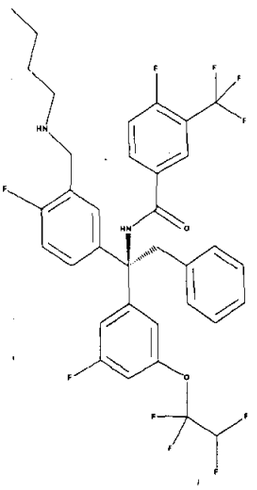
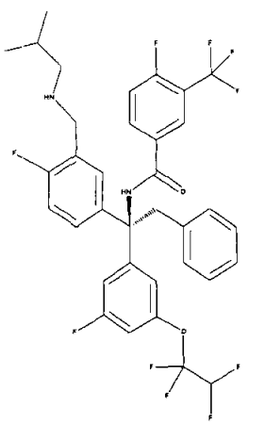
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 702 |  | 2-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletilamino)-2-oxo-1-fenilacetato de etilo | 4.05 CL(1) 602.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 703 |  | N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-2-hidroxi-2-fenilacetamida | 3.82 CL(1) 560.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7 y 23 |
| 704 |  | (R)-N-(1-(4-(bromometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 1.77 CL(9) 602.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 56, 57, 100 y 32 |

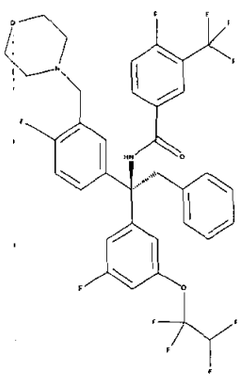
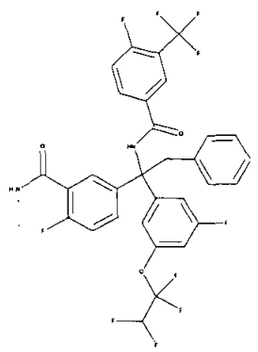
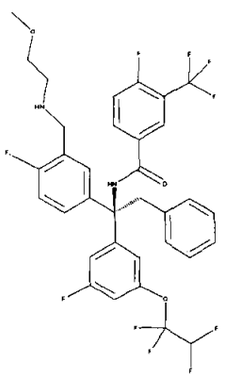
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 705 |  | (R)-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxipicolin amida | 2.22 CL(2) 547.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 71 |
| 706 |  | (R)-N-(1-(4-((dimetilamino) metil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 0.89 CL(12) 655 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 56, 57, 100 y 102 |
| 707 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) butanamida | 3.1 CL(1) 565.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 139, 140 y 141 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 708 |  | Ácido 2-(2-fluoro-5-((R)-1-(4-fluoro-3-(trifluorometil) benzamido)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) fenoxi)propanoico | 3.51 CL(1) 704.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 68 y 23 |
| 709 |  | 4-fluoro-N-((1R)-1-(4-fluoro-3-(1-hidroxipropan-2-iloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.588 CL(1) 690.6 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 68, 23 y 100 |
| 710 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(viniloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.948 CL(1) 658.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 106 |

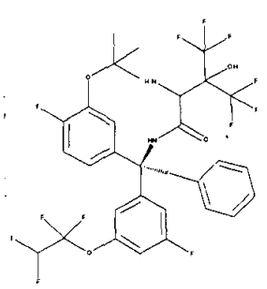
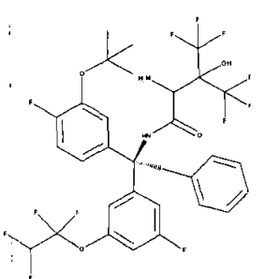
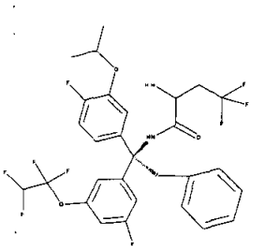
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
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| 711 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(prop-1-en-2-iloxi)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.053 CL(1) 672.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 712 |  | 1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-4-oxobutan-2-ilcarbamato de ter-butilo | 3.7 CL(1) 695.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 128 |
| 713 |  | 3-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) butanamida | 2.518 CL(1) 595.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 128 y 39 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 714 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-((isopropilamino) metil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 8.099 CL(7) 687 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |
| 715 |  | (R)-N-(1-(3-((ciclopropil amino)metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 3.656 CL(15) 685 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |

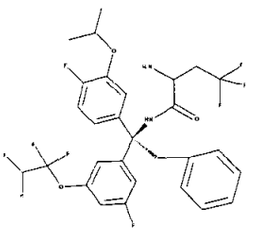
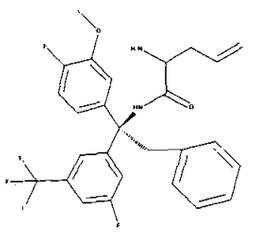
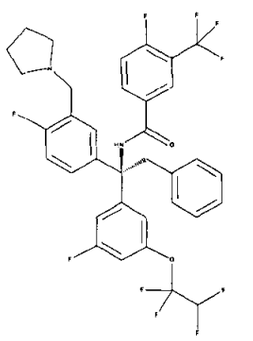
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 716 |  | (R)-N-(1-(3-((butilamino) metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 3.723 CL(15) 701 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |
| 717 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-((isobutilamino) metil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.725 CL(15) 701 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |

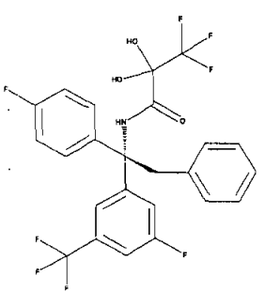
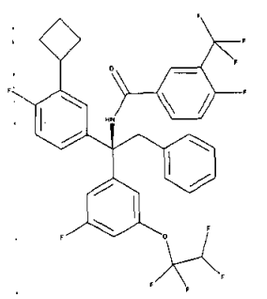
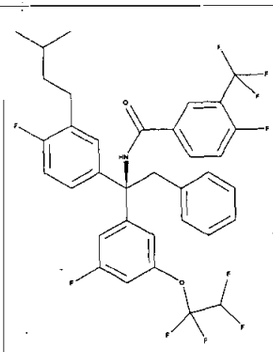
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 718 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(morfolinometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.650 CL(15) 715 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |
| 719 |  | N-(1-(3-carbamoil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.243 CL(13) 659 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7, 56, 57, 23 y 136 |
| 720 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-((2-metoxietilamino) metil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.636 CL(15) 703 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |

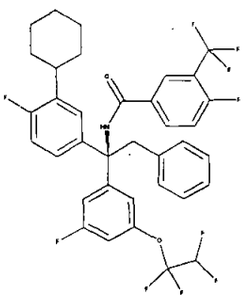
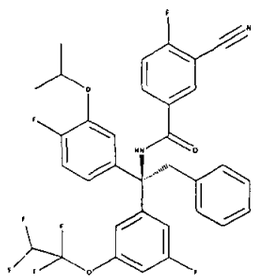
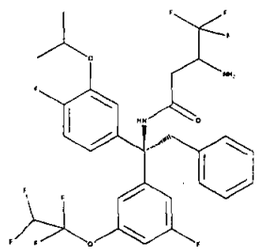
1715

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 721 |  | 2-amino-N-((R)-1-(3-ter-butoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4,4,4-trifluoro-3-hidroxi-3-(trifluorometil) butanamida | 2.09 CL(1) 721.0 $[M+H]^+$ | Procedimientos 3, 109, 110, 111, 112, 108, 90, 91 y 92 |
| 722 |  | 2-amino-N-((R)-1-(3-ter-butoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4,4,4-trifluoro-3-hidroxi-3-(trifluorometil) butanamida | 2.11 CL(1) 721.0 $[M+H]^+$ | Procedimientos 3, 109, 110, 111, 112, 108, 90, 91 y 92 |
| 723 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) butanamida | 2.01 CL(2) 623.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68, 139, 140 y 141 |

1716

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 724 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) butanamida | 2.04 CL(2) 623.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68, 139, 140 y 141 |
| 725 |  | 2-amino-N-((R)-1-(4-fluoro-3-metoxifenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-feniletil)pent-4-enamida | 2.2 CL(2) 505.2 $[M+H]^+$ | Procedimientos 4, 5, 6, 140 y 39 |
| 726 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(pirrolidin-1-ilmetil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 3.606 CL(15) 699 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 146, 7, 147 y 148 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 727 |  | (S)-3,3,3-trifluoro-N-(1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-2,2-dihidroxipropan amida | 1.70 CL(14) 518.1 $[M-H]^-$ | Procedimiento 4, 149, 150, 151, 152 y 159 |
| 728 |  | (R)-N-(1-(3-ciclobutil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 8.654 CL(16) 670.29 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7 y 121 |
| 729 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopentilfenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-(trifluorometil) benzamida | 4.62 CL(4) 686.33 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7 y 162 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 730 |  | (R)-N-(1-(3-ciclohexil-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-4-fluoro-3-(trifluorometil) benzamida | 4.67 CL(4) 698.37 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 7 y 162 |
| 731 |  | (R)-3-ciano-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) benzamida | 3.785 CL(1) 631.6 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68 y 7 |
| 732 |  | 3-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) butanamida | 2.69 CL(1) 623.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 59, 68, 143 y 144 |

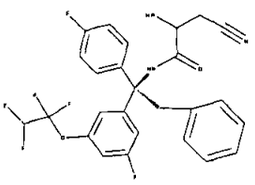
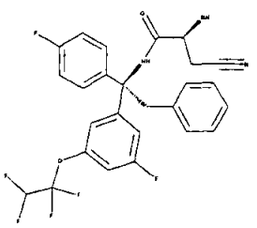
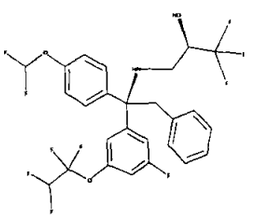
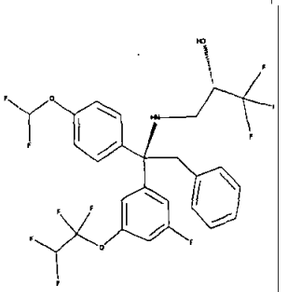
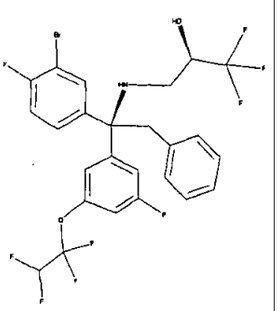
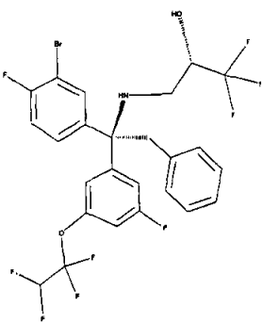
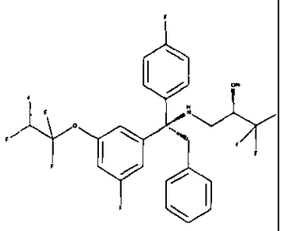
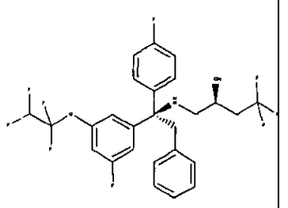
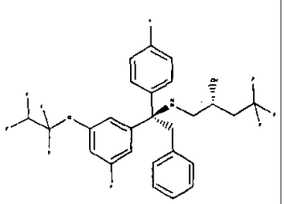
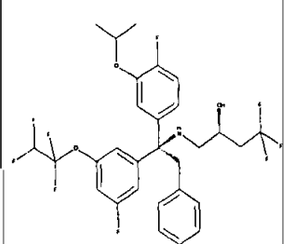
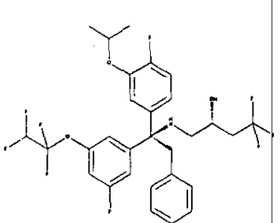
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 733 |  | 2-amino-3-ciano-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) propanamida | 1.83 CL(2) 522.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 140 y 39 |
| 734 |  | (S)-2-amino-3-ciano-N-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) Propanamida | 3.12 CL(8) 522.0 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 140 y 39 |

**TABLA 11**

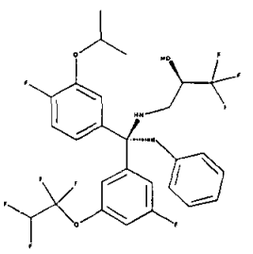
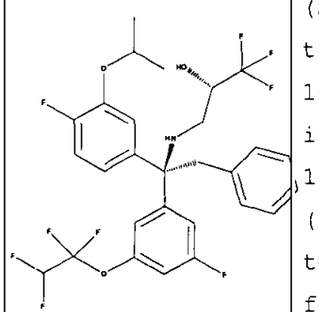
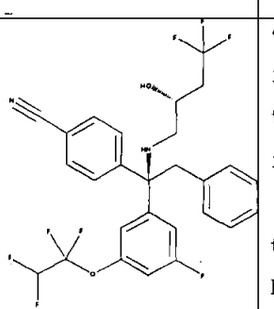
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 735 |  | (R)-3-((R)-1-(4-(difluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 3.97 CL(4) 586.39 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27 y 8 |
| 736 |  | (S)-3-((R)-1-(4-(difluorometoxi) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 3.98 CL(4) 586.41 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27 y 8 |
| 737 |  | (R)-3-((S)-1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 4.23 CL(4) 616.31 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 27 y 8 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 738 |  | (S)-3-((S)-1-(3-bromo-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 4.21 CL(4) 616.32 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 27 y 8 |
| 739 |  | (R)-1,1,1-trifluoro-3-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletilamino) propan-2-ol | 2.097 CL(2) 538.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27 y 8 |
| 740 |  | (S)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletilamino) butan-2-ol | 3.805 CL(1) 552.33 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27 y 8 |

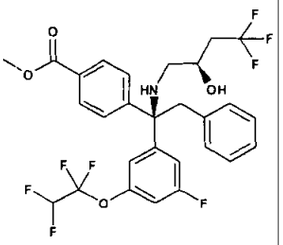
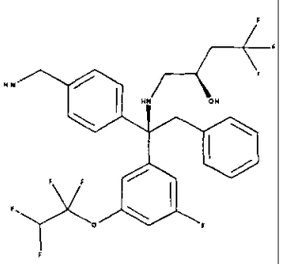
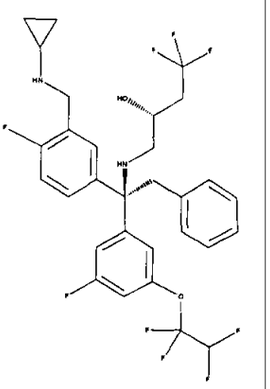
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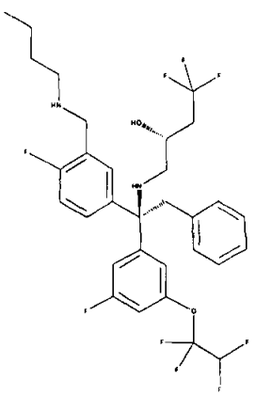
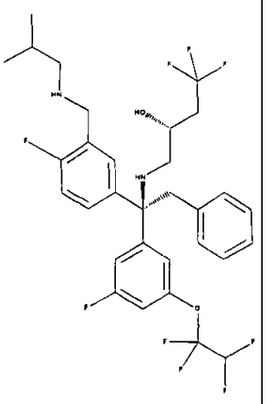
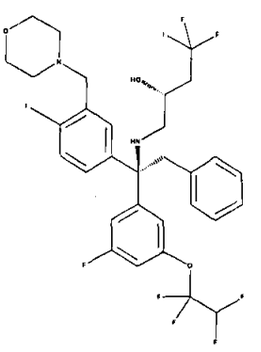
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 741 |  | (R)-4,4,4-trifluoro-1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletilamino) butan-2-ol | 1.835 CL(2) 552.33 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27 y 8 |
| 742 |  | (S)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino) butan-2-ol | 2.00 CL(2) 610.4 $[M+H]^+$ | Procedimientos 3, 109, 110, 111, 112, 113, 114, 27 y 8 |
| 743 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino) butan-2-ol | 2.002 CL(2) 610.4 $[M+H]^+$ | Procedimientos 3, 109, 110, 111, 112, 113, 114, 27 y 8 |

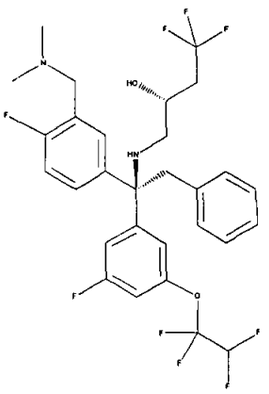
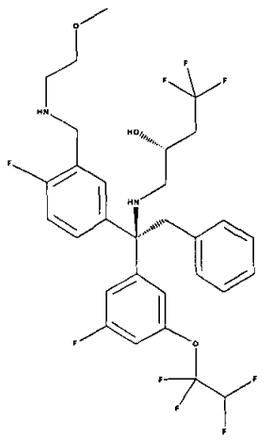
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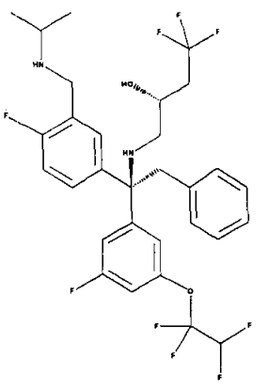
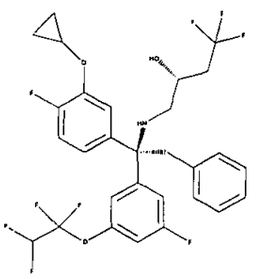
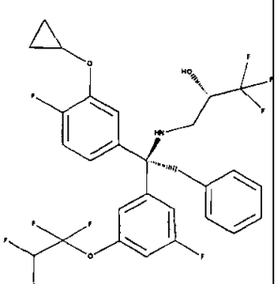
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 744 |  | (R)-1,1,1-trifluoro-3-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino) propan-2-ol | 2.25 CL(2) 596.2 $[M+H]^+$ | Procedimientos 3, 109, 110, 111, 112, 113, 114, 27 y 8 |
| 745 |  | (S)-1,1,1-trifluoro-3-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino) propan-2-ol | 2.21 CL(2) 596.1 $[M+H]^+$ | Procedimientos 3, 109, 110, 111, 112, 113, 114, 27 y 8 |
| 746 |  | 4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-((R)-4,4,4-trifluoro-2-hidroxibutilamino) etil) benzonitrilo | 0.92 CL(12) 592 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, y 56 |

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| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 747 |  | 4-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-fenil-1-((R)-4,4,4-trifluoro-2-hidroxibutilamino) etil)benzoato de metilo | 0.91 CL(12) 592 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, 56 y 57 |
| 748 |  | (R)-1-((R)-1-(4-(aminometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-4,4,4-trifluorobutan-2-ol | 1.33 CL(2) | Procedimientos 3, 4, 5, 6, 27, 8, 56 y 101 |
| 749 |  | (R)-1-((R)-1-(3-((ciclopropilamino )metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-4,4,4-trifluorobutan-2-ol | 7.418 CL(7) 621 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, 146, 147 y 148 |

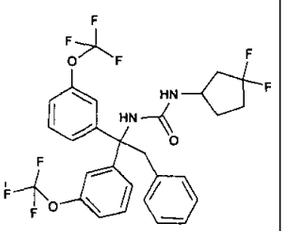
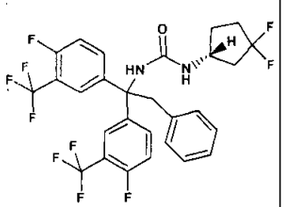
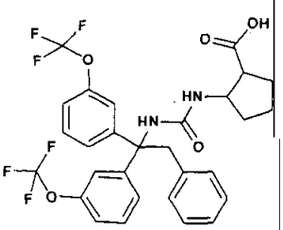
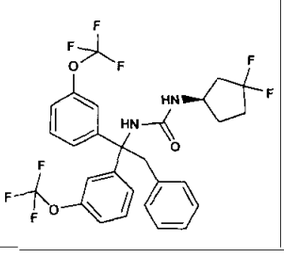
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 750 |  | (R)-1-((R)-1-(3-((butilamino)metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)-4,4,4-trifluorobutan-2-ol | 7.418 CL(7) 637 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, 146, 147 y 148 |
| 751 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-((isobutilamino)metil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)butan-2-ol | 4.46 CL(15) 637 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, 146, 147 y 148 |
| 752 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-(morfolinmetil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)butan-2-ol | 7.033 CL(7) 651 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 27, 8, 146, 147 y 148 |

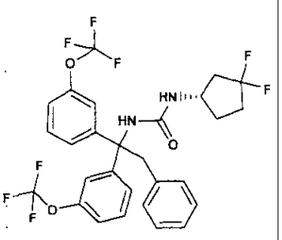
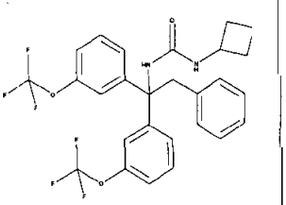
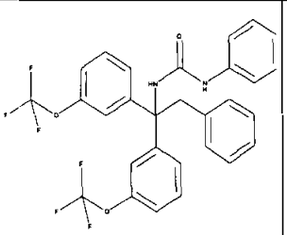
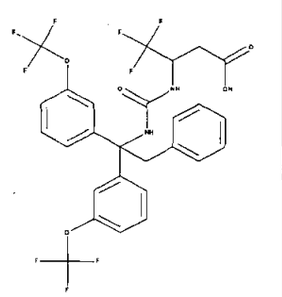
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 753 |  | (R)-1-((R)-1-(3-((dimetilamino) metil)-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-4,4,4-trifluorobutan-2-ol | 7.133 CL(7) 609 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 27, 8, 146, 147 y 148 |
| 754 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-((2-metoxietilamino) metil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino) butan-2-ol | 6.90 CL(7) 639 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 27, 8, 146, 147 y 148 |

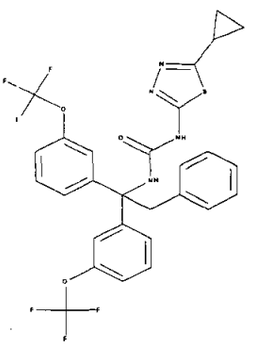
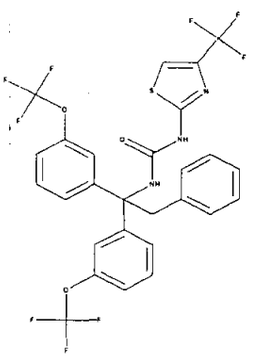
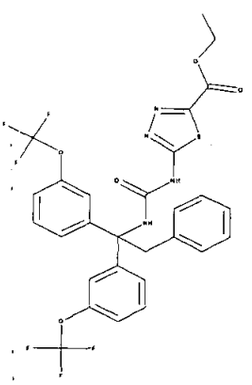
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 755 |  | (R)-4,4,4-trifluoro-1-((R)-1-(4-fluoro-3-((isopropilamino)metil)fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)butan-2-ol | 7.241 CL(7) 623 $[M+H]^+$ | Procedimientos 3, 62, 5, 6, 27, 8, 146, 147 y 148 |
| 756 |  | (R)-1-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)-4,4,4-trifluorobutan-2-ol | 3.99 CL(1) 608.0 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, 59, 106 y 107 |
| 757 |  | (S)-3-((R)-1-(3-ciclopropoxi-4-fluorofenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi)fenil)-2-feniletilamino)-1,1,1-trifluoropropan-2-ol | 4.19 CL(1) 594.0 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 27, 8, 59, 106 y 107 |

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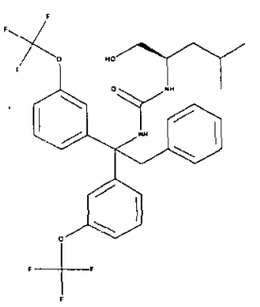
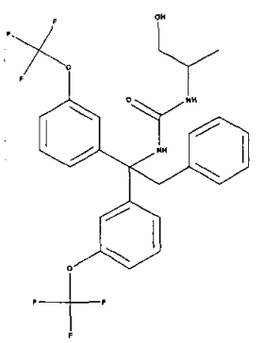
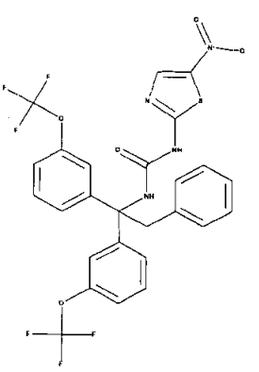
**TABLA 12**

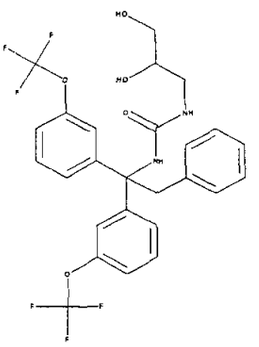
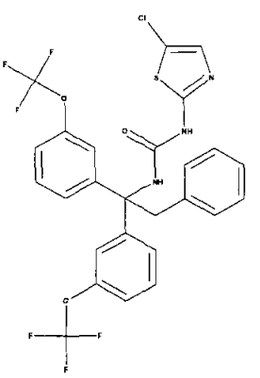
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 758 |  | 1-(3,3-difluorociclopentil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)urea | 4.25 CL(3) 589.3 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 759 |  | (R)-1-(1,1-bis(4-fluoro-3-(trifluorometil)fenil)-2-feniletil)-3-(3,3-difluorociclopentil)urea | 4.13 CL(3) 593.3 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 760 |  | Acido 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)ureido)ciclopentano carboxílico | 3.408 CL(1) 597.03 $[M+H]^+$ | Procedimientos 11, 6 y 10 |
| 761 |  | (R)-1-(3,3-difluorociclopentil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)urea | 4.21 CL(3) 589.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 762 |  | (S)-1-(3,3-difluorociclopentil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)urea | 4.206 CL(3) 589.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 763 |  | 1-ciclobutil-3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)urea | 4.25 CL(4) 539.11 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 764 |  | 1-fenil-3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)urea | 4.281 CL(4) 561.06 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 765 |  | Acido 4,4,4-trifluoro-3-(3-(2-fenil-1,1-bis(3-(trifluorometoxi)fenil)etil)ureido)butanoico | 624.452 CL(4) LC 625.10 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

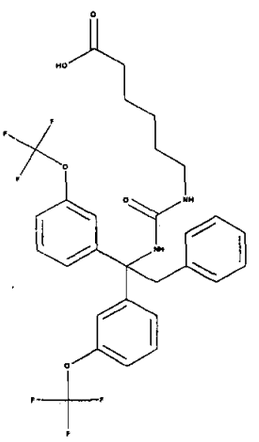
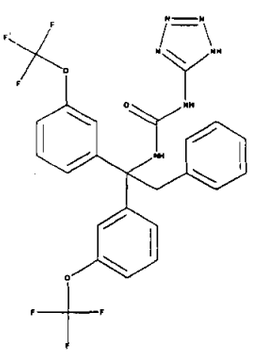
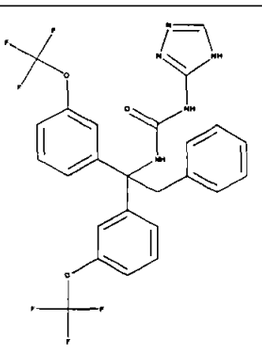
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 766 |  | 1-(5-ciclopropil-1,3,4-tiadiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.39 CL(4) 609.11 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 767 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(4-(trifluorometil) tiazol-2-il)urea | 4.44 CL(4) 636.06 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 768 |  | 5-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido)-1,3,4-tiadiazol-2-carboxilato de etilo | 4.42 CL(4) 641.09 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

(731)

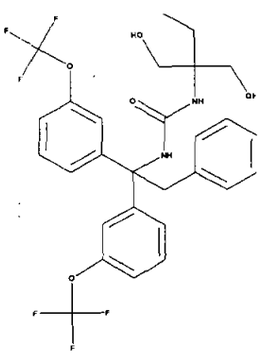
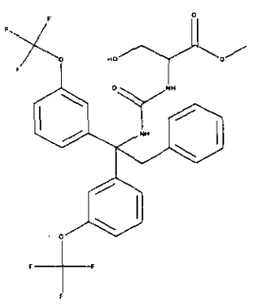
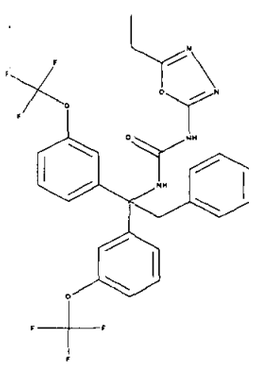
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 769 |  | (R)-1-(1-hidroxi-4-metilpentan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.27 CL(4) 585.23 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 770 |  | 1-(1-hidroxipropan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.18 CL(4) 543.21 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 771 |  | 1-(5-nitrotiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.40 CL(4) 612.50 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 772 |  | 1-(2,3-dihidroxipropil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.11 CL(4) 559.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 773 |  | 1-(5-clorotiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.56 CL(4) 602.05 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

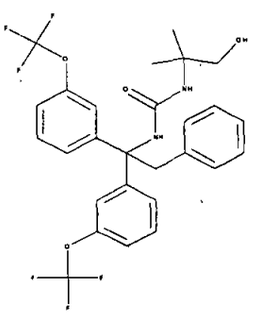
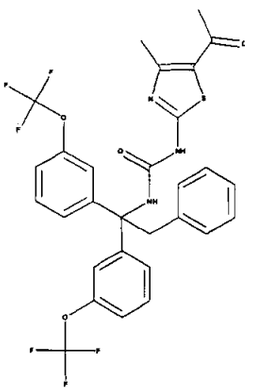
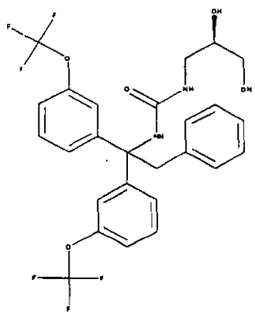
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| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 774 |  | Ácido 6-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) hexanoico | 4.20 CL(4) 599.18 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 775 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(1H-tetrazol-5-il)urea | 4.06 CL(4) 553.16 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 776 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(4H-1,2,4-triazol-3-il)urea | 4.05 CL(4) 552.17 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

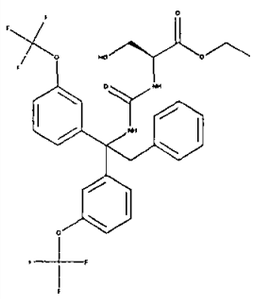
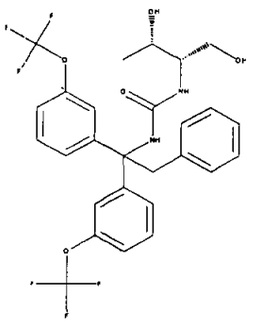
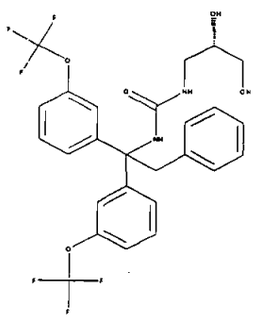
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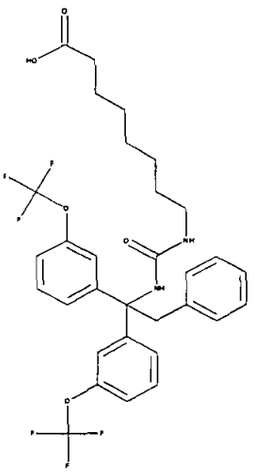
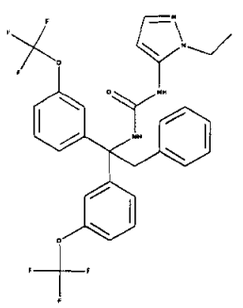
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 777 |  | 1-(1-hidroxi-2-(hidroximatil)butan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.20 CL(4) 587.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 778 |  | 3-hidroxi-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de metilo | 4.07 CL(4) 587.16 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 779 |  | 1-(5-etil-1,3,4-oxadiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.25 CL(4) 581.16 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

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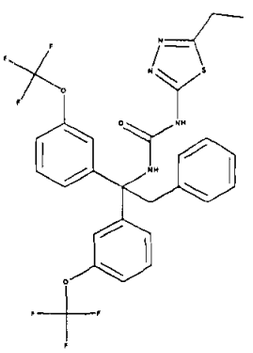
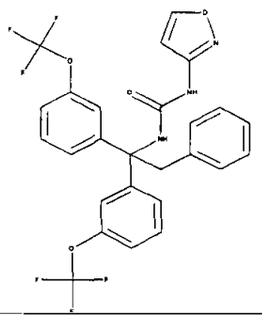
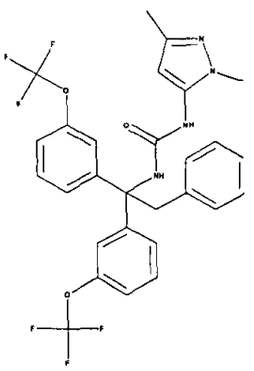
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 780 |  | 1-(1-hidroxi-2-metilpropan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.14 CL(4) 557.25 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 781 |  | 1-(5-acetil-4-metiltiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.28 CL(4) 624.11 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 782 |  | (R)-1-(2,3-dihidroxipropil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.04 CL(4) 559.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

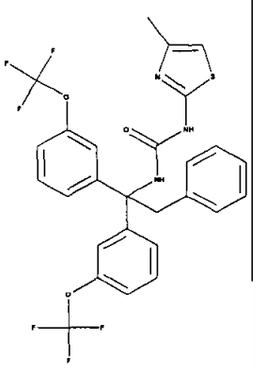
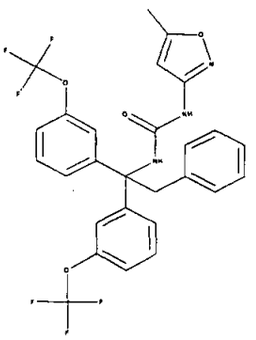
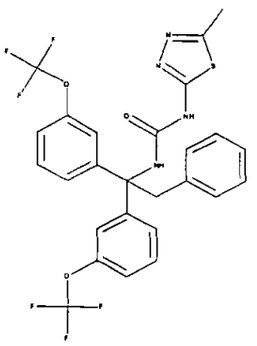
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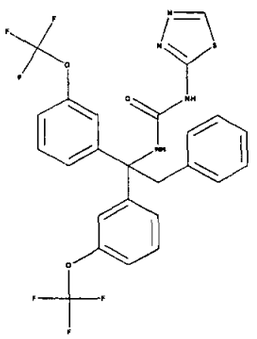
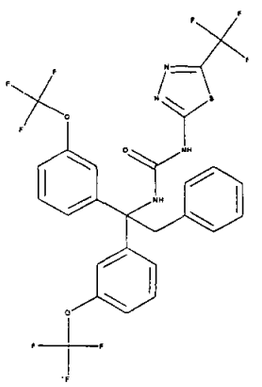
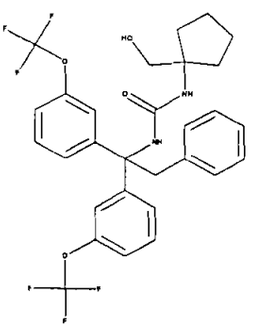
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 783 |  | (S)-etil 3-hidroxi-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato | 4.13 CL(4) 601.17 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 784 |  | 1-((2S,3S)-1,3-dihidroxibutan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.07 CL(4) 573.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 785 |  | (S)-1-(2,3-dihidroxipropil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.03 CL(4) 559.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

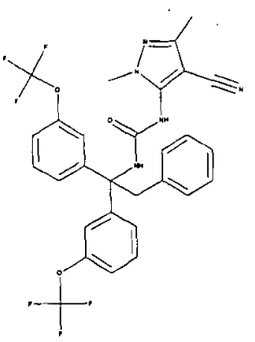
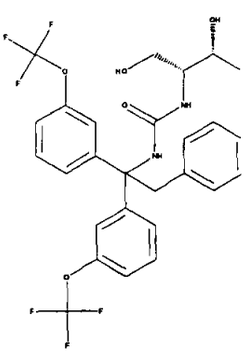
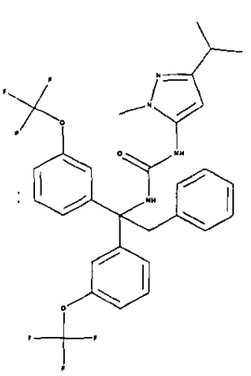
| Ej. No: | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 786 |  | Ácido 8-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) octanoico | 4.22 CL(4) 627.26 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 787 |  | 1-(1-etil-1H-pirazol-5-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.09 CL(4) 579.21 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

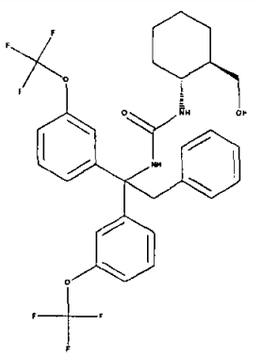
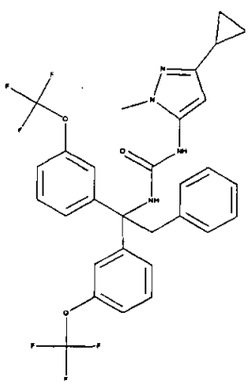
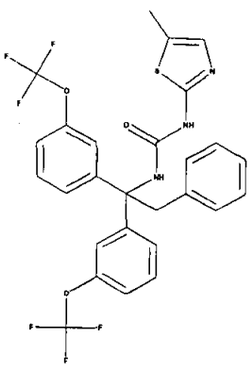
1738

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 788 |  | 1-(5-etil-1,3,4-tiadiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.27 CL(4) 597.11 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 789 |  | 1-(isoxazol-3-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.16 CL(4) 552.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 790 |  | 1-(1,3-dimetil-1H-pirazol-5-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.99 CL(4) 579.20 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

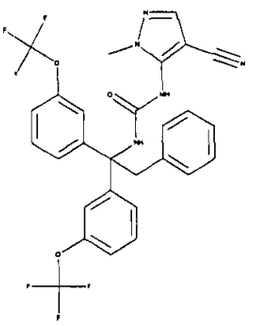
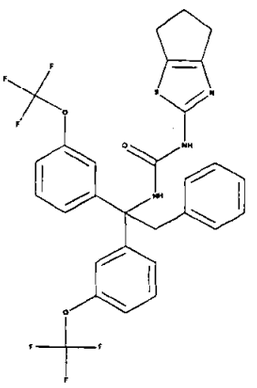
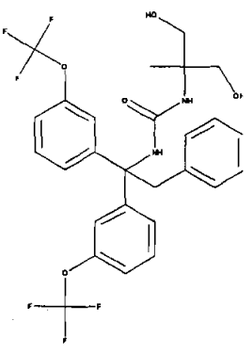
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 791 |  | 1-(4-metiltiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.21 CL(4) 582.12 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 792 |  | 1-(5-metilisoxazol-3-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.23 CL(4) 566.18 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 793 |  | 1-(5-metil-1,3,4-tiadiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.18 CL(4) 583.12 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

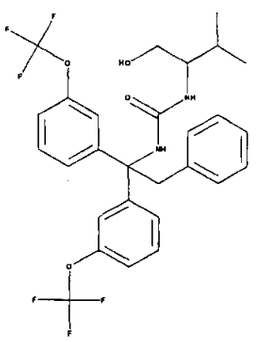
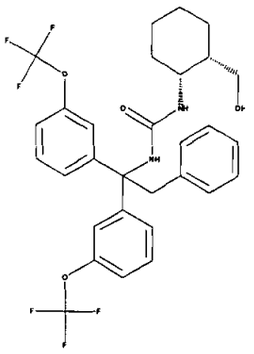
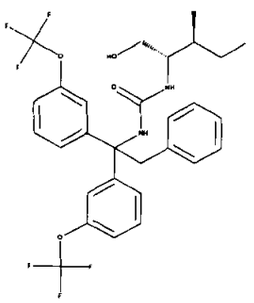
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 794 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(1,3,4-tiadiazol-2-il)urea | 4.13 CL(4) 569.13 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 795 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(5-(trifluorometil)-1,3,4-tiadiazol-2-il)urea | 4.49 CL(4) 637.07 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 796 |  | 1-(1-(hidroximetil) ciclopentil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.22 CL(4) 583.23 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 797 |  | 1-(4-ciano-1,3-dimetil-1H-pirazol-5-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.04 CL(4) 603.98 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 798 |  | 1-((2R,3R)-1,3-dihidroxibutan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.07 CL(4) 573.19 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 799 |  | 1-(3-isopropil-1-metil-1H-pirazol-5-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.12 CL(4) 607.23 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

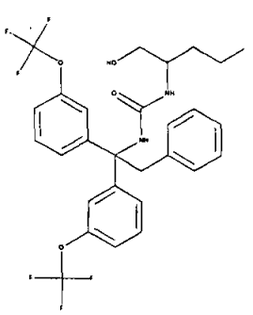
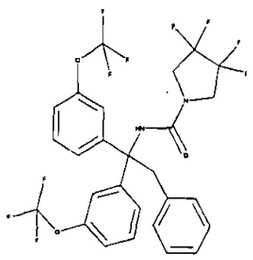
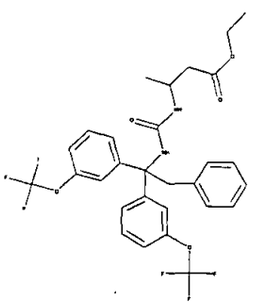
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 800 |  | 1-((1R,2R)-2-(hidroximetil) ciclohexil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.24 CL(4) 597.21 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 801 |  | 1-(3-ciclopropil-1-metil-1H-pirazol-5-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.09 CL(4) 605.21 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 802 |  | 1-(5-metiltiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.21 CL(4) 582.12 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

1743

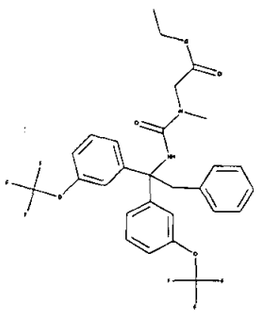
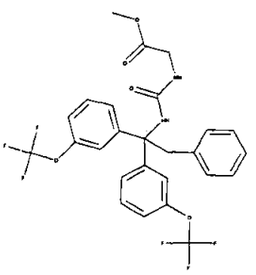
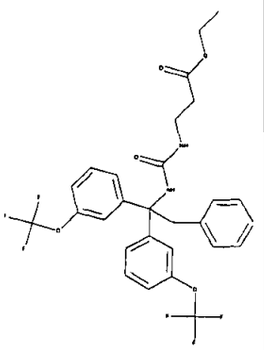
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 803 |  | 1-(4-ciano-1-metil-1H-pirazol-5-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.05 CL(4) 590.18 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 804 |  | 1-(5,6-dihidro-4H-ciclopenta[d]tiazol-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.40 CL(4) 608.12 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 805 |  | 1-(1,3-dihidroxi-2-metilpropan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.08 CL(4) 573.22 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 806 |  | 1-(1-hidroxi-3-metilbutan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.20 CL(4) 571.24 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 807 |  | 1-((1R,2S)-2-(hidroximetil) ciclohexil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.23 CL(4) 597.23 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 808 |  | 1-((2S,3S)-1-hidroxi-3-metilpentan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.26 CL(4) 585.24 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

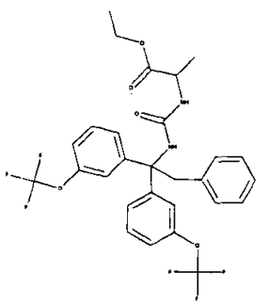
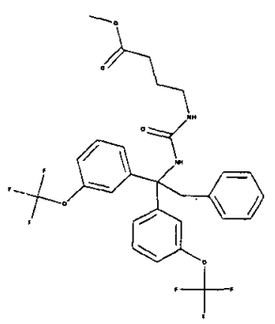
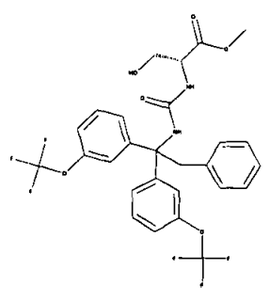
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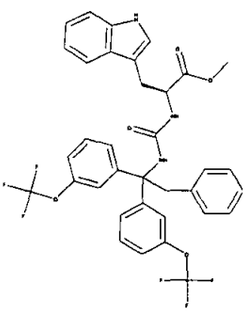
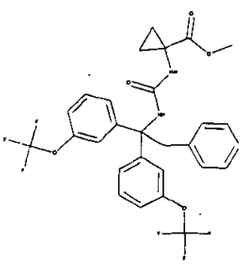
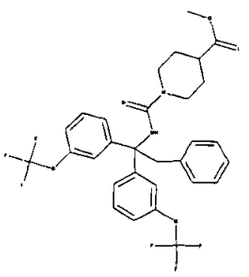
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 809 |  | 1-(1-hidroxipentan-2-il)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.21 CL(4) 571.23 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 810 |  | 3,3,4,4-tetrafluoro-N-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)pirrolidin-1-carboxamida | 3.868 CL(3) 611.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 811 |  | etil 3-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) butanoato | 3.81 CL(10) 599.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

1746

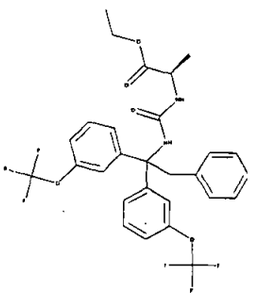
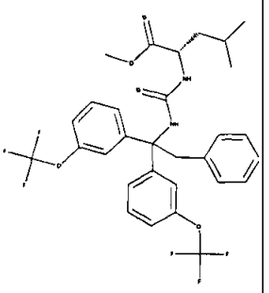
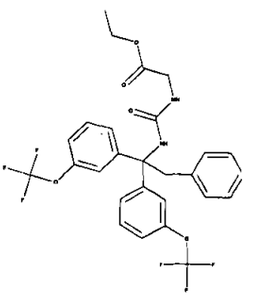
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 812 |  | 2-(1-metil-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) acetato de etilo | 3.85 CL(10) 585.4 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 813 |  | 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) acetato de metilo | 3.57 CL(10) 557.4 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 814 |  | 3-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de etilo | 3.71 CL(10) 585.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

1147

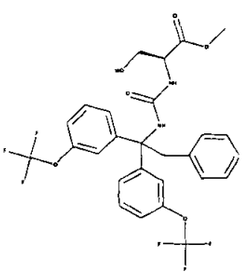
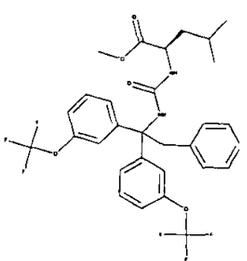
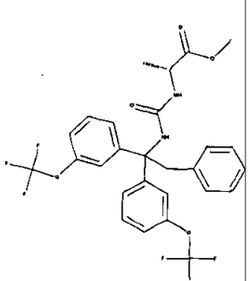
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 815 |  | 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de etilo | 3.78 CL(10) 585.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 816 |  | 4-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) butanoato de metilo | 3.62 CL(10) 585.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 817 |  | 3-hidroxi-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de (R)-metilo | 3.39 CL(10) 587.4 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

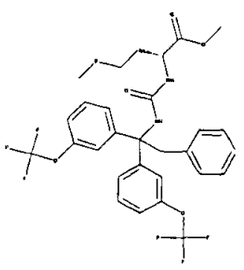
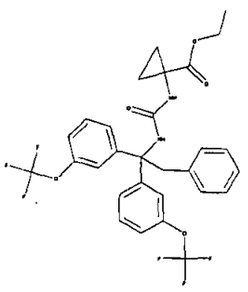
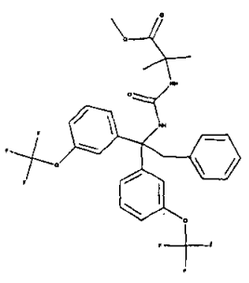
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 818 |  | 3-(1H-indol-3-il)-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de (S)-metilo | 3.85 CL(10) 685.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 819 |  | 1-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) ciclopropano carboxilato de metilo | 3.63 CL(10) 583.4 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 820 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilcarbamoil) piperidin-4-carboxilato de metilo | 3.81 CL(10) 611.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

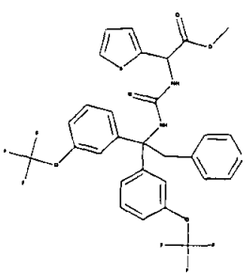
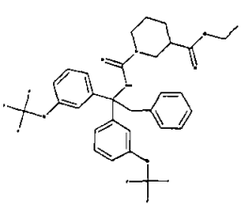
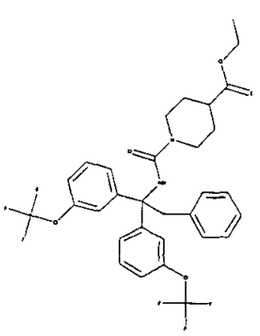
1749

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 821 |  | 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) propanoato de (R)-etilo | 3.79 CL(10) 585.5 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 822 |  | 4-metil-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) pentanoato de (S)-metilo | 4.04 CL(10) 613.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 823 |  | 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) acetato de etilo | 3.74 CL(10) 571.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

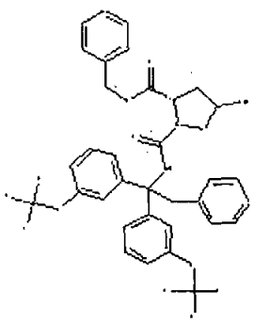
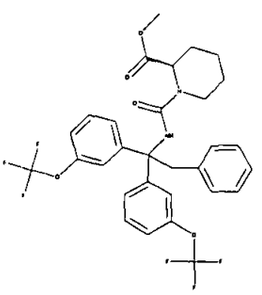
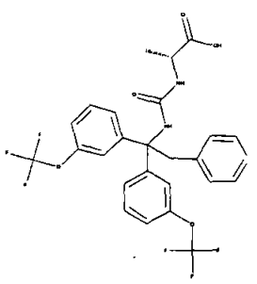
1250

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 824 |  | 3-hidroxi-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de (S)-metilo | 3.44 CL(10) 587.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 825 |  | 4-metil-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) pentanoato de (R)-metilo | 4.04 CL(10) 613.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 826 |  | 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) propanoato de (R)-metilo | 3.73 CL(10) 571.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 827 |  | 4-(metiltio)-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) butanoato de (R)-metilo | 3.88 CL(10) 631.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 828 |  | 1-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) ciclopropano carboxilato de etilo | 3.80 CL(10) 597.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 829 |  | 2-metil-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoato de metilo | 3.80 CL(10) 585.0 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 830 |  | 2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)ureido) -2-(tiofen-2-il)acetato de metilo | 3.92 CL(10) 639.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 831 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilcarbamoil) piperidin-3-carboxilato de etilo | 3.99 CL(10) 625.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 832 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilcarbamoil) piperidin-4-carboxilato de etilo | 3.90 CL(10) 625.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |

1753

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 833 |  | 4-hidroxi-1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etilcarbamoil) pirrolidin-2-carboxilato de (2S)-bencilo | 3.76 CL(10) 689.2 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 834 |  | 1-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil carbamoil) piperidin-2-carboxilato de (R)-metilo | 3.95 CL(10) 611.1 $[M+H]^+$ | Procedimientos 11, 6 y 12 |
| 835 |  | Ácido (R)-2-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) propanoico | 2.62 CL(10) 557.1 $[M+H]^+$ | Procedimientos 11, 6, 12 y 23 |

1759

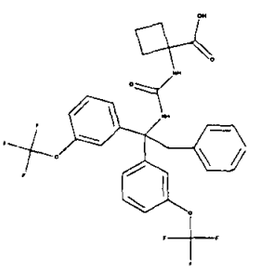
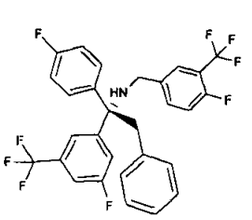
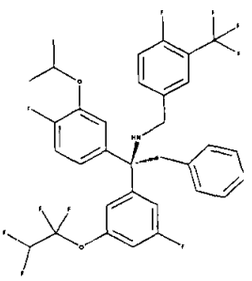
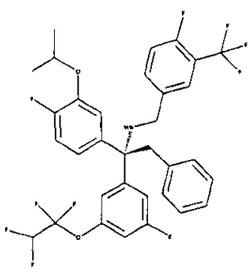
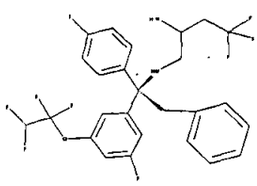
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 836 |  | Ácido 1-(3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)ureido) ciclobutano carboxílico | 2.94 CL(10) 583.1 $[M+H]^+$ | Procedimientos 11, 6, 12 y 23 |

**TABLA 13**

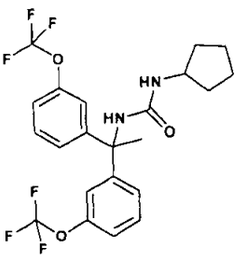
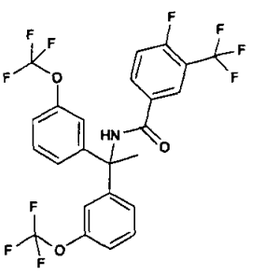
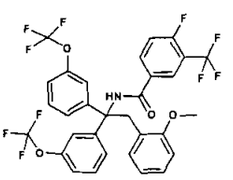
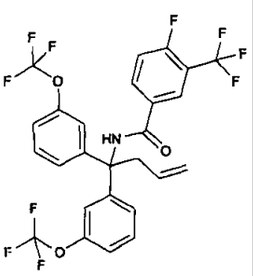
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 837 |  | (S)-N-(4-fluoro-3-(trifluorometil)bencil)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletanamina | 4.32 CL(1) 553.90 $[M+H]^+$ | Procedimientos 4, 5, 6 y 13 |

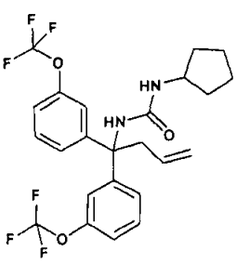
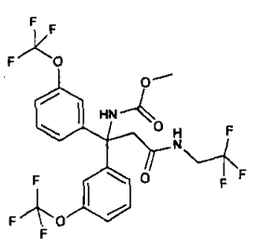
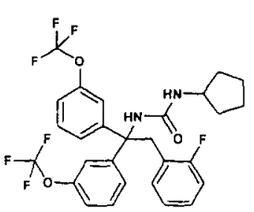
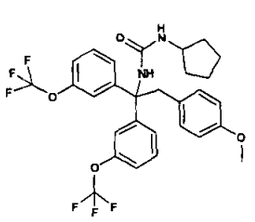
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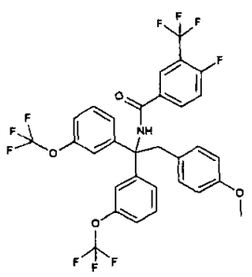
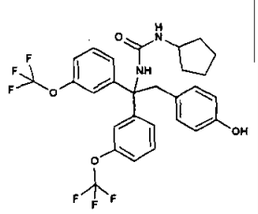
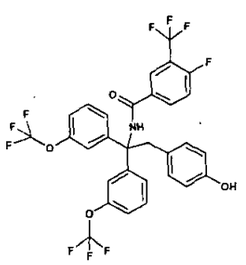
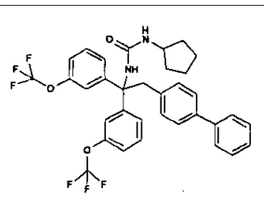
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 838 |  | (R)-N-(4-fluoro-3-(trifluorometil) bencil)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletanamina | 2.23 CL(2) 660.39 $[M+H]^+$ | Procedimientos 109, 110, 111, 112, 113, 114 y 13 |
| 839 |  | (S)-N-(4-fluoro-3-(trifluorometil) bencil)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletanamina | 2.23 CL(2) 660.38 $[M+H]^+$ | Procedimientos 109, 110, 111, 112, 113, 114 y 13 |
| 840 |  | 4,4,4-trifluoro-N1-((R)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-feniletil) butano-1,2-diamina | 3.55 CL(1) 551.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 13 y 141 |

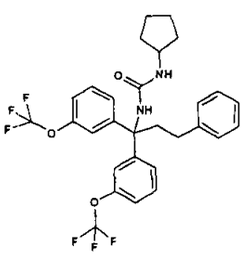
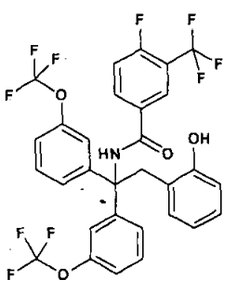
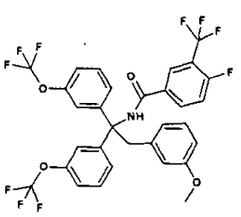
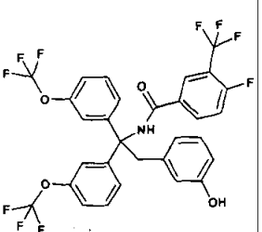
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**TABLA 14**

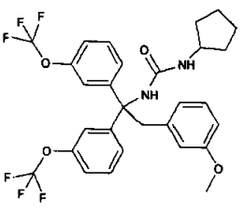
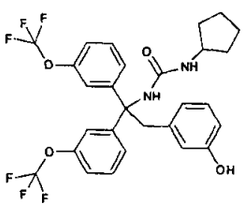
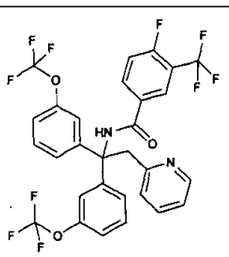
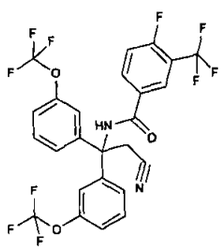
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 841 |  | 1-(1,1-bis(3-(trifluorometoxi) fenil) etil)-3-ciclopentilurea | 4.26 CL(1) 477.34 $[M+H]^+$ | Procedimientos 11, 6 y 2 |
| 842 |  | N-(1,1-bis(3-(trifluorometoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 4.38 CL(1) 556.24 $[M+H]^+$ | Procedimientos 11, 6 y 7 |
| 843 |  | 4-fluoro-N-(2-(2-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.116 CL(1) 661.98 $[M+H]^+$ | Procedimientos 11, 6 y 7 |
| 844 |  | N-(1,1-bis(3-(trifluorometoxi) fenil)but-3-enil)-4-fluoro-3-(trifluorometil) benzamida | 4.37 CL(1) 582.25 $[M+H]^+$ | Procedimientos 11, 6 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 845 |  | 1-(1,1-bis(3-(trifluorometoxi) fenil)but-3-enil)-3-ciclopentilurea | 4.26 CL(1) 503.33 $[M+H]^+$ | Procedimientos 11, 6 y 2 |
| 846 |  | 3-oxo-3-(2,2,2-trifluoroetil amino)-1,1-bis(3-(trifluorometoxi) fenil) propilcarbamato de metilo | 3.81 CL(1) 548.90 $[M+H]^+$ | Procedimientos 11, 6, 14, 23, 128 y 82 |
| 847 |  | 1-ciclopentil-3-(2-(2-fluorofenil)-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 3.766 CL(1) 571.06 $[M+H]^+$ | Procedimientos 11, 6 y 2 |
| 848 |  | 1-ciclopentil-3-(2-(4-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil)etil)urea | 4.37 CL(11) 583.03 $[M+H]^+$ | Procedimientos 11, 6 y 2 |

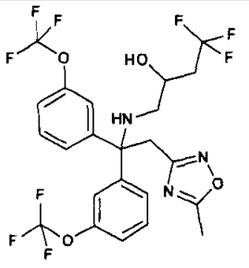
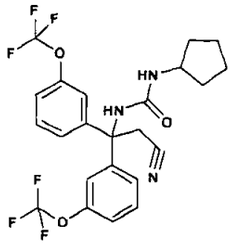
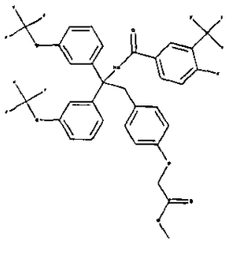
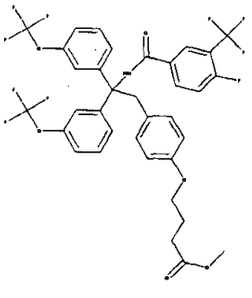
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 849 |  | 4-fluoro-N-(2-(4-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil)etil)-3-(trifluorometil) benzamida | 4.52 CL(11) 661.96 $[M+H]^+$ | Procedimientos 11, 6 y 7 |
| 850 |  | 1-ciclopentil-3-(2-(4-hidroxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.21 CL(11) 569.17 $[M+H]^+$ | Procedimientos 11, 6, 2 y 59 |
| 851 |  | 4-fluoro-N-(2-(4-hidroxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.28 CL(11) 648.12 $[M+H]^+$ | Procedimientos 11, 6, 7 y 59 |
| 852 |  | 1-(2-(bifenil-4-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-ciclopentilurea | 4.74 CL(11) 629.20 $[M+H]^+$ | Procedimientos 11, 6 y 2 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 853 |  | 1-ciclopentil-3-(3-fenil-1,1-bis(3-(trifluorometoxi) fenil)propil)urea | 4.54 CL(11) 567.2 $[M+H]^+$ | Procedimientos 11, 6 y 2 |
| 854 |  | 4-fluoro-N-(2-(2-hidroxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 3.953 CL(1) 648.2 $[M+H]^+$ | Procedimientos 11, 6, 7 y 59 |
| 855 |  | 4-fluoro-N-(2-(3-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.50 CL(11) 662.1 $[M+H]^+$ | Procedimientos 11, 6 y 7 |
| 856 |  | 4-fluoro-N-(2-(3-hidroxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.30 CL(11) 648.1 $[M+H]^+$ | Procedimientos 11, 6, 7 y 59 |

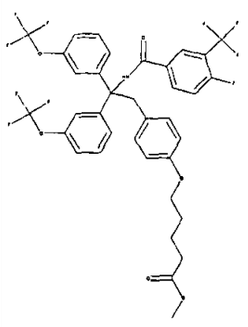
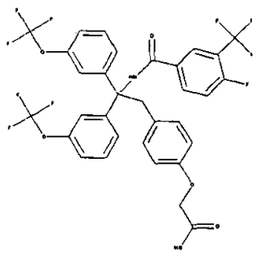
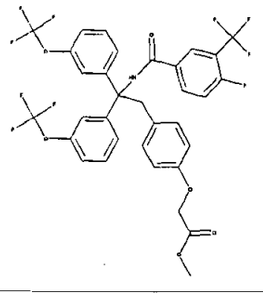
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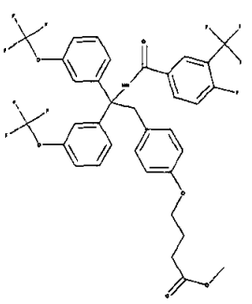
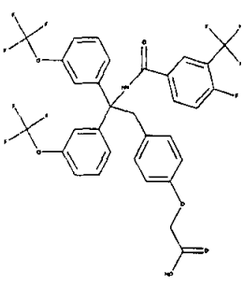
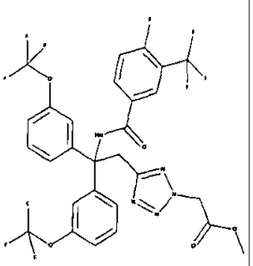
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 857 |  | 1-ciclopentil-3-(2-(3-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.44 CL(11) 583.2 $[M+H]^+$ | Procedimientos 11, 6 y 2 |
| 858 |  | 1-ciclopentil-3-(2-(3-hidroxifenil)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 4.19 CL(11) 569.2 $[M+H]^+$ | Procedimientos 11, 6, 2 y 59 |
| 859 |  | 4-fluoro-N-(2-(pyridin-2-il)-1,1-bis(3-(trifluorometoxi) fenil)etil)-3-(trifluorometil) benzamida | 4.03 CL(1) 633.13 $[M+H]^+$ | Procedimientos 11, 20, 6 y 7 |
| 860 |  | N-(2-ciano-1,1-bis(3-(trifluorometoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 4.04 CL(1) 581.16 $[M+H]^+$ | Procedimientos 11, 18, 6 y 7 |

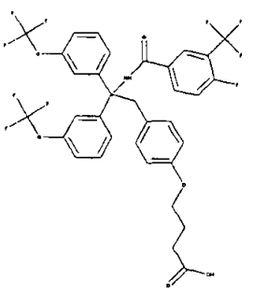
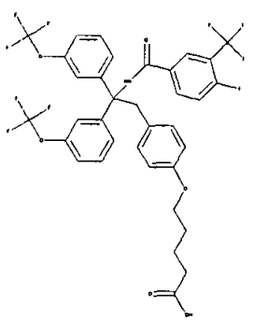
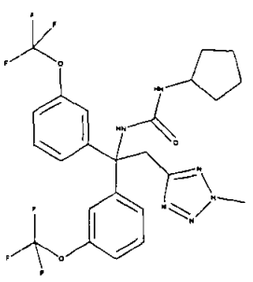
(761)

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 861 |  | 4,4,4-trifluoro-1-(2-(5-metil-1,2,4-oxadiazol-3-il)-1,1-bis(3-(trifluorometoxi) fenil)etilamino) butan-2-ol | 3.78 CL(1) 574.22 $[M+H]^+$ | Procedimientos 11, 17 y 8 |
| 862 |  | 1-(2-ciano-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-ciclopentilurea | 3.83 CL(1) 502.3 $[M+H]^+$ | Procedimientos 11, 18, 6 y 2 |
| 863 |  | 2-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acetato de metilo | 4.37 CL(11) 720.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 68 |
| 864 |  | 4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) butanoato de metilo | 4.50 CL(11) 748.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 68 |

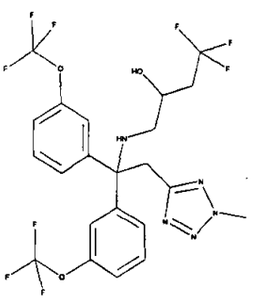
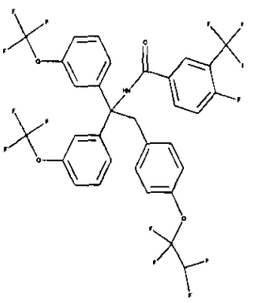
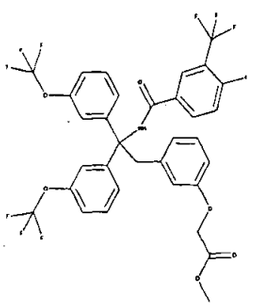
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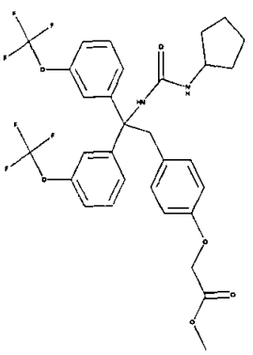
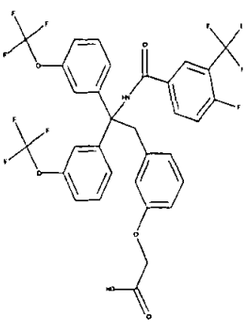
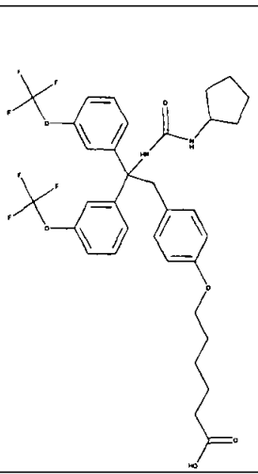
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 865 |  | 5-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) pentanoato de metilo | 4.59 CL(11) 762.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 68 |
| 866 |  | Ácido 2-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acético | 4.28 CL(11) 706.1 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |
| 867 |  | 2-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acetato de metilo | 4.365 CL(11) 720.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 68 |

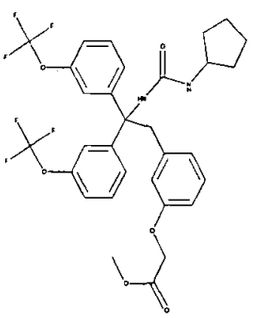
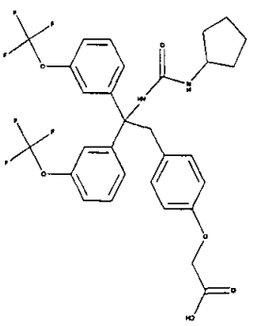
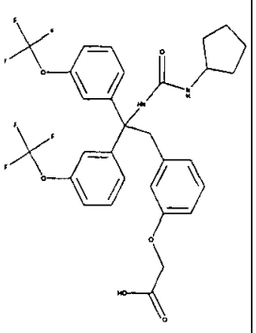
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 868 |  | metil 4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) butanoato | 4.503 CL(11) 748.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 68 |
| 869 |  | Ácido 2-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acético | 4.281 CL(11) 706.1 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |
| 870 |  | metil 2-(5-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)-2H-tetrazol-2-il)acetato | 4.04 CL(1) 696.1 $[M+H]^+$ | Procedimientos 11, 18, 6, 7, 79 y 163 |

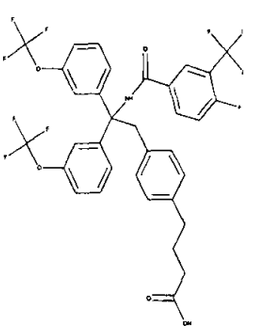
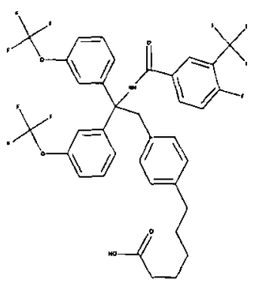
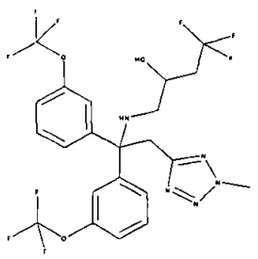
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 871 |  | Ácido 4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) butanoico | 4.336 CL(11) 734.1 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |
| 872 |  | Ácido 5-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) pentanoico | 4.376 CL(11) 748.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |
| 873 |  | 1-ciclopentil-3-(2-(2-metil-2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi) fenil) etil)urea | 3.89 CL(1) 559.26 $[M+H]^+$ | Procedimientos 11, 18, 6, 2, 79 y 80 |

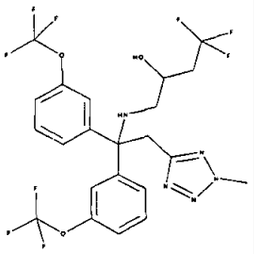
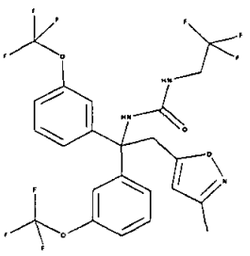
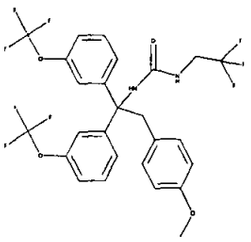
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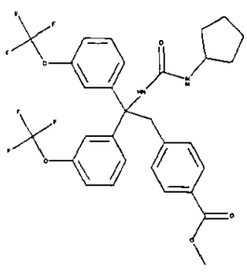
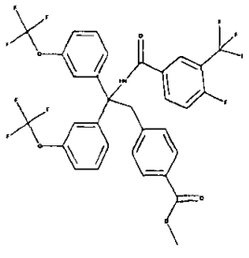
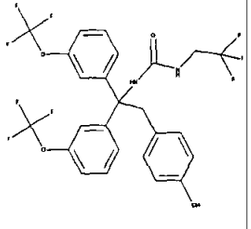
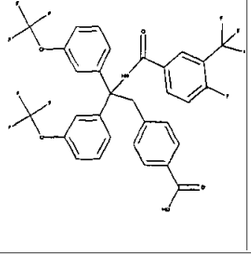
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 874 |  | 4,4,4-trifluoro-1-(2-(2-metil-2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi) fenil) etilamino)butan-2-ol | 3.72 CL(1) 574.23 $[M+H]^+$ | Procedimientos 11, 18, 6, 8, 79 y 80 |
| 875 |  | 4-fluoro-N-(2-(4-(1,1,2,2-tetrafluoroetoxi) fenil)-1,1-bis(3-(trifluorometoxi) fenil)etil)-3-(trifluorometil) benzamida | 4.305 CL(11) 748.1 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 3 |
| 876 |  | 2-(3-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acetato de metilo | 4.363 CL(11) 720.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 68 |

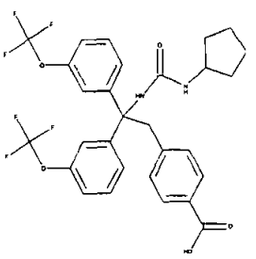
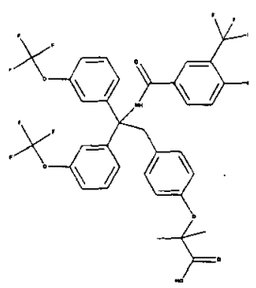
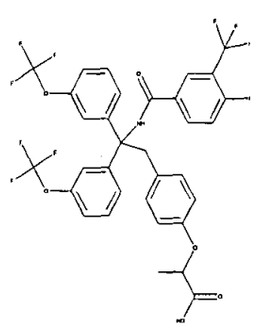
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 877 |  | 2-(4-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)acetato de metilo | 4.293 CL(11) 641.2 $[M+H]^+$ | Procedimientos 11, 6, 2, 59 y 68 |
| 878 |  | Ácido 2-(3-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)acético | 4.286 CL(11) 706.1 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |
| 879 |  | Ácido 6-(4-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)hexanoico | 4.39 CL(11) 683.2 $[M+H]^+$ | Procedimientos 11, 6, 2, 59, 129 y 23 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 880 |  | 2-(3-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)acetato de metilo | 4.278 CL(11) 641.2 $[M+H]^+$ | Procedimientos 11, 6, 2, 59, y 68 |
| 881 |  | Ácido 2-(4-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)acético | 4.223 CL(11) 627.2 $[M+H]^+$ | Procedimientos 11, 6, 2, 59, 68 y 23 |
| 882 |  | Ácido 2-(3-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)acético | 4.198 CL(11) 627.2 $[M+H]^+$ | Procedimientos 11, 6, 2, 59, 68 y 23 |

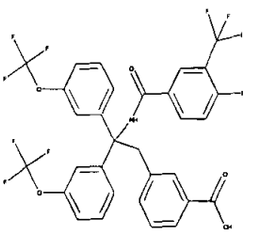
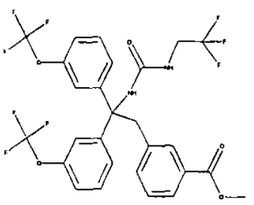
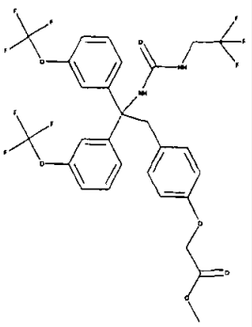
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 883 |  | Ácido 4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenil) butanoico | 2.21 CL(2) 718.1 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75 y 76 |
| 884 |  | Ácido 6-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenil) hexanoico | 2.28 CL(2) 746.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75 y 76 |
| 885 |  | 4,4,4-trifluoro-1-(2-(2-metil-2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi) fenil) etilamino)butan-2-ol | 3.62 CL(1) 574.04 $[M+H]^+$ | Procedimientos 11, 18, 6, 8, 79 y 80 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 886 |  | 4,4,4-trifluoro-1-(2-(2-metil-2H-tetrazol-5-il)-1,1-bis(3-(trifluorometoxi) fenil) etilamino)butan-2-ol | 3.69 CL(1) 574.13 $[M+H]^+$ | Procedimientos 11, 18, 6, 8, 79 y 80 |
| 887 |  | 1-(2-(3-metilisoxazol-5-il)-1,1-bis(3-(trifluorometoxi) fenil)etil)-3-(2,2,2-trifluoroetil)urea | 3.81 CL(1) 572.11 $[M+H]^+$ | Procedimientos 11, 17, 2 y 9 |
| 888 |  | 1-(2-(4-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil)etil)-3-(2,2,2-trifluoroetil)urea | 4.291 CL(11) 597.2 $[M+H]^+$ | Procedimientos 11, 6 y 25 |

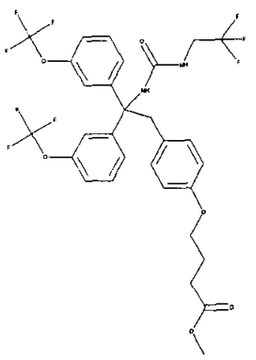
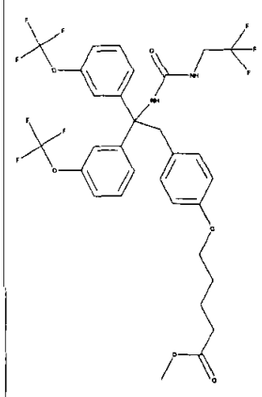
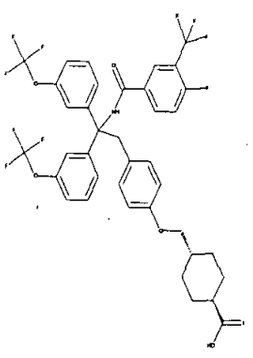
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 889 |  | metil 4-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)benzoato | 4.345 CL(11) 611.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75 y 2 |
| 890 |  | 4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)benzoato de metilo | 4.448 CL(11) 690.1 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75 y 7 |
| 891 |  | 1-(2-(4-hidroxifenil)-1,1-bis(3-(trifluorometoxi)fenil)etil)-3-(2,2,2-trifluoroetil)urea | 4.101 CL(11) 583.2 $[M+H]^+$ | Procedimientos 11, 6, 25 y 59 |
| 892 |  | Acido 4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)benzoico | 4.286 CL(11) 676.1 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75, 7 y 23 |

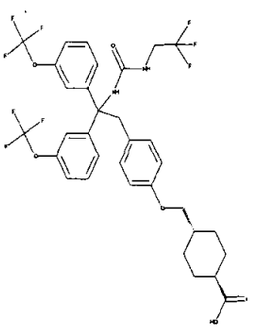
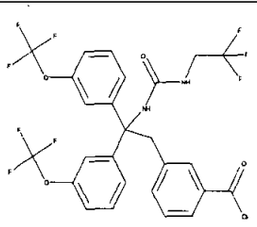
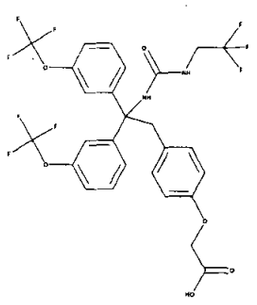
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 893 |  | Acido 4-(2-(3-ciclopentilureido)-2,2-bis(3-(trifluorometoxi)fenil)etil)benzoico | 4.208 CL(11) 597.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75, 2 y 23 |
| 894 |  | Acido 2-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)-2-metilpropanoico | 4.366 CL(11) 734.1 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |
| 895 |  | Acido 2-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2,2-bis(3-(trifluorometoxi)fenil)etil)fenoxi)propanoico | 4.388 CL(11) 719.87 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 68 y 23 |

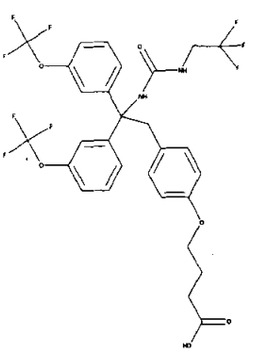
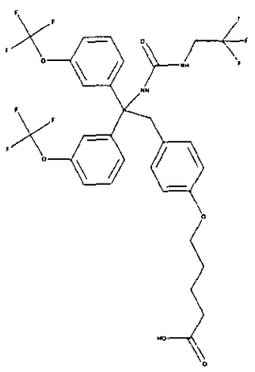
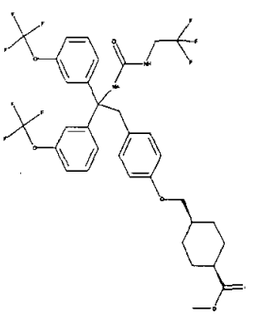
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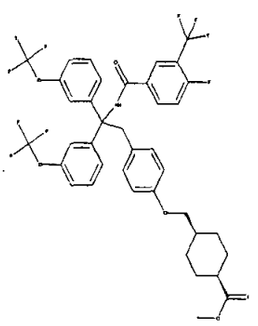
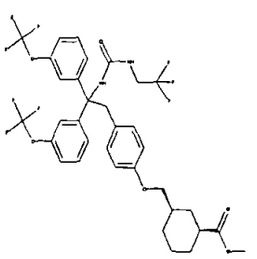
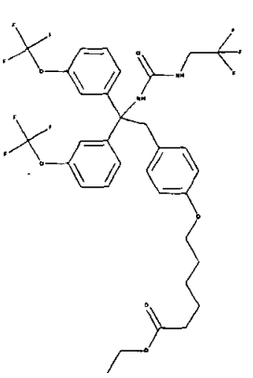
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 896 |  | Acido 3-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil) benzoico | 4.266 CL(11) 675.84 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75, 7 y 23 |
| 897 |  | 3-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil) benzoato de metilo | 4.246 CL(11) 625.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75 y 25 |
| 898 |  | 2-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acetato de metilo | 4.196 CL(11) 655.1 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 68 |

1273

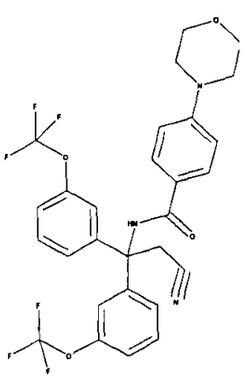
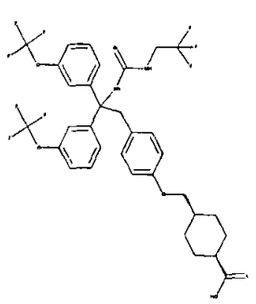
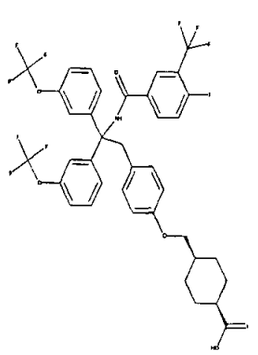
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 899 |  | 4-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) butanoato de metilo | 4.31 CL(11) 683.1 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 68 |
| 900 |  | 5-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) pentanoato de metilo | 4.371 CL(11) 697.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 68 |
| 901 |  | Acido (1r,4 r)-4-((4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclo hexancarboxílico | 4.546 CL(11) 788.3 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 129 |

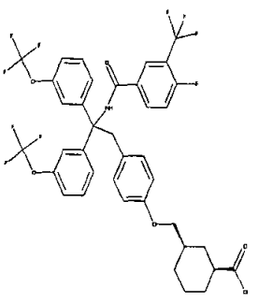
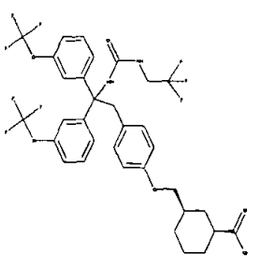
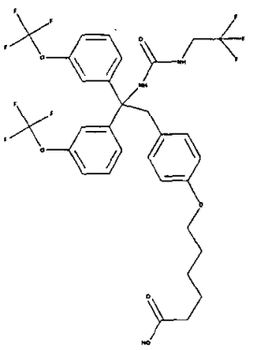
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 902 |  | Acido (1r,4r)-4-((4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxílico | 4.35 CL(11) 723.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 129 |
| 903 |  | Acido 3-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil) benzoico | 4.07 CL(11) 611.1 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 75, 25 y 23 |
| 904 |  | Acido 2-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) acético | 4.13 CL(11) 641.1 $[M+H]^+$ | Procedimientos 11, 6, 25, 59, 68 y 23 |

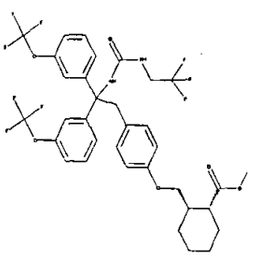
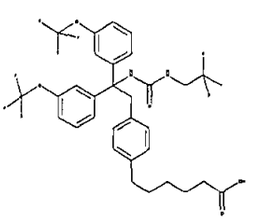
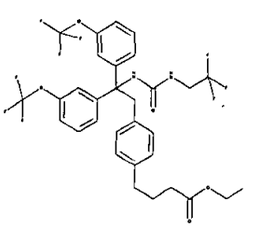
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 905 |  | Acido 4-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) butanoico | 4.188 CL(11) 669.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59, 68 y 23 |
| 906 |  | Acido 5-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) pentanoico | 4.243 CL(11) 683.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59, 68 y 23 |
| 907 |  | 4-((4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxilato de (1s,4s)-metilo | 4.611 CL(11) 737.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 129 |

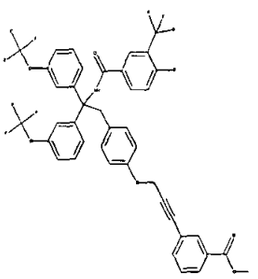
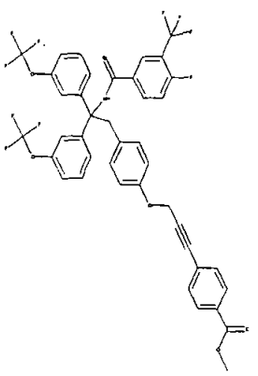
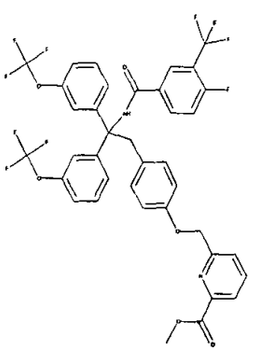
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 908 |  | 4-((4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil) etil)fenoxi)metil) ciclohexano carboxilato de (1s,4s)-metilo | 4.943 CL(11) 802.3 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 129 |
| 909 |  | 3-((4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxilato de (1S,3R)-metilo | 4.61 CL(11) 737.3 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 129 |
| 910 |  | 6-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) hexanoato de etilo | 4.535 CL(11) 725.3 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 129 |

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| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 911 |  | N-(2-ciano-1,1-bis(3-(trifluorometoxi) fenil) etil)-4-morfolinobenzamida | 3.83 CL(1) 580.15 $[M+H]^+$ | Procedimientos 11, 18, 6, y 7 |
| 912 |  | Acido (1s,4s)-4-((4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxílico | 4.413 CL(11) 723.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59, 129 y 23 |
| 913 |  | Acido (1s,4s)-4-((4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxílico | 4.633 CL(11) 788.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 129 y 23 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 914 |  | Acido (1S,3R)-3-((4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxílico | 4.625 CL(11) 788.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59, 129 y 23 |
| 915 |  | Acido (1S,3R)-3-((4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxílico | 4.431 CL(11) 723.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59, 129 y 23 |
| 916 |  | Acido 6-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) hexanoico | 4.315 CL(11) 697.2 $[M+H]^+$ | Procedimientos 11, 6, 25, 59, 129 y 23 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 917 |  | 2-((4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)ciclohexano carboxilato de (1R,2R)-metilo | 4.583 CL(11) 737.3 $[M+H]^+$ | Procedimientos 11, 6, 25, 59 y 129 |
| 918 |  | Acido 6-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenil) hexanoico | 2.205 CL(2) 681.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 77, 24 y 23 |
| 919 |  | 4-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenil) butanoato de etilo | 2.233 CL(2) 681.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 77 y 24 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 920 |  | 3-(3-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) prop-1-inil)benzoato de metilo | 4.90 CL(11) 820.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 129 |
| 921 |  | 4-(3-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) prop-1-inil)benzoato de metilo | 4.856 CL(11) 820.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 129 |
| 922 |  | 6-((4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenoxi) metil)picolinato de metilo | 4.506 CL(11) 797.2 $[M+H]^+$ | Procedimientos 11, 6, 7, 59 y 129 |

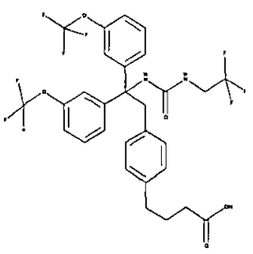
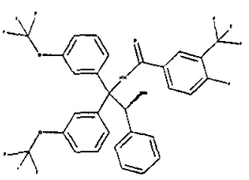
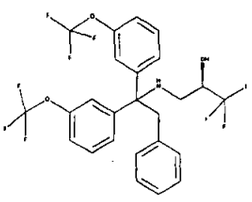
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 923 |  | Acido 4-(4-(2-(3-(2,2,2-trifluoroetil) ureido)-2,2-bis(3-(trifluorometoxi) fenil)etil)fenil) butanoico | 2.128 CL(2) 653.2 $[M+H]^+$ | Procedimientos 11, 72, 73, 74, 77, 24 y 23 |
| 924 |  | (R)-4-fluoro-N-(2-hidroxi-2-fenil-1,1-bis(3-(trifluorometoxi) fenil) etil)-3-(trifluorometil) benzamida | 4.128 CL(11) 648.0 $[M+H]^+$ | Procedimientos 11, 123, 124, 125, 126 y 127 |

**TABLA 15**

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 925 |  | (R)-1,1,1-trifluoro-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etilamino) propan-2-ol | 2.188 CL(2) 554.2 $[M+H]^+$ | Procedimientos 11, 6, 27 y 8 |

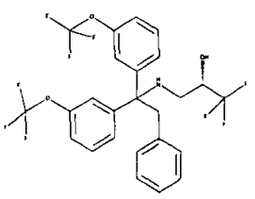
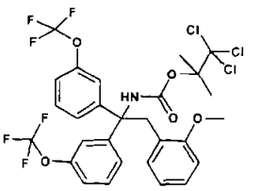
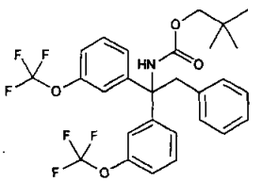
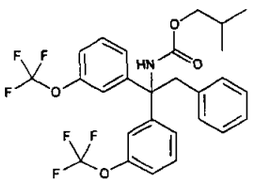
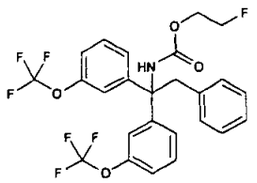
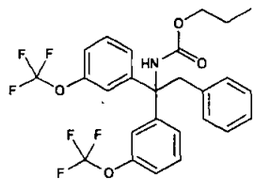
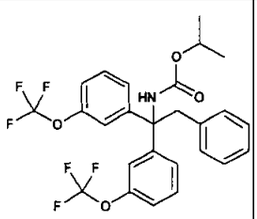
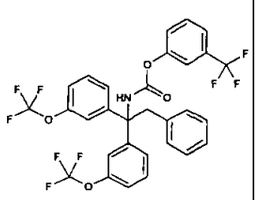
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 926 |  | (S)-1,1,1-trifluoro-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etilamino) propan-2-ol | 2.193 CL(2) 554.2 $[M+H]^+$ | Procedimientos 11, 6, 27 y 8 |

**TABLA 16**

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 927 |  | 1,1,1-tricloro-2-metilpropan-2-il 2-(2-metoxifenil)-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato | 4.266 CL(1) 675.33 $[M+H]^+$ | Procedimientos 11, 6 y 82 |
| 928 |  | 2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato de neopentilo | 4.45 CL(1) 556.25 $[M+H]^+$ | Procedimientos 11, 6 y 82 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 929 |  | 2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato de isobutilo | 4.38 CL(1) 542.20 $[M+H]^+$ | Procedimientos 11, 6 y 82 |
| 930 |  | 2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato de 2-fluoroetilo | 4.17 CL(1) 532.17 $[M+H]^+$ | Procedimientos 11, 6 y 82 |
| 931 |  | 2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato de propilo | 4.30 CL(1) 528.20 $[M+H]^+$ | Procedimientos 11, 6 y 82 |
| 932 |  | 2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato de isopropilo | 4.30 CL(1) 528.20 $[M+H]^+$ | Procedimientos 11, 6 y 82 |
| 933 |  | 2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil-carbamato de 3-(trifluorometil) fenilo | 4.42 CL(1) 630.26 $[M+H]^+$ | Procedimientos 11, 6 y 82 |

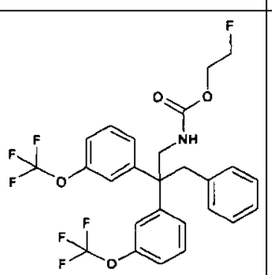
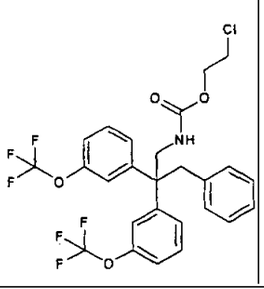
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 934 |  | 3-fenil-2,2-bis(3-(trifluorometoxi) fenil)propil carbamato de 2-fluoroetilo | 4.20 CL(4) 546.14 $[M+H]^+$ | Procedimientos 11, 6 y 82 |
| 935 |  | 3-fenil-2,2-bis(3-(trifluorometoxi) fenil)propil carbamato de 2-cloroetilo | 4.28 CL(4) 562.08 $[M+H]^+$ | Procedimientos 11, 6 y 82 |

**TABLA 17**

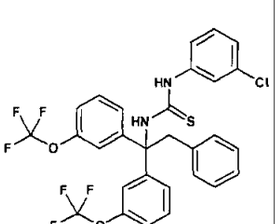
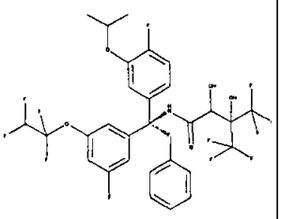
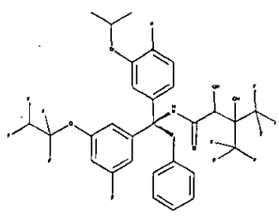
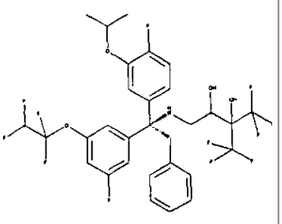
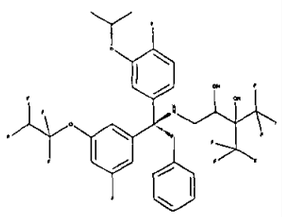
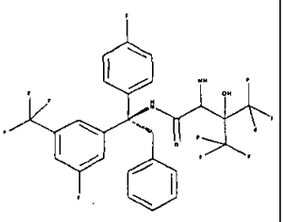
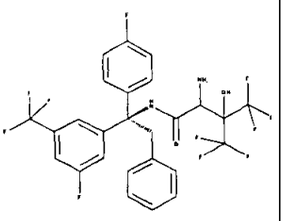
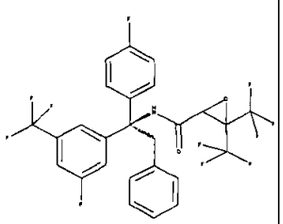
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 936 |  | 1-(3-clorofenil)-3-(2-fenil-1,1-bis(3-(trifluorometoxi) fenil)etil)tiourea | 4.51 CL(1) 612.5 $[M+H]^+$ | Procedimientos 11, 6 y 83 |

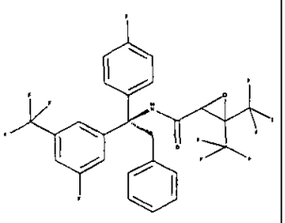
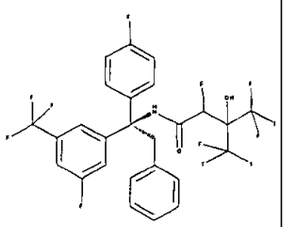
**TABLA 18**

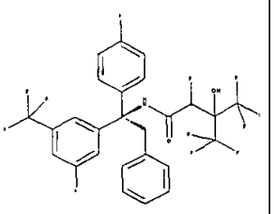
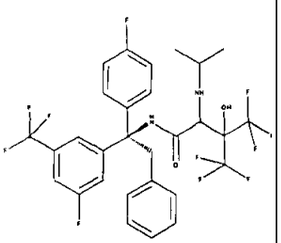
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 937 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil) butanamida | 4.181 CL(11) 708.38 $[M+H]^+$ TR = 40 min (AD, EtOH/MeOH/ heptano, 4% isocrático, 40 ml/min) | Procedimientos 3, 109, 110, 111, 112, 113, 114, 84, 85 y 86 |
| 938 |  | 4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-2,3-dihidroxi-3-(trifluorometil) butanamida | 4.178 CL(11) 708.39 $[M+H]^+$ TR = 50 min (AD, EtOH/MeOH/ heptano, 4% isocrático, 40 ml/min) | Procedimientos 3, 109, 110, 111, 112, 113, 114, 84, 85 y 86 |

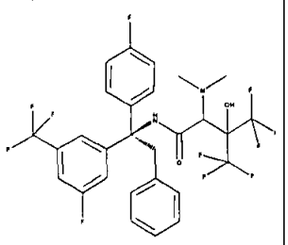
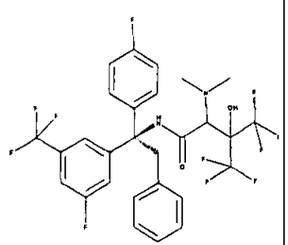
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 939 |  | 1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-2-(trifluorometil)butano-2,3-diol | 4.12 CL(11) 694.39 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 937) | Procedimientos 3, 109, 110, 111, 112, 113, 114, 84, 85, 86 y 89 |
| 940 |  | 1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-2-(trifluorometil)butano-2,3-diol | 4.108 CL(11) 694.39 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 938) | Procedimientos 3, 109, 110, 111, 112, 113, 114, 84, 85, 86 y 89 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 941 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 2.065 CL(2) 601.2 $[M+H]^+$ TR = 11.458 min (Prep CLAR, YMC Sunfire 5µ, C18, 30 X 100 mm, MeOH/$H_2O$/ TFA, 30-100% durante 12 min) | Procedimientos 4, 5, 6, 90, 91 y 92 |

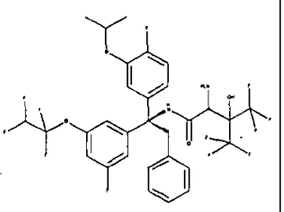
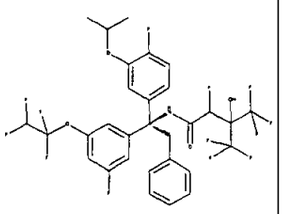
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 942 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 2.085 CL(2) 601.3 $[M+H]^+$ TR = 11.619 min (PrepCLAR, YMC Sunfire 5µ, C18, 30 X 100 mm, MeOH/$H_2O$/ TFA, 30-100% durante 12 min) | Procedimientos 4, 5, 6, 90, 91 y 92 |
| 943 |  | N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3,3-bis(trifluorometil) oxirano-2-carboxamida | 4.186 CL 582.3 $[M-H]^-$ TR = 28-30 min (AD, IPA/heptano, 5% isocrático, 50 ml/min) | Procedimientos 4, 5, 6, 90 y 91 |

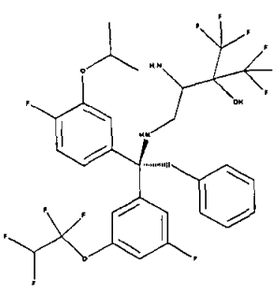
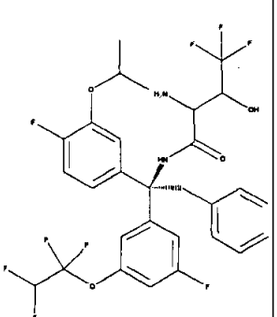
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 944 |  | N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3,3-bis(trifluorometil ) oxirano-2-carboxamida | 4.161 CL 582.3 $[M-H]^-$ TR = 40-45 min (AD, IPA/heptano, 5% isocrático, 50 ml/min) | Procedimientos 4, 5, 6, 90 y 91 |
| 945 |  | 2,4,4,4-tetrafluoro-N-((R)-1-(3-fluoro-5-(trifluorometil)fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 3.98 CL(3) 602.3 $[M-H]^-$ TR = 26.94 min (PrepCLAR, YMC Sunfire 5 µ, C18, 30 X 100mm, MeOH/$H_2O$/ TFA, 40-100% durante 30 min) | Procedimientos 4, 5, 6, 90, 91 y 93 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 946 |  | 2,4,4,4-tetrafluoro-N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 4.043 CL(3) 602.3 $[M-H]^-$ TR = 27.40 min (PrepCLAR, YMC Sunfire 5 µ, C18, 30 X 100mm, MeOH/$H_2O$/ TFA, 40-100% durante 30 min) | Procedimientos 4, 5, 6, 90, 91 y 93 |
| 947 |  | 4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-2-(isopropilamino)-3-(trifluorometil) butanamida | 4.258 CL 643.4 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 944) | Procedimientos 4, 5, 6, 90, 91 y 95 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 948 |  | 2-(dimetilamino)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 4.013 CL 629.2 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 944) | Procedimientos 4, 5, 6, 90, 91 y 95 |
| 949 |  | 2-(dimetilamino)-4,4,4-trifluoro-N-((R)-1-(3-fluoro-5-(trifluorometil) fenil)-1-(4-fluorofenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 4.348 CL 629.3 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 943) | Procedimientos 4, 5, 6, 90, 91 y 95 |

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| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 950 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 2.118 CL(2) 707.4 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 292B) | Procedimientos 3, 109, 110, 111, 112, 113, 114, 90, 91 y 92 |
| 951 |  | 2,4,4,4-tetrafluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-hidroxi-3-(trifluorometil) butanamida | 2.27 CL(2) 710.8 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 292B) | Procedimientos 3, 109, 110, 111, 112, 113, 114, 90, 91 y 92 |

| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 952 |  | 3-amino-1,1,1-trifluoro-4-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletilamino)-2-(trifluorometil) butan-2-ol | 2.06 CL(1) 693.1 $[M+H]^+$ (preparado a partir del precursor del Ejemplo 950) | Procedimientos 109, 110, 111, 112, 113, 114, 90, 91, 92 y 145 |
| 953 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-hidroxibutanamida | 3.69 CL(1) 639.1 $[M+H]^+$ Precursor epóxido quiral tiempo de retención 12.52 min:Chiral pak AD 4.6 x 250mm 10% heptano/IPA | Procedimientos 3, 109, 110, 111, 112, 113, 114, 90, 91 y 92 |

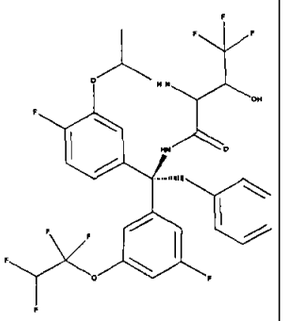
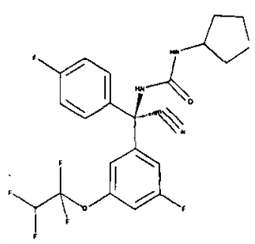
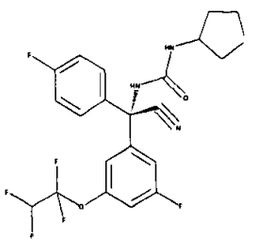
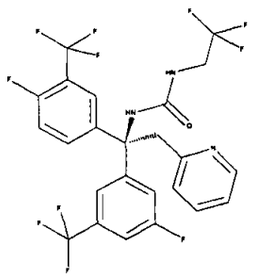
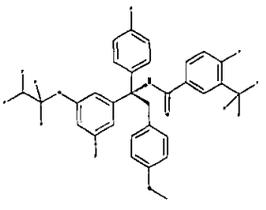
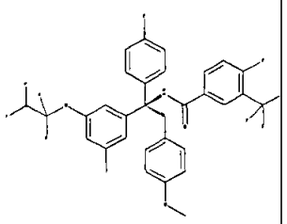
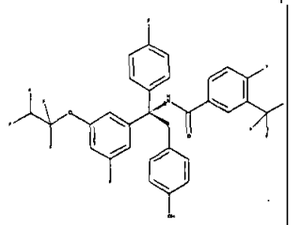
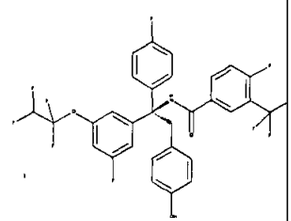
| Ej. No. | Estructura | Nombre | Tiempo de retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 954 |  | 2-amino-4,4,4-trifluoro-N-((R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-3-hidroxibutanamida | 3.67 CL(1) 639.1 $[M+H]^+$ Precursor epóxido quiral tiempo de retención 7.77 min:Chiral pak AD 4.6 x 250mm 10% heptano/IPA | Procedimientos 3, 109, 110, 111, 112, 113, 114, 90, 91 y 92 |

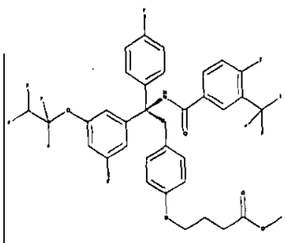
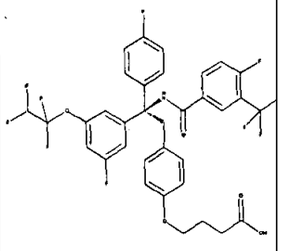
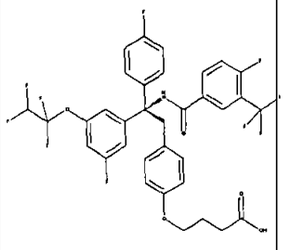
**TABLA 19**

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 955 |  | (R)-1-(ciano(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)(4-fluorofenil) metil)-3-ciclopentilurea | 3.71 CL(1) 472.20 $[M+H]^+$ | Procedimientos 3, 4, 18, 6 y 2 |

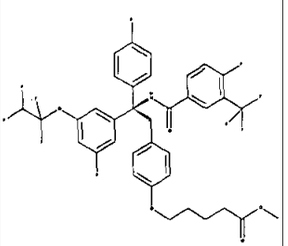
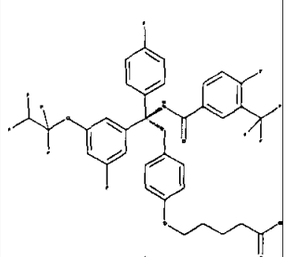
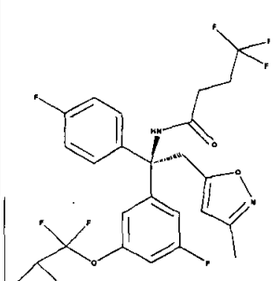
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 956 |  | (S)-1-(ciano(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)(4-fluorofenil) metil)-3-ciclopentilurea | 3.71 CL(1) 472.20 $[M+H]^+$ | Procedimientos 3, 4, 18, 6 y 2 |
| 957 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(trifluorometil) fenil)-2-(pyridin-2-il)etil)-3-(2,2,2-trifluoroetil)urea | 3.25 CL(1) 572.04 $[M+H]^+$ | Procedimientos 4, 5, 6, 2 y 9 |
| 958 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(4-metoxifenil)etil)-3-(trifluorometil) benzamida | 4.326 CL(11) 646.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |

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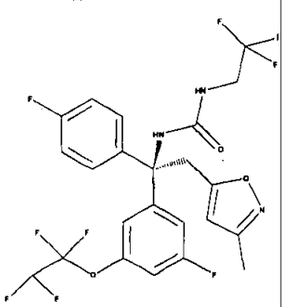
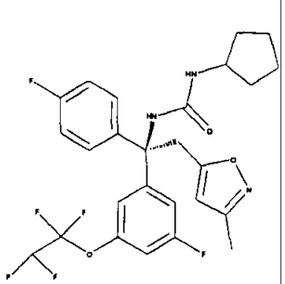
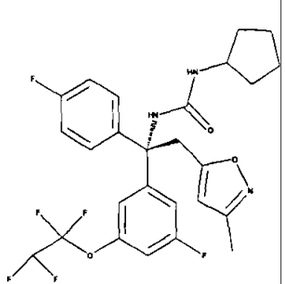
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 959 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(4-metoxifenil)etil)-3-(trifluorometil) benzamida | 4.326 CL(11) 646.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 960 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(4-hidroxifenil)etil) -3-(trifluorometil) benzamida | 4.146 CL(11) 632.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7 y 59 |
| 961 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(4-hidroxifenil)etil) -3-(trifluorometil) benzamida | 4.146 CL(11) 632.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7 y 59 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 962 |  | 4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil) etil)fenoxi) butanoato de (R)-metilo | 4.326 CL(11) 732.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 963 |  | Acido (R)-4-(4-(2-(4-fluoro-3-(trifluorometil)benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)etil) fenoxi)butanoico | 4.215 CL(11) 718.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 68 y 23 |
| 964 |  | Acido (S)-4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)etil) fenoxi)butanoico | 4.193 CL(11) 718.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 68 y 23 |

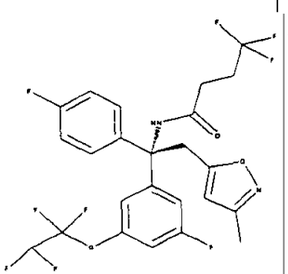
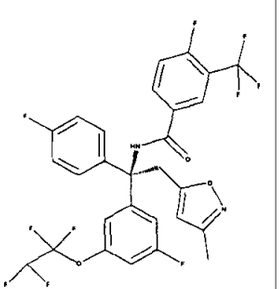
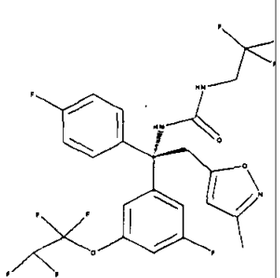
1298

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 965 |  | 5-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil) etil)fenoxi) pentanoato de (R)-metilo | 2.217 CL(2) 746.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 68 |
| 966 |  | Ácido (R)-5-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)etil) fenoxi)pentanoico | 4.230 CL(11) 732.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 68 y 23 |
| 967 |  | (R)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil) butanamida | 3.73 CL(1) 555.65 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17 y 128 |

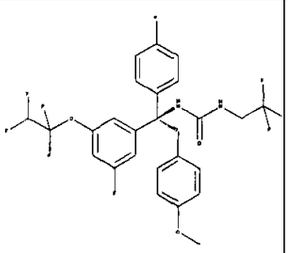
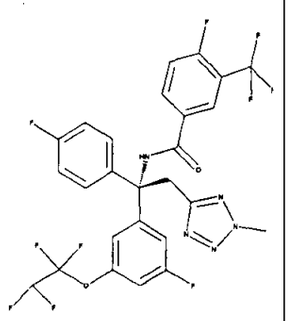
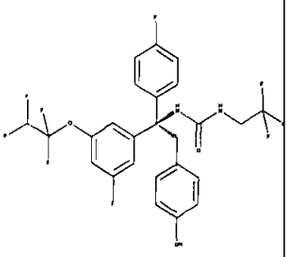
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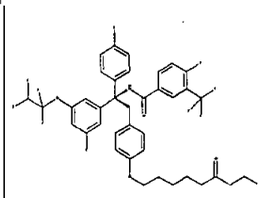
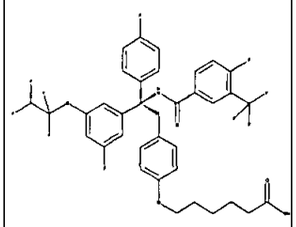
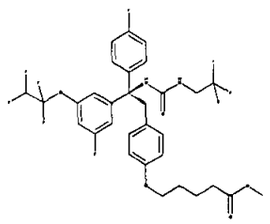
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 968 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil)-3-(2,2,2-trifluoroetil)urea | 3.70 CL(1) 556.68 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17, 2 y 9 |
| 969 |  | (R)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil)urea | 3.80 CL(1) 542.74 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17 y 2 |
| 970 |  | (S)-1-ciclopentil-3-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil)urea | 3.84 CL(1) 542.79 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17 y 2 |

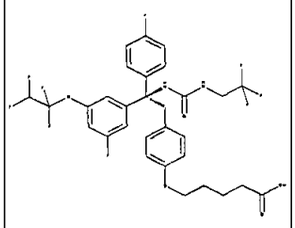
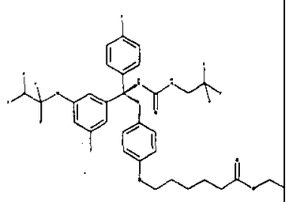
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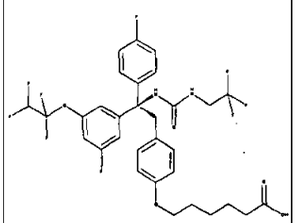
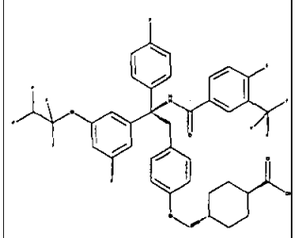
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 971 |  | (S)-4,4,4-trifluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil)butanamida | 3.77 CL(1) 555.73 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17 y 128 |
| 972 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil)-3-(trifluorometil) benzamida | 4.00 CL(1) 621.71 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17 y 7 |
| 973 |  | (S)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(3-metilisoxazol-5-il)etil)-3-(2,2,2-trifluoroetil)urea | 3.71 CL(1) 556.68 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 17, 2 y 9 |

1301

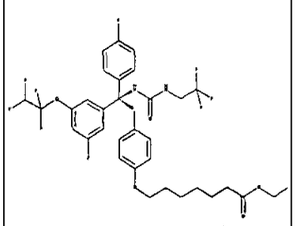
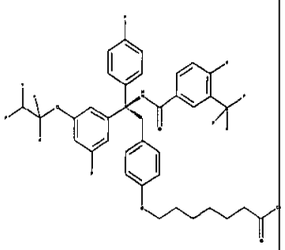
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 974 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(4-metoxifenil)etil)-3-(2,2,2-trifluoroetil)urea | 4.118 CL 581.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 25 |
| 975 |  | (S)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(2-metil-2H-tetrazol-5-il)etil)-3-(trifluorometil) benzamida | 3.97 CL 622.67 $[M+H]^+$ | Procedimientos 3, 4, 5, 18, 6, 7, 79 y 80 |
| 976 |  | (R)-1-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-(4-hidroxifenil)etil) -3-(2,2,2-trifluoroetil)urea | 1.945 CL(2) 567.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25 y 59 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 977 |  | 6-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)etil) fenoxi)hexanoato de (R)-etilo | 2.277 CL(2) 774.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59 y 129 |
| 978 |  | Acido (R)-6-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)etil) fenoxi)hexanoico | 2.172 CL(2) 746.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 129 y 23 |
| 979 |  | 5-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenoxi) pentanoato de (R)-metilo | 2.092 CL(2) 681.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 59 y 68 |

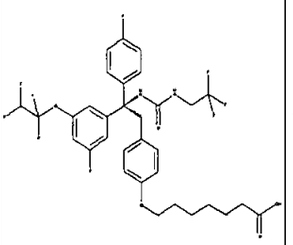
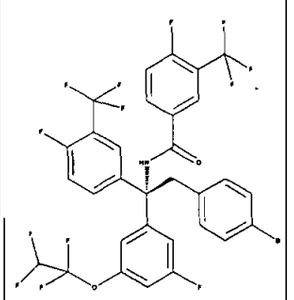
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 980 |  | Acido (R)-5-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenoxi) pentanoico | 2.058 CL(2) 667.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 59, 68 y 23 |
| 981 |  | 6-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenoxi) hexanoato de (R)-etilo | 2.188 CL(2) 709.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 59 y 129 |

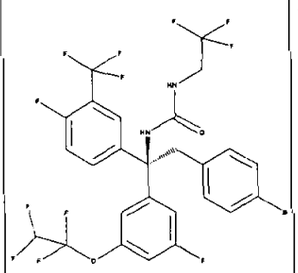
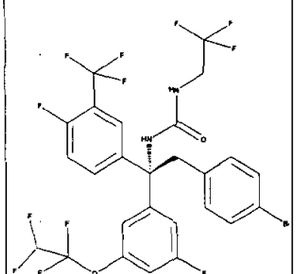
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 982 |  | Acido (R)-6-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenoxi) hexanoico | 2.097 CL(2) 681.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 59, 129 y 23 |
| 983 |  | Acido (1r,4r)-4-((4-((R)-2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil) etil)fenoxi)metil) ciclohexano carboxílico | 2.207 CL(2) 772.1 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 129 y 23 |

805

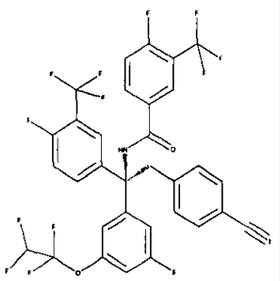
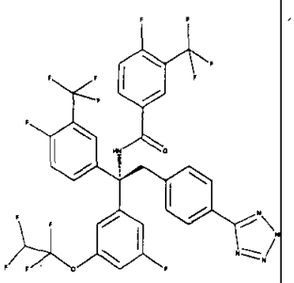
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 984 |  | 7-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenoxi) heptanoato de (R)-etilo | 2.232 CL(2) 723.3 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 59 y 129 |
| 985 |  | Acido (R)-7-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)etil) fenoxi)heptanoico | 2.202 CL(2) 760.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 7, 59, 129 y 23 |

1906

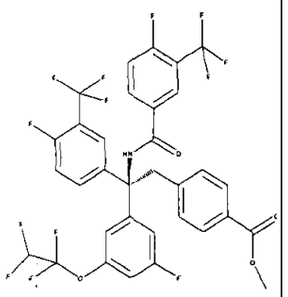
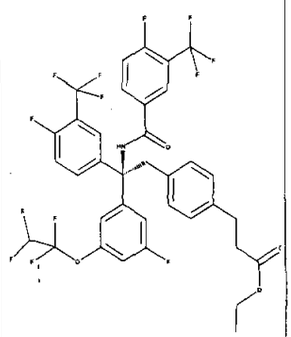
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 986 |  | Acido (R)-7-(4-(2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-fluorofenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenoxi) heptanoico | 2.130 CL(2) 695.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, 25, 59, 129 y 23 |
| 987 |  | (S)-N-(2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.30 CL(2) 763.8 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98 y 7 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 988 |  | (R)-1-(2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-3-(2,2,2-trifluoroetil)urea | 4.04 CL(6) 698.0 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98 y 25 |
| 989 |  | (S)-1-(2-(4-bromofenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-3-(2,2,2-trifluoroetil)urea | 4.05 CL(6) 699.0 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98 y 25 |

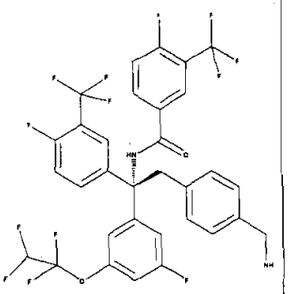
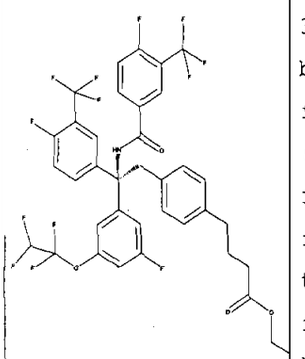
1808

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 990 |  | (R)-N-(2-(4-cianofenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.130 CL(2) 709.0 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7 y 56 |
| 991 |  | (S)-N-(2-(4-(2H-tetrazol-5-il)fenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 4.26 CL(6) 752.3 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7 y 99 |

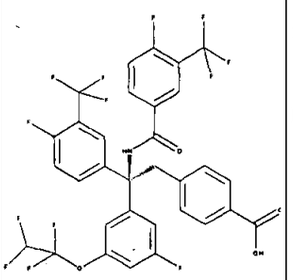
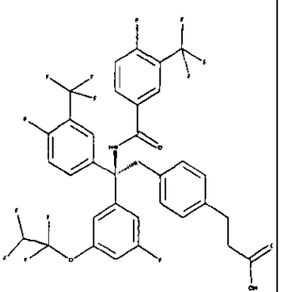
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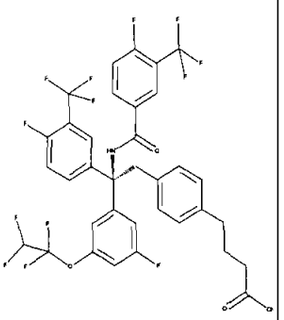
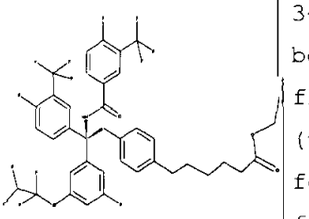
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 992 |  | (R)-metil 4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)etil) benzoato | 2.17 CL(2) 742.19 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56 y 57 |
| 993 |  | 3-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) propanoato de (R)-etilo | 4.49 CL(6) 784.34 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98 y 24 |

1810

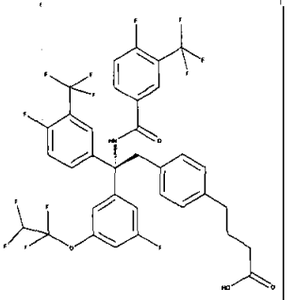
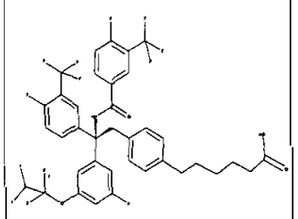
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 994 |  | (S)-N-(2-(4-(aminometil) fenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 4.3 CL(6) 713.31 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56 y 101 |
| 995 |  | 4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) butanoato de (R)-etilo | 4.39 CL(6) 798.36 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7 y 25 |

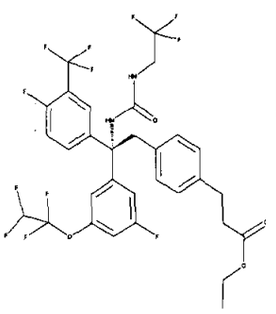
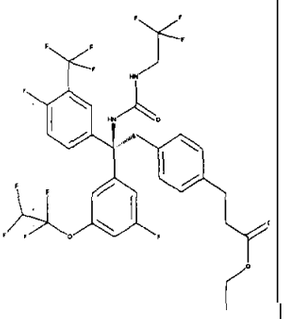
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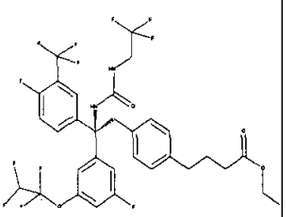
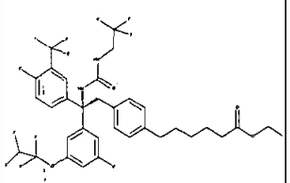
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparadó de la manera descrita en: |
|---|---|---|---|---|
| 996 |  | Acido (R)-4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)benzoico | 2.11 CL(2) 728.32 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56, 57 y 23 |
| 997 |  | Acido (R)-3-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) propanoico | 4.12 CL(6) 756.3 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 24 y 23 |

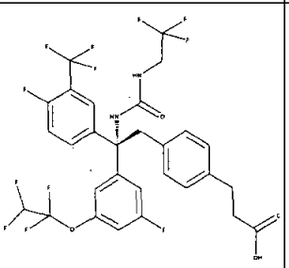
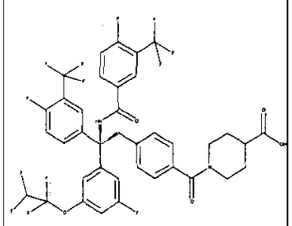
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 998 |  | Ácido (R)-4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) butanoico | 4.18 CL(6) 770.0 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 24 y 23 |
| 999 |  | 6-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) hexanoato de (R)-etilo | 4.54 CL(6) 826.52 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7 y 24 |

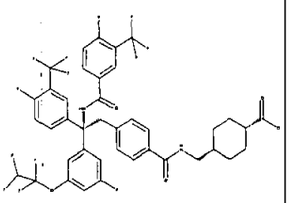
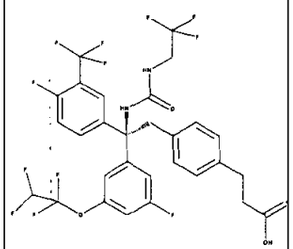
1813

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1000 |  | Acido (S)-4-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) butanoico | 4.16 CL(6) 770.3 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 24 y 23 |
| 1001 |  | Acido (S)-6-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) hexanoico | 4.20 CL(6) 798.47 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 24 y 23 |

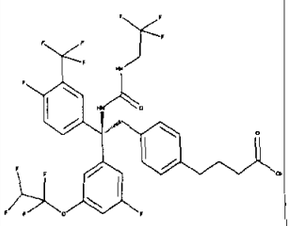
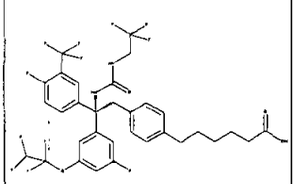
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1002 |  | 3-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) propanoato de (S)-etilo | 4.15 CL(6) 719.37 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25 y 24 |
| 1003 |  | 3-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) propanoato de (R)-etilo | 2.20 CL(2) 719.4 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25 y 24 |

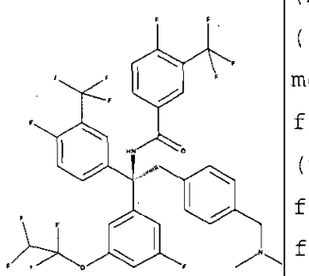
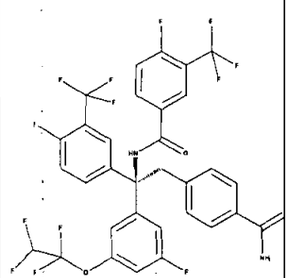
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1004 |  | 4-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) butanoato de (R)-etilo | 4.22 CL(6) 733.39 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25 y 24 |
| 1005 |  | 6-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) hexanoato de (R)-etilo | 4.34 CL(6) 761.47 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25 y 24 |

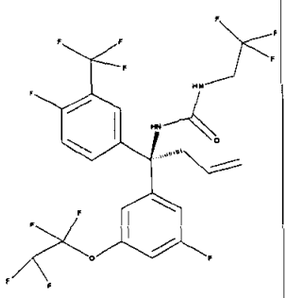
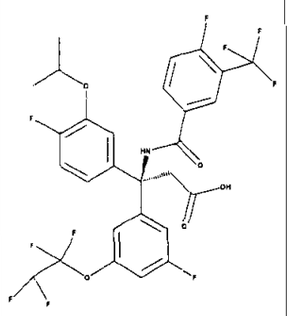
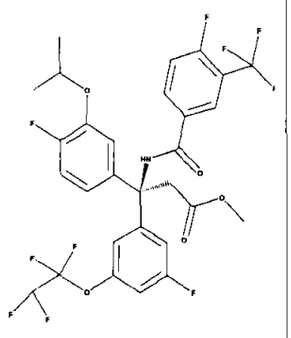
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1006 |  | Acido (S)-3-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) propanoico | 3.97 CL(6) 691.36 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25, 24 y 23 |
| 1007 |  | Acido (R)-1-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)benzoil) piperidin-4-carboxílico | 4.0 CL(6) 839.5 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56, 57, 23 y 103 |

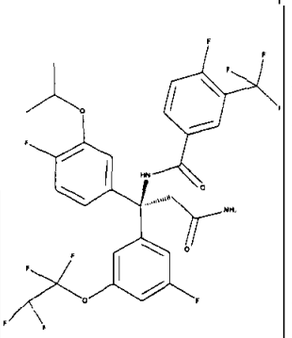
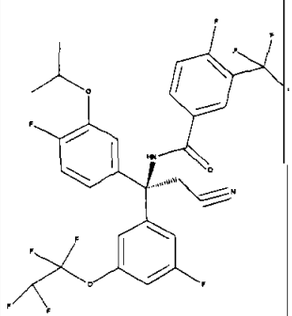
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1008 |  | Acido (1r,4r)-4-((4-((R)-2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)benzamido) metil)ciclohexano carboxílico | 4.0 CL(6) 867.5 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56, 57, 23 y 103 |
| 1009 |  | Acido (R)-3-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) propanoico | 4.0 CL(6) 691.37 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25, 24 y 23 |

1818

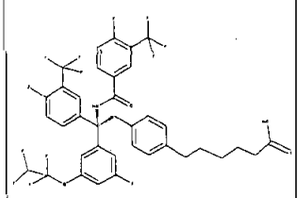
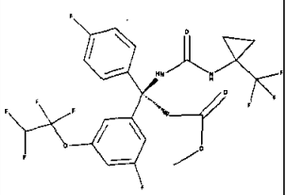
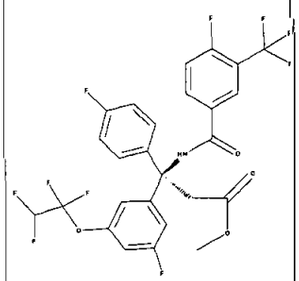
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1010 |  | Acido (R)-4-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) butanoico | 4.02 CL(6) 705.4 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25, 24 y 23 |
| 1011 |  | Acido (R)-6-(4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)fenil) hexanoico | 4.2 CL(6) 733.5 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 25, 24 y 23 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1012 |  | (R)-N-(2-(4-((dimetilamino) metil)fenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 3.45 CL(6) 741.5 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56, 57, 100 y 102 |
| 1013 |  | (R)-N-(2-(4-carbamoilfenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 3.97 CL(6) 727.41 $[M+H]^+$ | Procedimientos 3, 4, 72, 96, 97, 98, 7, 56, 57, 23 y 103 |

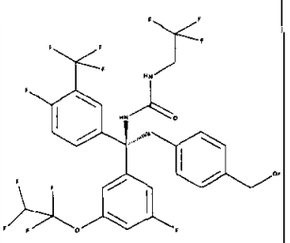
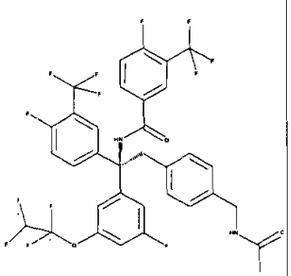
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1014 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)but-3-enil)-3-(2,2,2-trifluoroetil) urea | 568.355 | Procedimientos 3, 4, 5, 6 y 10 |
| 1015 |  | Acido (R)-3-(4-fluoro-3-(trifluorometil) benzamido)-3-(4-fluoro-3-isopropoxifenil)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) propanoico | 641.454 | Procedimientos 3, 4, 5, 14, 6, 7, 59, 68 y 23 |
| 1016 |  | 3-(4-fluoro-3-(trifluorometil) benzamido)-3-(4-fluoro-3-isopropoxifenil)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)propanoato de (R)-metilo | 655.481 | Procedimientos 3, 4, 5, 14, 6, 7, 59 y 68 |

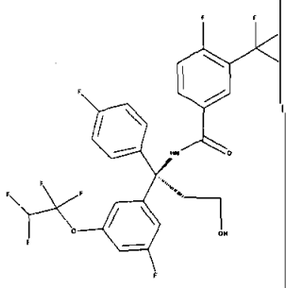
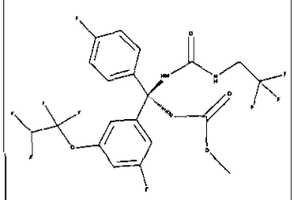
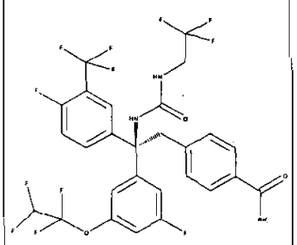
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1017 |  | (R)-N-(3-amino-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-3-oxopropil)-4-fluoro-3-(trifluorometil) benzamida | 2.0 CL(2) 641.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 14, 6, 7, 59, 68, 23 y 103 |
| 1018 |  | (R)-N-(2-ciano-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.0 CL(2) 623.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 18, 6, 7, 59 y 68 |

1822

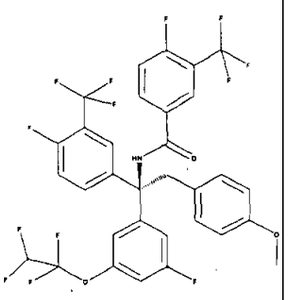
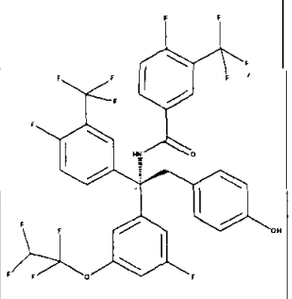
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1019 |  | Acido (R)-6-(4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)fenil) hexanoico | 4.3 CL(6) 798.4 $[M+H]^+$ | Procedimientos 3, 4, 96, 97, 98, 24 y 23 |
| 1020 |  | 3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-3-(4-fluorofenil)-3-(3-(1-(trifluorometil) ciclopropil) ureido)propanoato de (R)-metilo | 1.94 CL(2) 559.4 $[M+H]^+$ | Procedimientos 3, 4, 5, 14, 6 y 30 |
| 1021 |  | 3-(4-fluoro-3-(trifluorometil) benzamido)-3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-3-(4-fluorofenil) propanoato (R)-metilo | 3.95 CL(1) 598.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 14, 6 y 7 |

1023

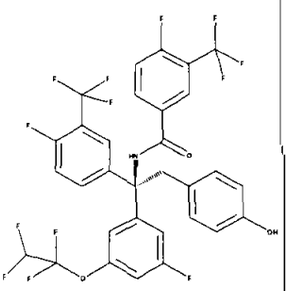
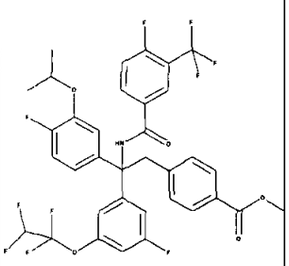
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1022 |  | (R)-1-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-(hidroximetil) fenil)etil)-3-(2,2,2-trifluoroetil)urea | 3.8 CL(6) 649.3 $[M+H]^+$ | Procedimientos 3, 4, 96, 97, 98, 56, y 100 |
| 1023 |  | (R)-N-(2-(4-(acetamidometil) fenil)-1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 4.0 CL(6) 755.38 $[M+H]^+$ | Procedimientos 3, 4, 96, 97, 98, 56, 101 y 65 |

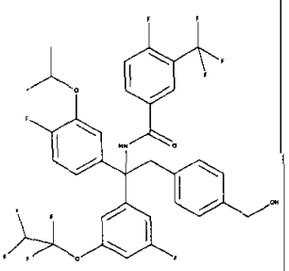
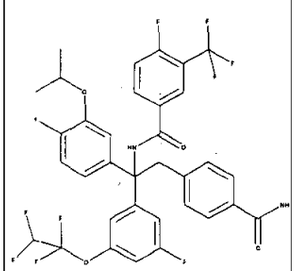
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1024 |  | (R)-4-fluoro-N-(1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-3-hidroxipropil)-3-(trifluorometil) benzamida | 2.05 CL(2) 570.5 $[M+H]^+$ | Procedimientos 3, 4, 5, 14, 6, 7 y 100 |
| 1025 |  | 3-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-3-(4-fluorofenil)-3-(3-(2,2,2-trifluoroetil) ureido)propanoato de (R)-metilo | 3.39 CL(1) 533.2 $[M+H]^+$ | Procedimientos 3, 4, 5, 14, 6 y 25 |
| 1026 |  | (R)-4-(2-(4-fluoro-3-(trifluorometil) fenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(3-(2,2,2-trifluoroetil) ureido) etil)benzamida | 3.74 CL(6) 662.3 $[M+H]^+$ | Procedimientos 3, 4, 96, 97, 98, 56, 57, 23 y 103 |

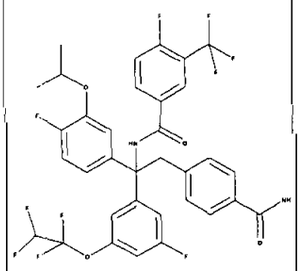
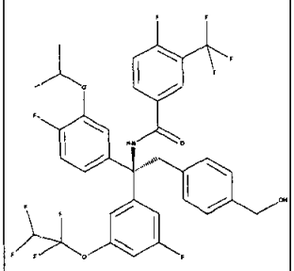
1825

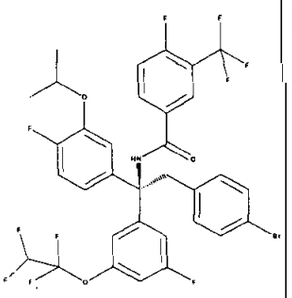
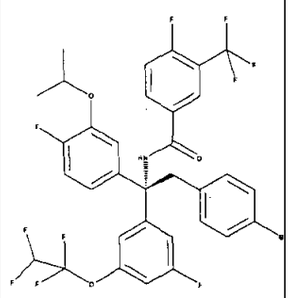
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1027 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-metoxifenil)etil)-3-(trifluorometil) benzamida | 4.3 CL(6) 714.0 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 7 |
| 1028 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-hidroxifenil)etil) -3-(trifluorometil) benzamida | 2.2 CL(2) 700.0 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 y 59 |

1826

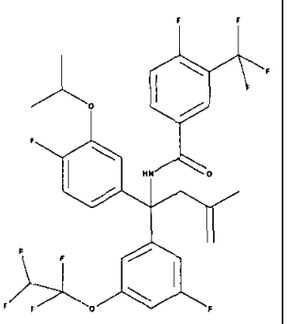
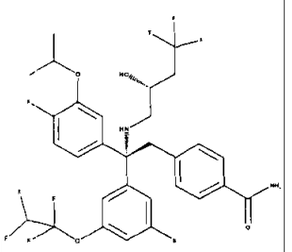
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1029 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-(trifluorometil) fenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-hidroxifenil)etil) -3-(trifluorometil) benzamida | 2.2 CL(2) 700.0 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 y 59 |
| 1030 |  | 4-(2-(4-fluoro-3-(trifluorometil) benzamido)-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)benzoato de metilo | 2.3 CL(2) 731.9 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56 y 57 |

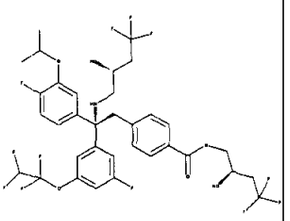
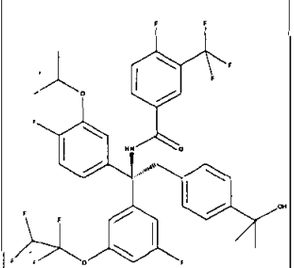
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1031 |  | 4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-(hidroximetil) fenil) etil)-3-(trifluorometil) benzamida | 2.17 CL(2) 704.0 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57 y 100 |
| 1032 |  | N-(2-(4-carbamoilfenil)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.13 CL(2) 716.9 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57, 23 y 103 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1033 |  | N-(2-(4-carbamoilfenil)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.13 CL(2) 716.9 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57, 23 y 103 |
| 1034 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-(hidroximetil) fenil) etil)-3-(trifluorometil) benzamida | 2.17 CL(2) 704.1 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 57 y 100 |

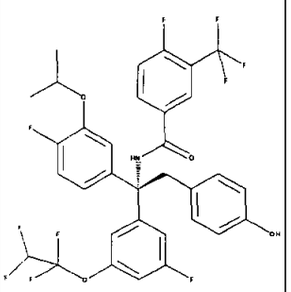
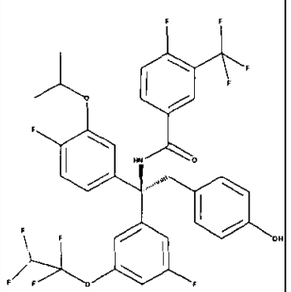
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1035 |  | (R)-N-(2-(4-bromofenil)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.17 CL(2) 753.8 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176 y 7 |
| 1036 |  | (S)-N-(2-(4-bromofenil)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil) etil)-4-fluoro-3-(trifluorometil) benzamida | 2.17 CL(2) 753.8 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176 y 7 |

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| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1037 |  | 4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-3-metilbut-3-enil)-3-(trifluorometil) benzamida | 2.19 CL(2) 638.9 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176 y 7 |
| 1038 |  | 4-((S)-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-((R)-4,4,4-trifluoro-2-hidroxibutilamino) etil) benzamida | 1.93 CL(2) 653.0 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 56, 57, 23, 136, 27 y 8 |

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1039 |  | (R)-4,4,4-trifluoro-2-hidroxibutil 4-((S)-2-(4-fluoro-3-isopropoxifenil)-2-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-((R)-4,4,4-trifluoro-2-hidroxibutilamino) etil) benzoato | 2.08 CL(2) 780.0 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 56, 57, 23, 136, 27 y 8 |
| 1040 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-(2-hidroxipropan-2-il)fenil)etil)-3-(trifluorometil) benzamida | 2.2 CL(2) 714.0 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7, 56, 52 y 53 |

1832

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1041 |  | (S)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-hidroxifenil)etil) -3-(trifluorometil) benzamida | 2.15 CL(2) 689.9 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 y 59 |
| 1042 |  | (R)-4-fluoro-N-(1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-(4-hidroxifenil)etil) -3-(trifluorometil benzamida | 2.15 CL(2) 689.9 $[M+H]^+$ | Procedimientos 3, 4, 59, 68, 172, 173, 174, 175, 176, 7 y 59 |

1833

**TABLA 20**

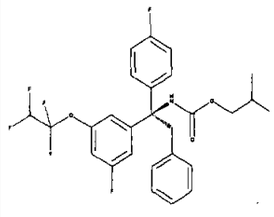
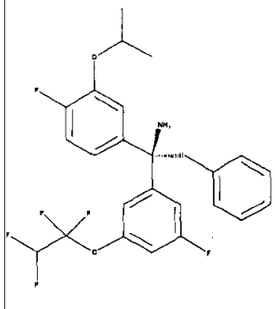
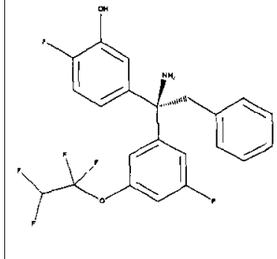
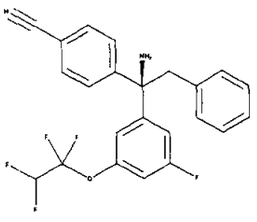
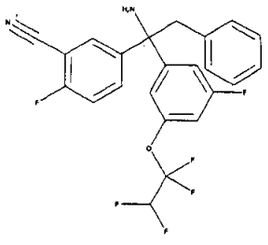
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1043 |  | (R)-isobutil 1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-1-(4-fluorofenil)-2-fenileticarbamato | 2.165 CL(2) 526.02 $[M+H]^+$ | Procedimientos 3, 4, 5, 6 y 82 |

**TABLA 21**

| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1044 |  | (R)-1-(4-fluoro-3-isopropoxifenil)-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletanamina | 1.89 CL(2) 467.46 $[M-NH_2]$ | Procedimiento 109, 110, 111, 112, 113 y 114 |
| 1045 |  | (R)-5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-2-fluorofenol | 1.70 CL(2) 425.1 $[M-NH_2]$ | Procedimiento 109, 110, 111, 112, 113 y 114 |

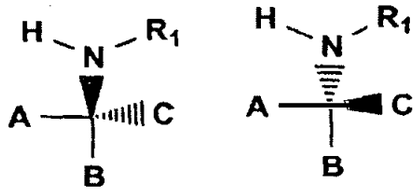
| Ej. No. | Estructura | Nombre | Tiempo de Retención Min./ Masa Molecular | Preparado de la manera descrita en: |
|---|---|---|---|---|
| 1046 |  | (R)-4-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil) benzonitrilo | 1.02 CL(12) 433 $[M+H]^+$ | Procedimientos 3, 4, 5, 6, y 56 |
| 1047 |  | 5-(1-amino-1-(3-fluoro-5-(1,1,2,2-tetrafluoroetoxi) fenil)-2-feniletil)-2-fluorobenzonitrilo | 3.281 CL(11) 451 $[M+H]^+$ | Procedimientos 3, 62, 5, 6 y 56 |

Se nota que los ejemplos precedentes, aunque son ilustrativos de la presente invención, no están en orden secuencial y algunos números de ejemplo pueden perderse.

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REIVINDICACIONES

1.- Un compuesto de la fórmula Ia o Ib




Ia y Ib

o estereoisómeros o profármacos o formas de sal farmacéuticamente aceptables de los mismos, caracterizado porque:

A es fenilo, el cual es substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$ el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$,

15) $-COR_6$, 16) =O, 17) $-S(O)_pR_6$, 18) $-SO_2NHR_6$, 19) $-COOR_6$, 20) $-NHC(CN)NHR_6$, 21) $-CONR_6R_6$, 22) alquinilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 23) alquenilo ($C_2$-$C_6$) el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 24) $-OCOR_6$, 25) $-OCOOR_6$, 26) $-OCONR_6R_6$; o 27) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$; o cualquiera de dos substituyentes adyacentes se pueden unir juntos para formar un anillo de 4 a 8 miembros, el cual puede contener opcionalmente 1-4 heteroátomos seleccionados de N, O y S, y se puede opcionalmente substituir con uno o más $R_{20}$;

B es:

(a) fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$,

15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NRH_6$, 18) $-COOR_6$, 19) $-NHC(CN)NRH_6$, 20) $-CONR_6R_6$; y 21) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$; o

(b) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, què puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$; 20) $-CONR_6R_6$, y 21) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

C es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo,

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que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, 17) $-NHC(CN)NHR_6$; y 18) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(b) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más de $R_{20}$, 3)-$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) haloalquilo de $C_1$-$C_6$; y 15) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual

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puede estar opcionalmente substituido con uno o más de $R_{20}$, 3) $-OR_6$, 4) -alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, 17) $-NHC(CN)NHR_6$; y 18) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$; o

(d) heterociclo que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3)-$OR_6$, 4 alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9NR_{10}$, 8) arilo, que puede substituirse opcionalmente por uno o más de $R_{20}$; 9) heteroarilo que puede substituirse opcionalmente por uno o más de $R_{20}$; 10) heterociclilo que puede substituirse opcionalmente por uno o más de $R_{20}$; 11) haloalquilo ($C_1$-$C_6$), 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NRH_6$, 16) $COOR_6$, 17) $-NHC(CN)NHR_6$; y 18) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

$R_1$ es H, $-C(O)R_3$, $-C(O)NR_2R_3$, $-C(O)OR_4$, $-SO_2R_5$, $-C(S)NHR_7$, $-CR_8R_8R_8$ o $-C(S)R_3$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, el cual puede estar opcionalmente substituido con uno o más $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo($C_2$-$C_6$), 15) alquinilo de $C_1$-$C_6$; 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$; y 20) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(c) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3)-$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo($C_2$-$C_6$), 17) alquinilo de $C_1$-$C_6$, 18) $-COR_6$, 19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, 22) $-NHC(CN)NHR_6$; y 23) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$; o

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CO_2$alquilo de $C_1$-$C_6$, 18) $-CONR_6R_6$, 19) alquenilo($C_2$-$C_6$), 20) alquinilo de $C_1$-$C_6$; y 21) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente

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con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$; y 20) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$,

15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$), que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -

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$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo ($C_1$-$C_6$), que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, 19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, 22) $-NHC(CN)NHR_6$; y 23) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido

opcionalmente con uno o más de $R_{20}$;

$R_4$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, 20) -$S(O)_pR_6$, 21) -$SO_2NHR_6$, 22) -$COOR_6$, 23) -$NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo ($C_1$-$C_6$), que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de

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$C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(d) alquenilo de $C_2$-$C_6$; o

(e) alquinilo de $C_2$-$C_6$;

$R_5$ es arilalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, 23) $-NHC(CN)NHR_6$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que

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consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$S(O)_pR_{36}$, 20) -$SO_2NHR_{36}$, 21) -$COOR_{36}$, 22) -NHC(CN)$NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20)

$-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, 24) $-NHC(CN)NHR_{36}$; y 25) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$,

9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; 14) heterociclilalquilo, que puede substituirse opcionalmente con

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uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10)

heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_7$ es arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo

de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

$R_8$ puede ser independientemente:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, 18) $-S(O)_pR_{26}$, 19) $-SO_2NHR_{26}$, 20) $-COOR_{26}$, 21) $-NHC(CN)NHR_{26}$; y 22) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(c) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo

de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

(e) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$; o

(f) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7)

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$-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, 23) $-NHC(CN)NHR_{26}$; y 24) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$; (c) $-[(C=O)O_r]_s$alquenilo ($C_2$-$C_8$), en donde el alquenilo puede substituirse opcionalmente con uno o más de $R_{20}$; (d) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$; (e) heterociclilo substituido opcionalmente con uno o más $R_{20}$; (f) $-CONR_{26}R_{26}$; (g) alquinilo de $C_2$-$C_6$; (h) $-COR_{26}$; (i) $-S(O)_pR_{26}$; (j) $-SO_2NHR_{26}$; (k) $-COOR_{26}$; (l) -

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$NHC(CN)NHR_{26}$; o m) $-[(C=O)O_r]_s$cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) =O; (q) alquinilo de $C_2$-$C_6$; (r) $-COR_{26}$; (s) $-S(O)_pR_{26}$; (t) $-SO_2NHR_{26}$; (u) $-COOR_{26}$; (v) $-NHC(CN)NHR_{26}$; (w) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (x) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (y) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$;

(d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) =O; (r) alquinilo de $C_2$-$C_6$; (s) cicloalquilo; (t) cicloalquilalquilo; (u) $-COR_{26}$; (v) $-S(O)_pR_{26}$; (w) $-SO_2NHR_{26}$; (x) $-COOR_{26}$; o (y) $-NHC(CN)NHR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$; y 23) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{40}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5)

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alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, 24) $-NHC(CN)NHR_{36}$; y 25) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{40}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{40}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y 26) cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{40}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3)

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alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, 25) $-NHC(CN)NHR_{36}$; y cicloalquilo, que puede substituirse opcionalmente con uno o más $R_{40}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$,

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13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, $-[(C=O)O_r]_s$arilo, $-[(C=O)O_r]_s$alquenilo, $-[(C=O)O_r]_s$alquilo, heterociclilo, $-CONR_{46}R_{46}$, alquinilo, $-COR_{36}$, $-S(O)_pR_{36}$, $-SO_2NHR_{36}$, $-COOR_{36}$, $-C(CN)NHR_{36}$, o cicloalquilo, en donde el

arilo, alquilo, alquenilo, cicloalquilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, o $-NHC(CN)NHR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo;

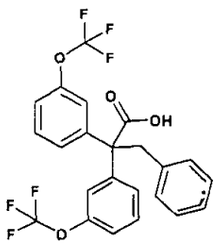
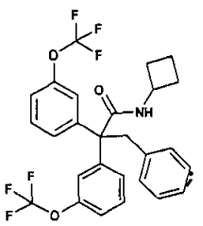
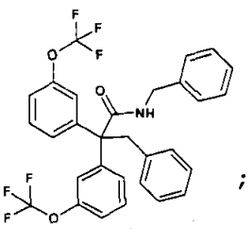
r es 0 hasta 5;

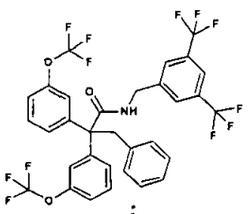
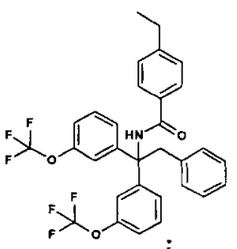
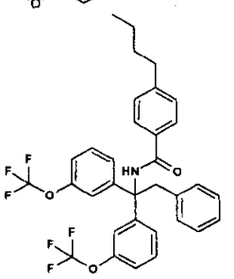
s es 0 hasta 4; y

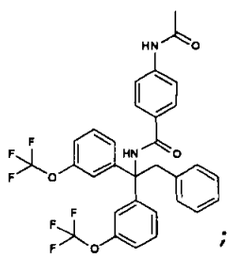
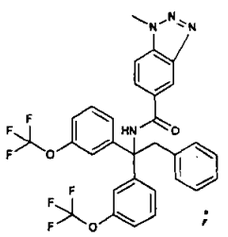
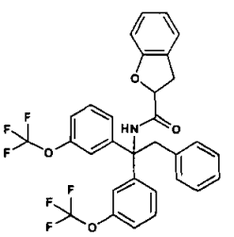
p es 1 ó 2;

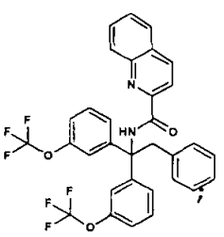
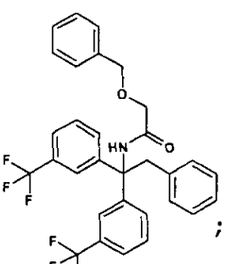
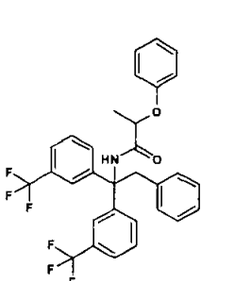
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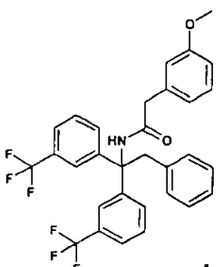
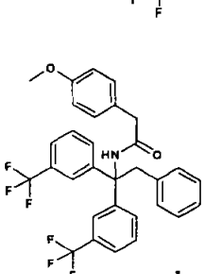
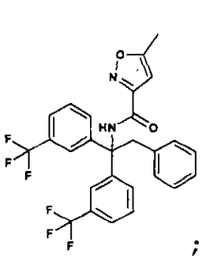
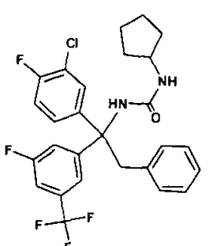
excluyendo los compuestos que tienen la siguiente fórmula:




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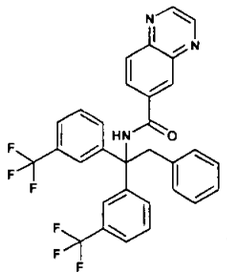
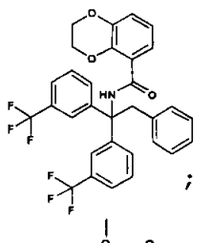
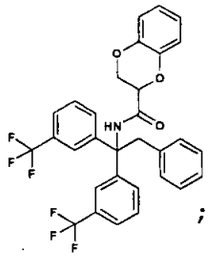
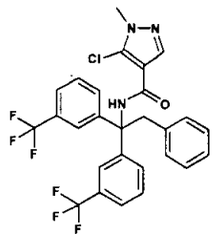

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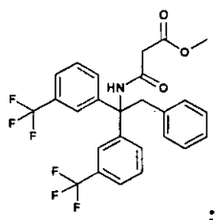
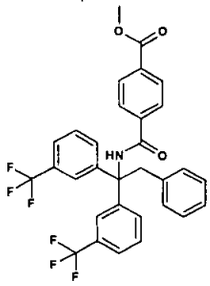
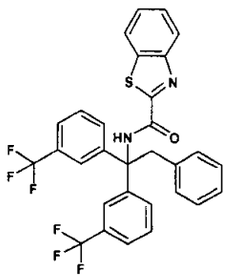
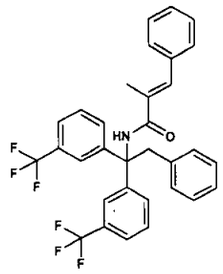

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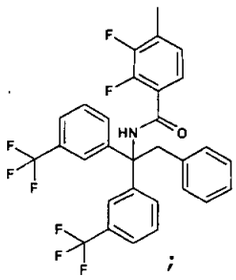
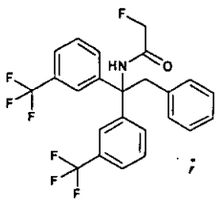
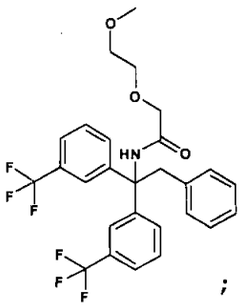

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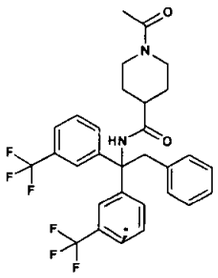
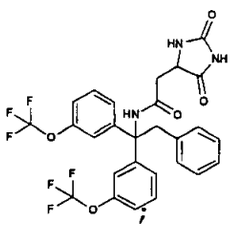
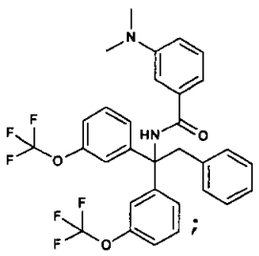




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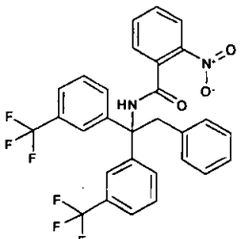
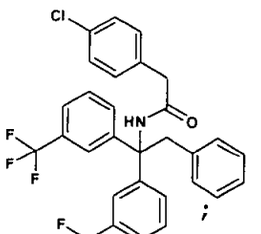
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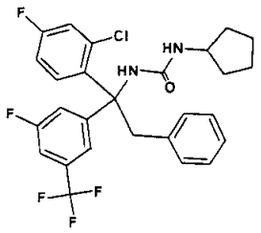
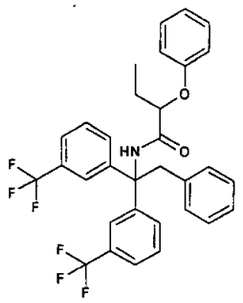

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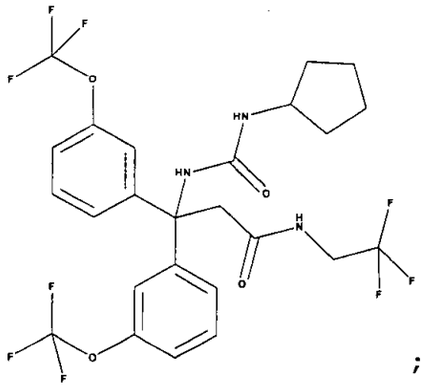
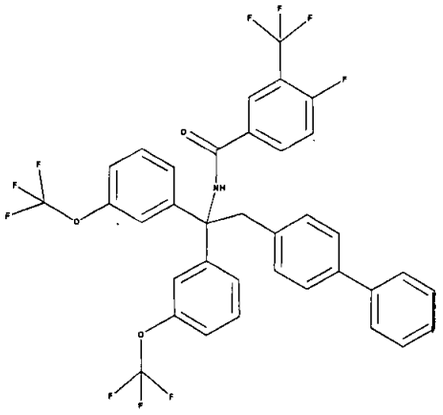

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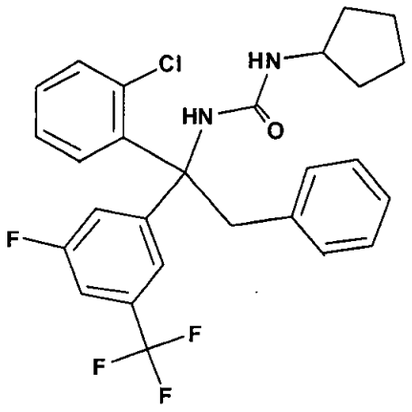
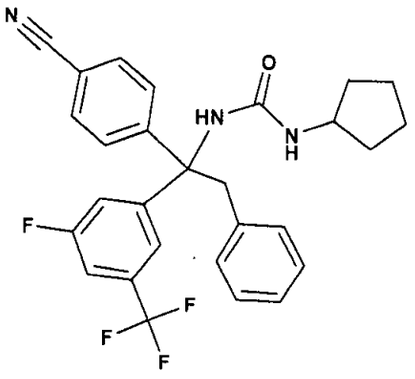

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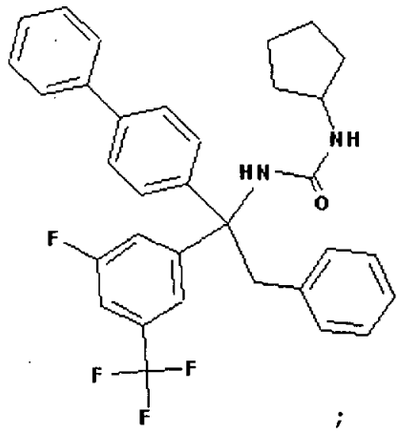
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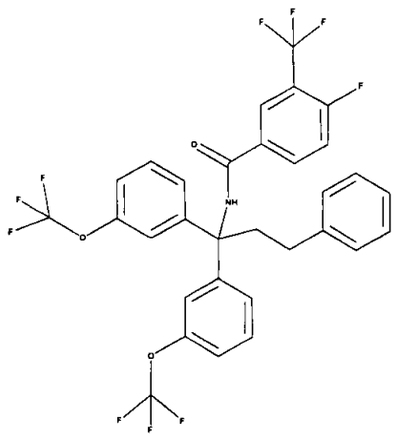

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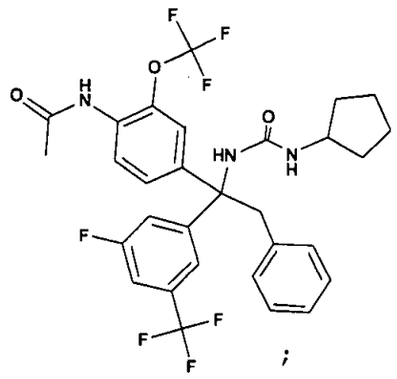

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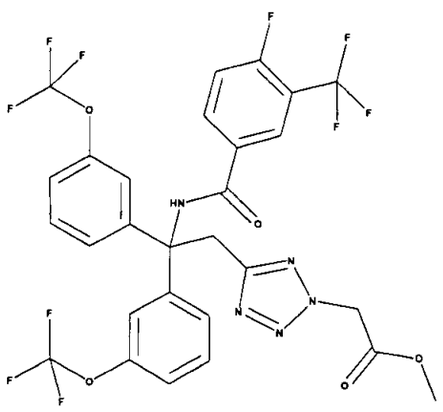
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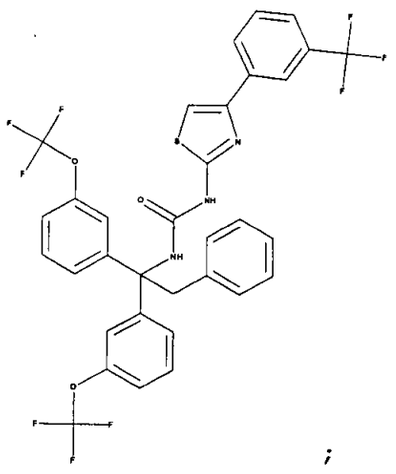
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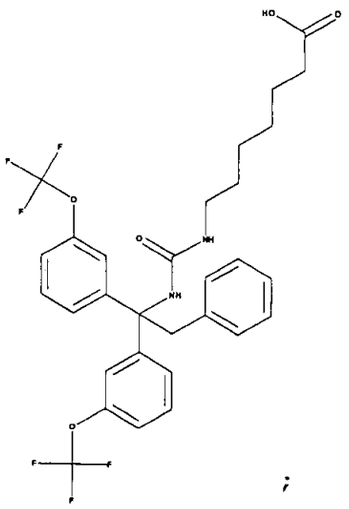
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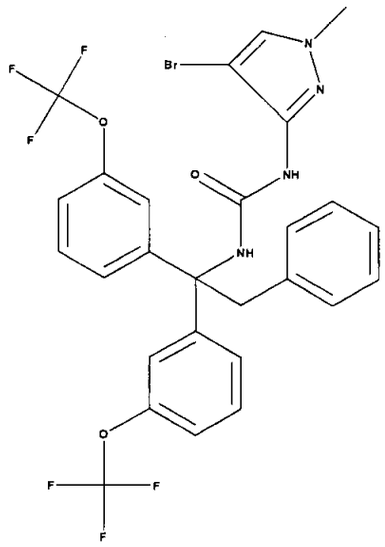


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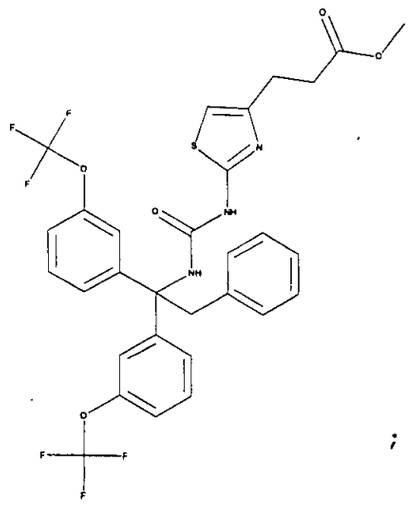


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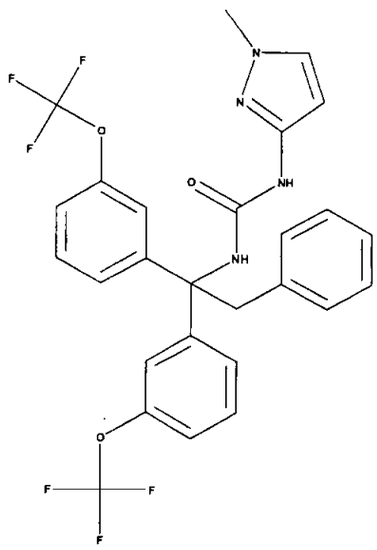
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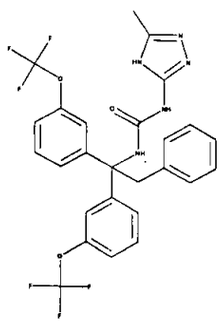
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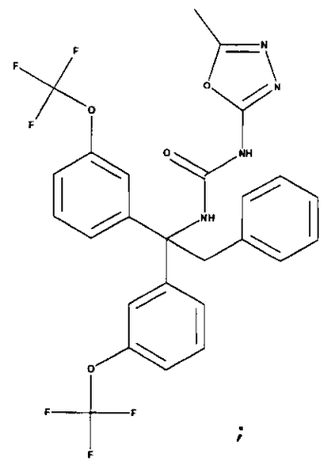


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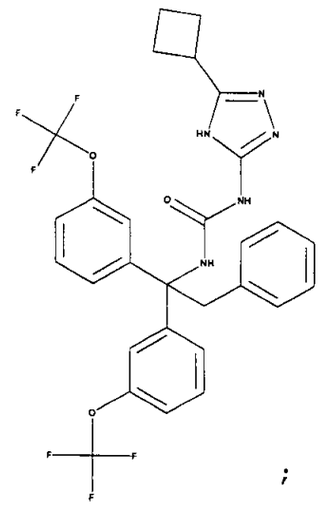


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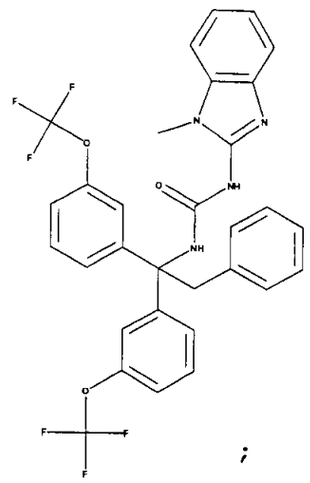
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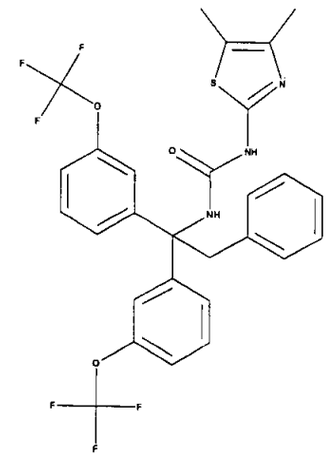
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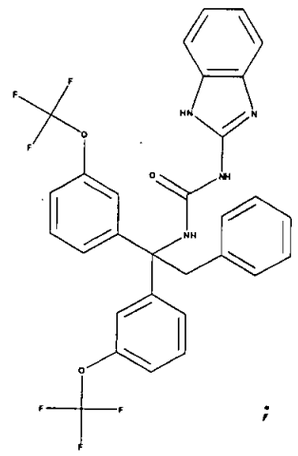
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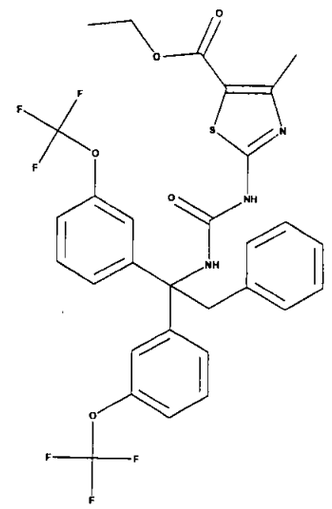
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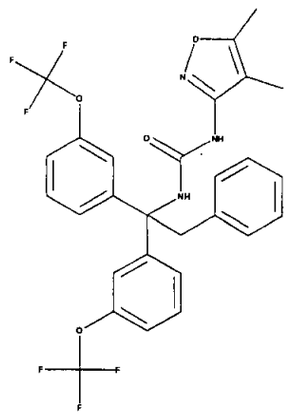


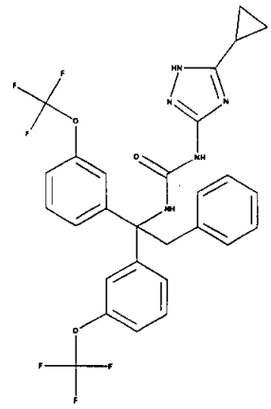
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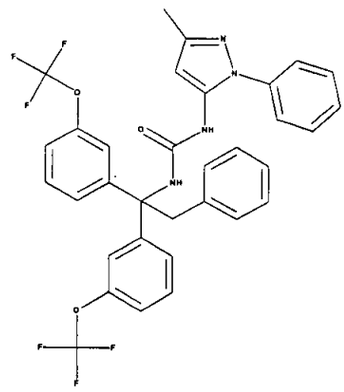
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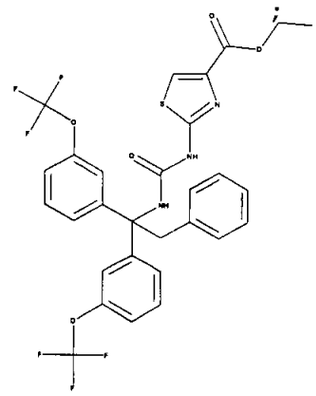
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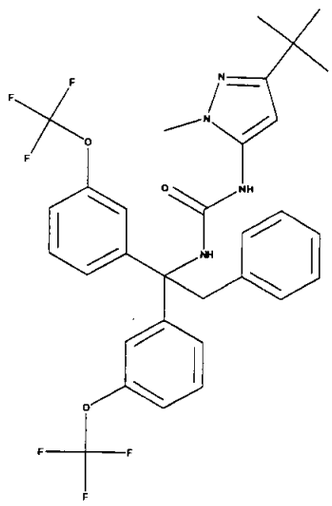
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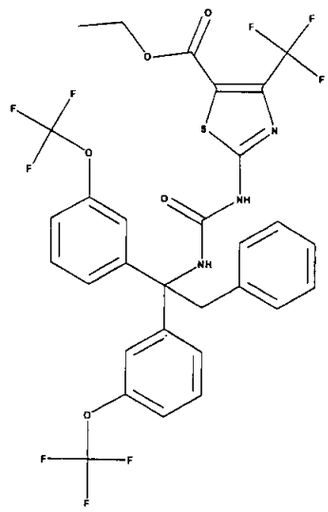




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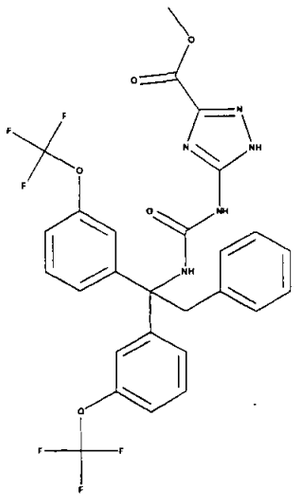
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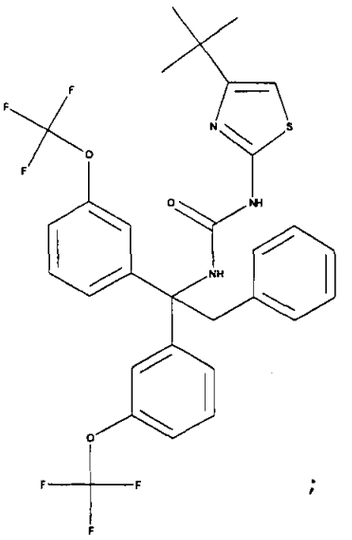


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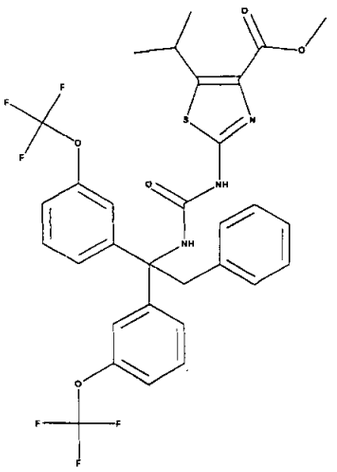
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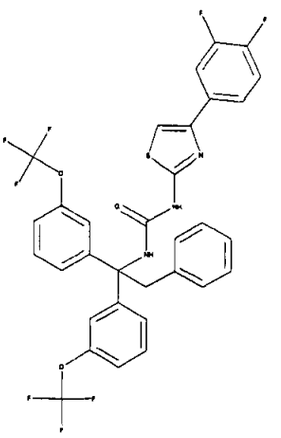
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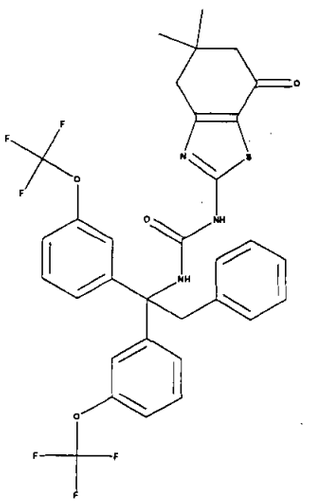
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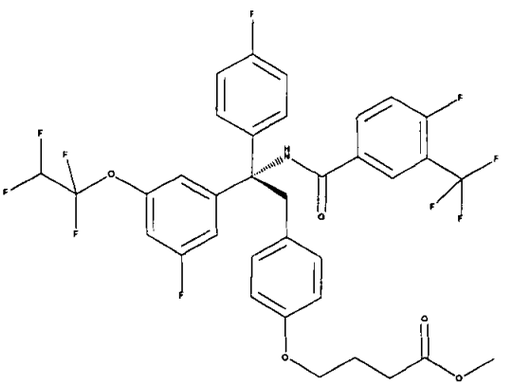
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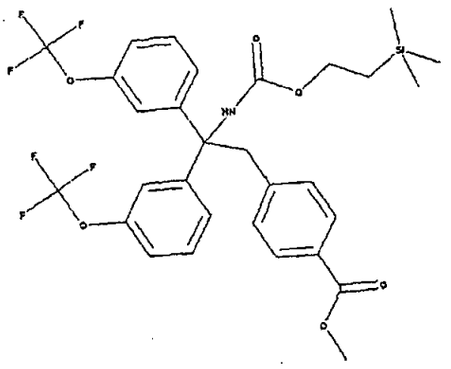


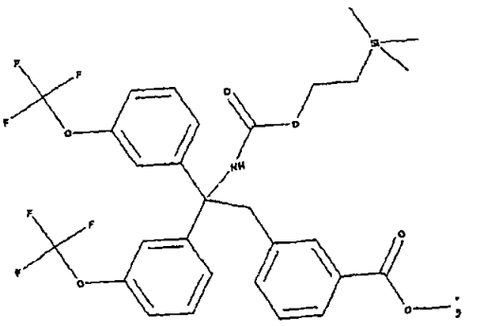
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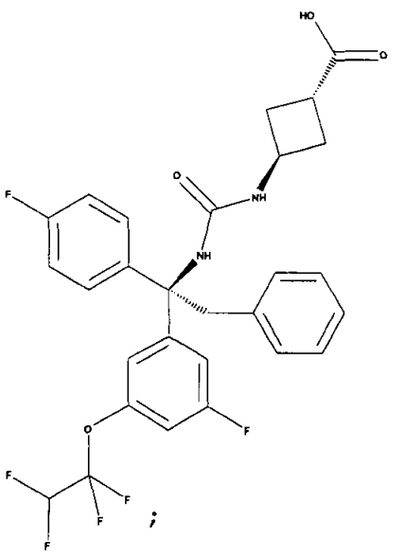


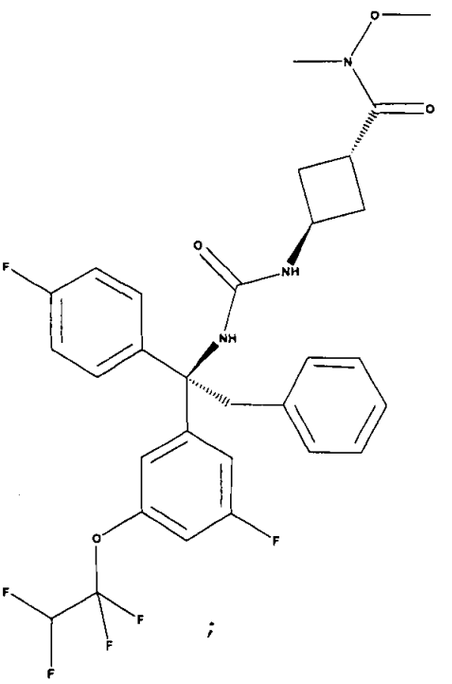
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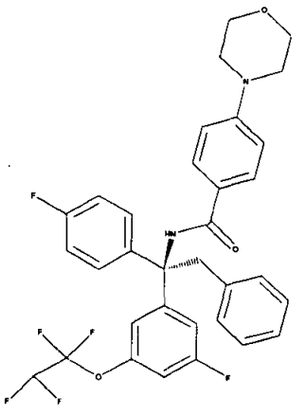
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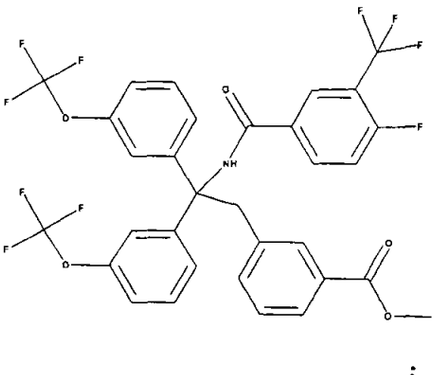

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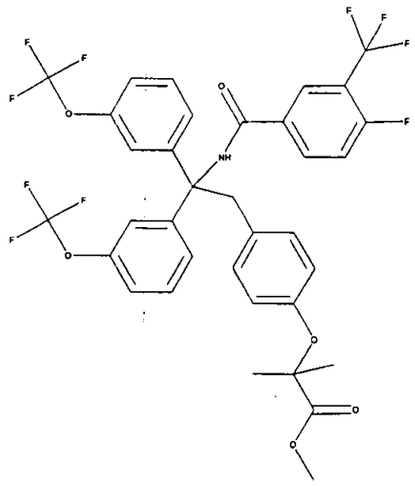

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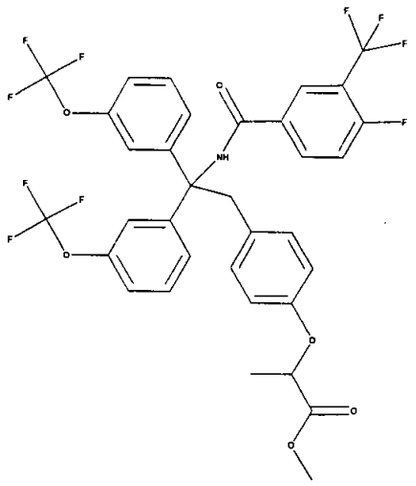

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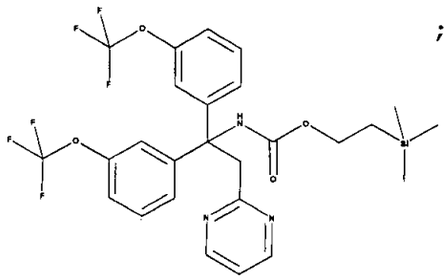

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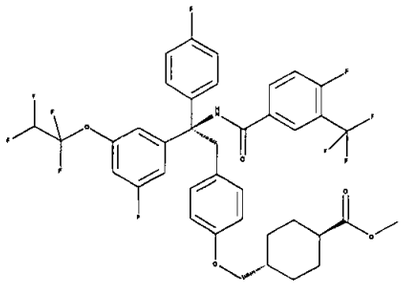
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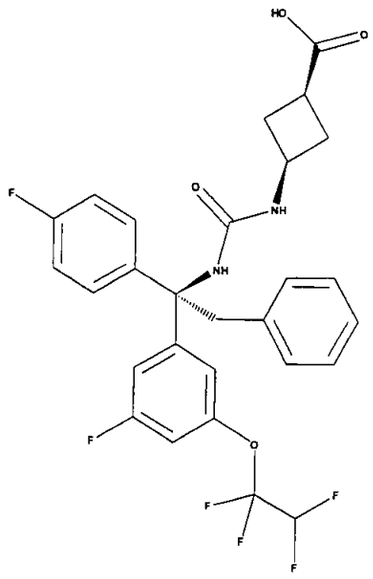


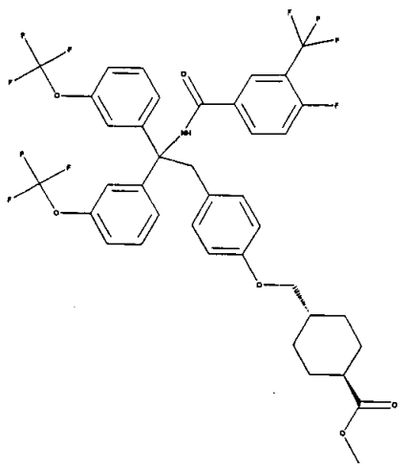
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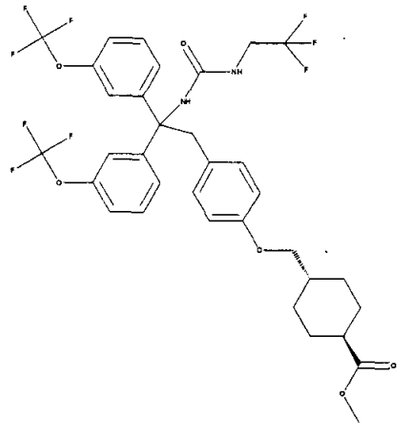
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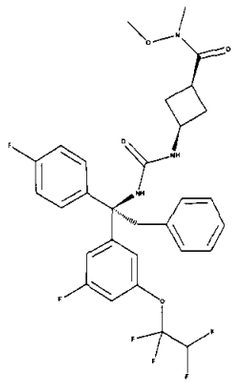


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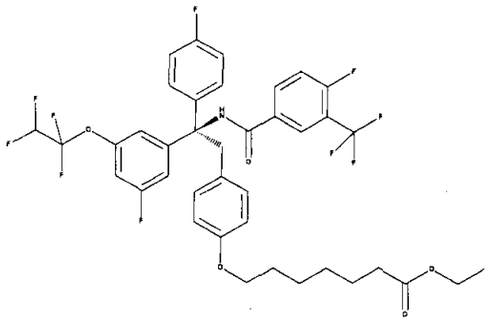
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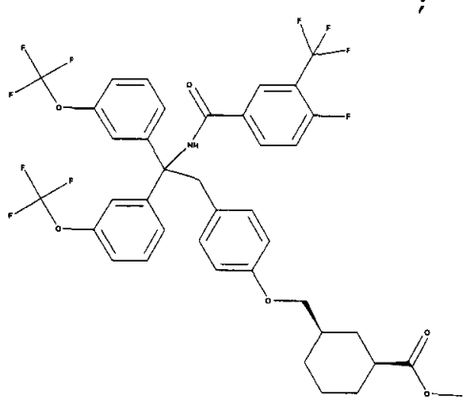
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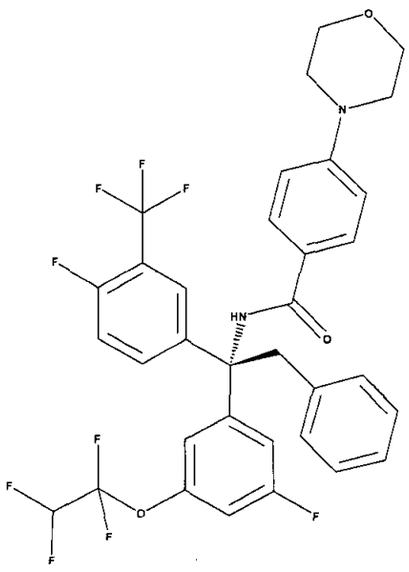
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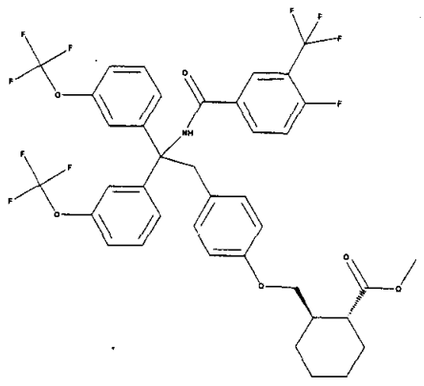
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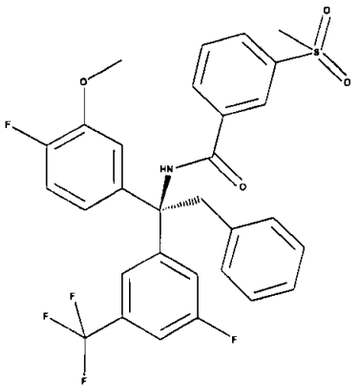


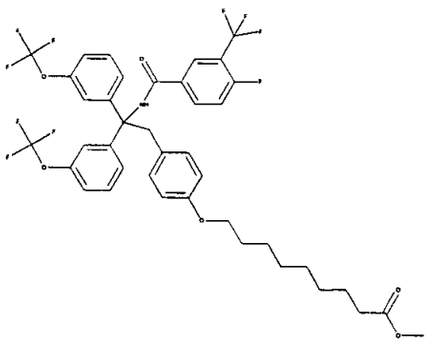
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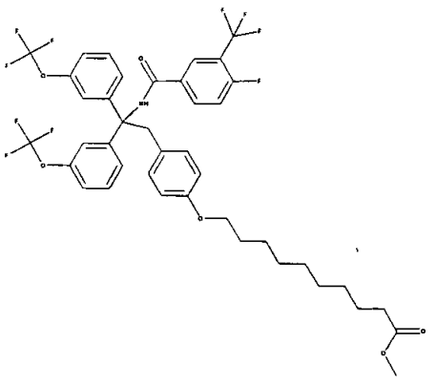
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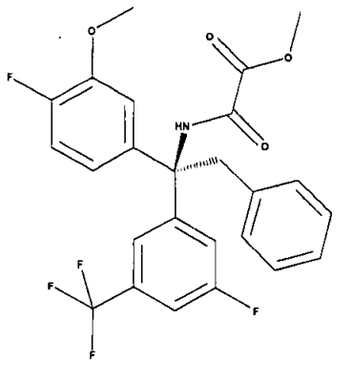
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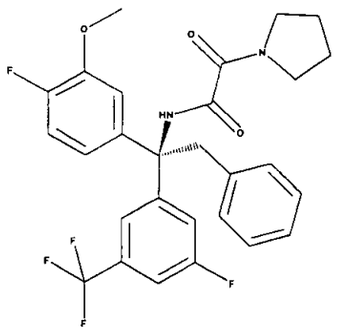
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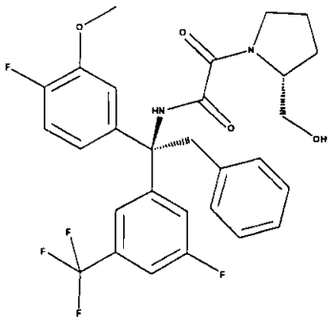




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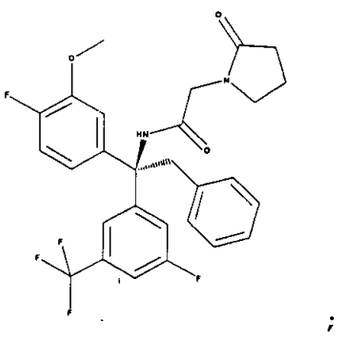
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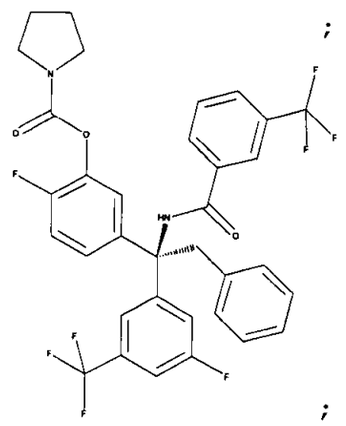




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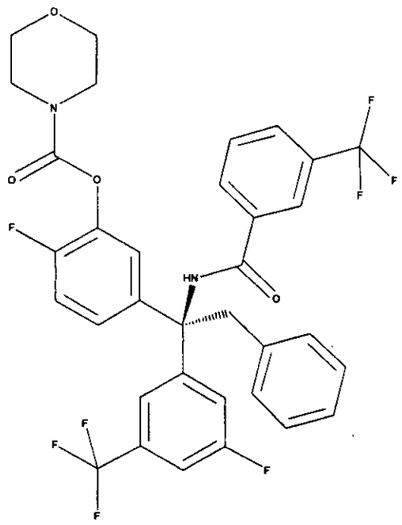
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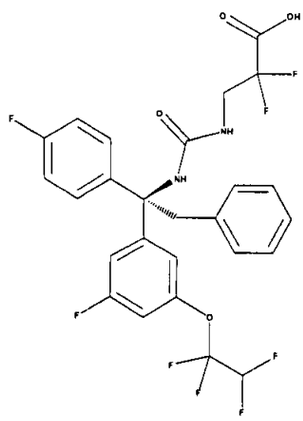


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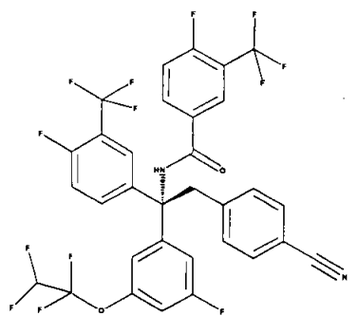
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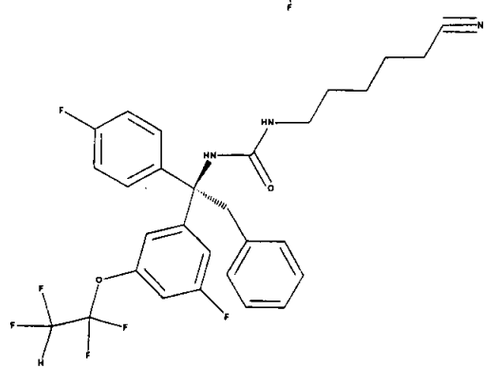
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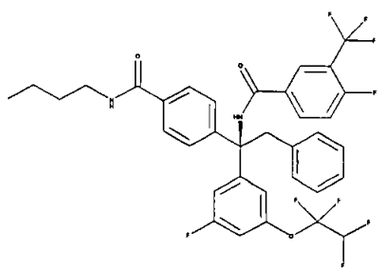
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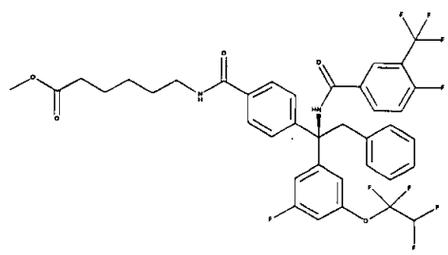
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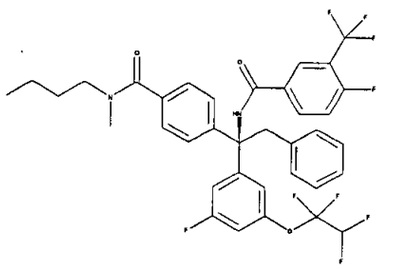
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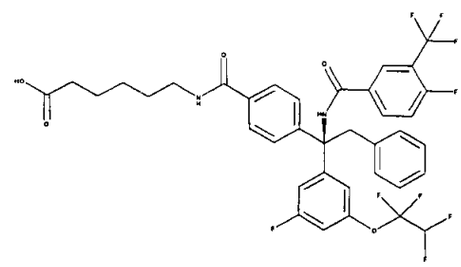
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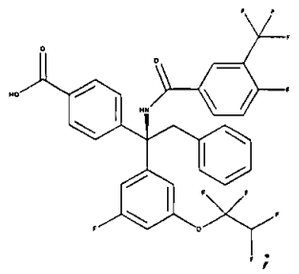


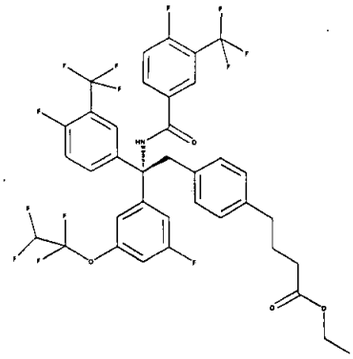
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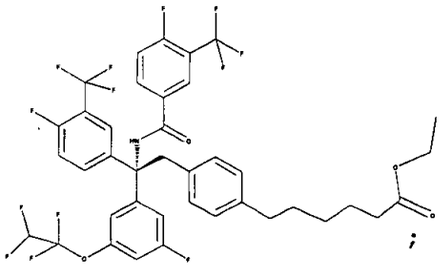


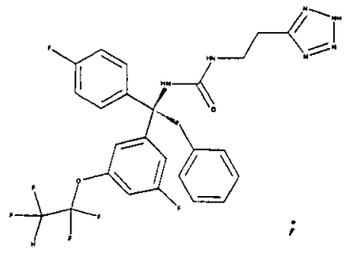
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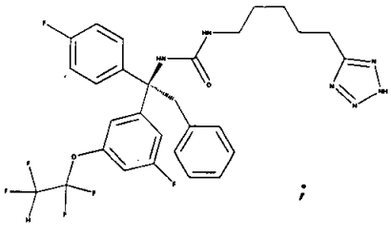
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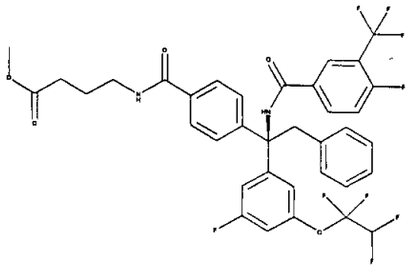

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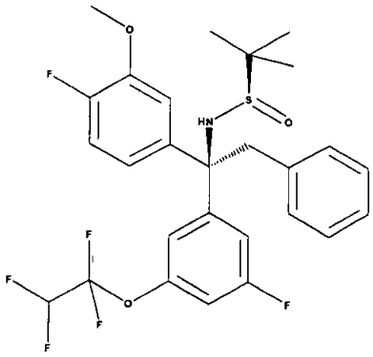

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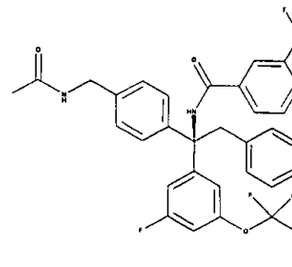

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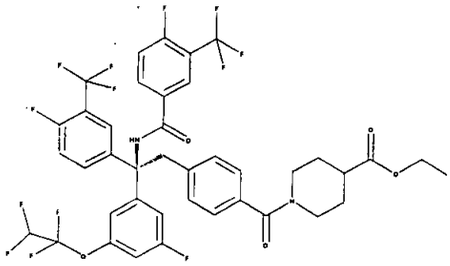

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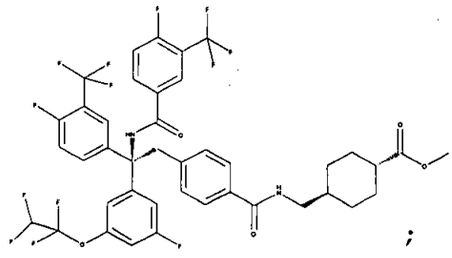

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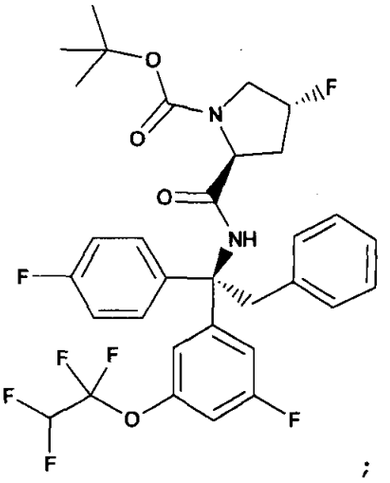

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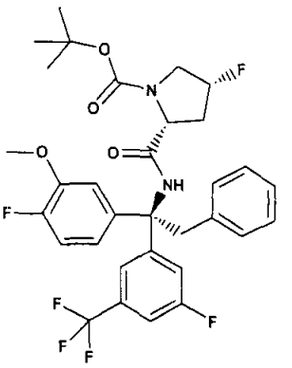

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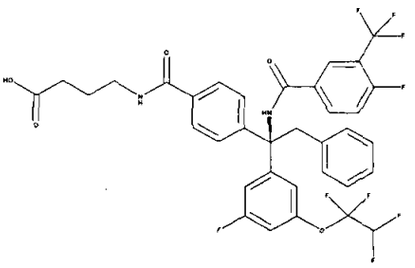
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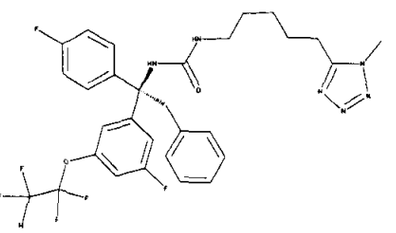
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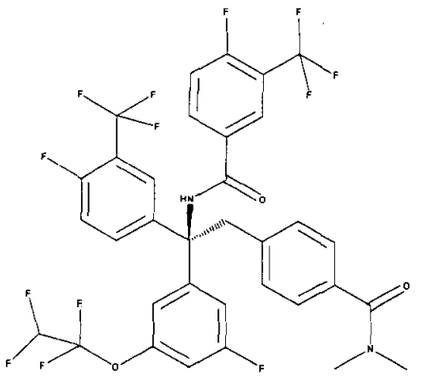
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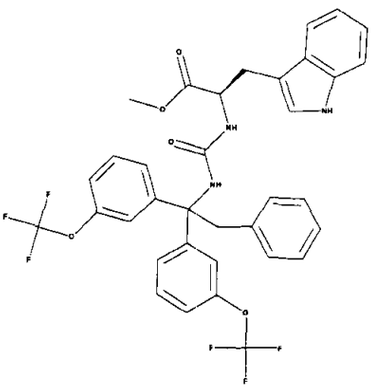
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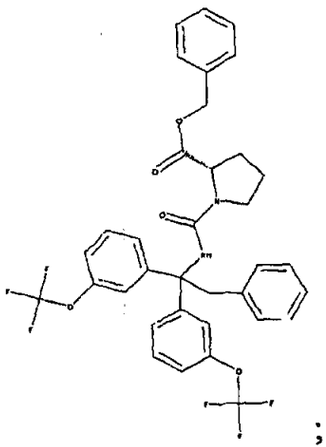
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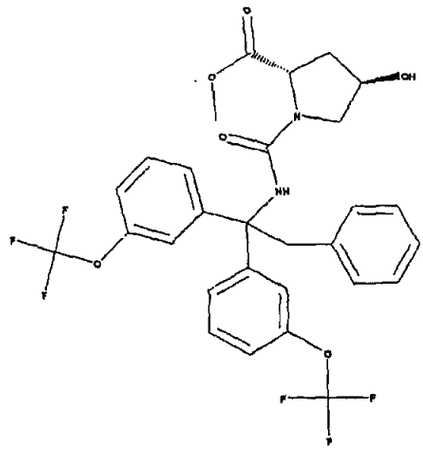


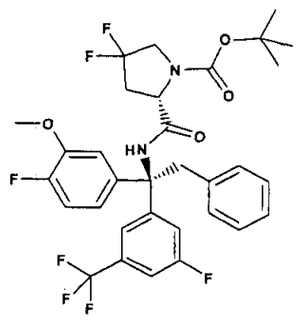
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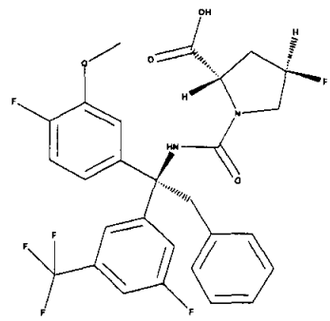


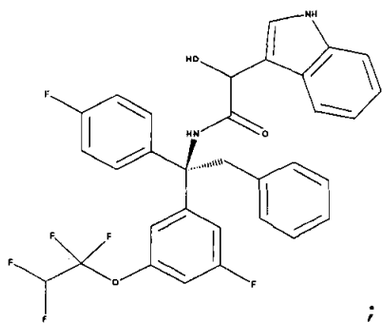
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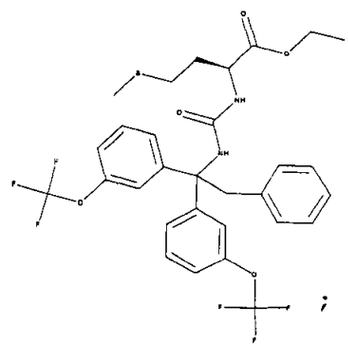

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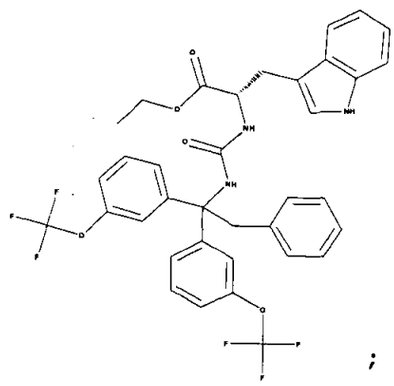

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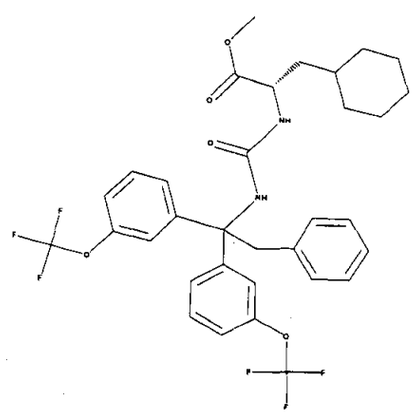

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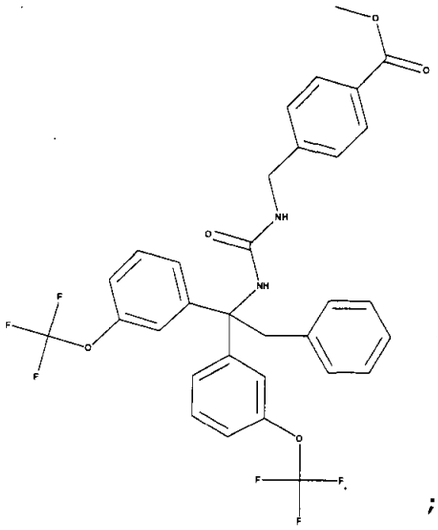

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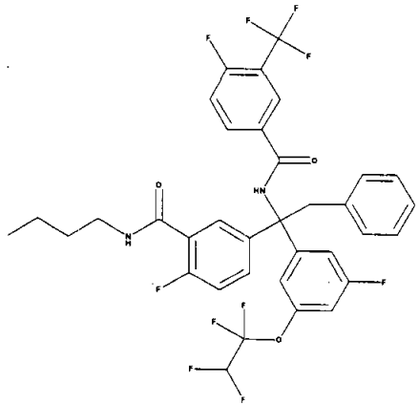

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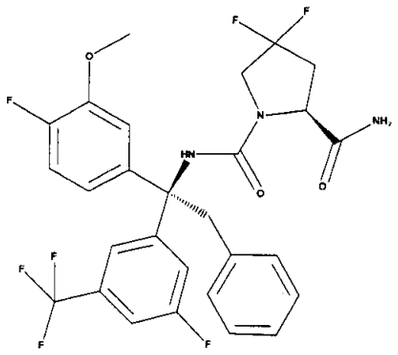

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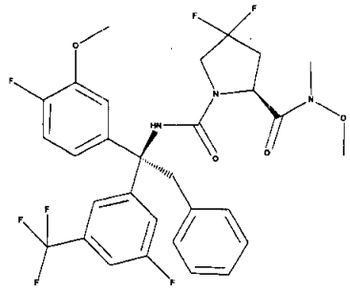

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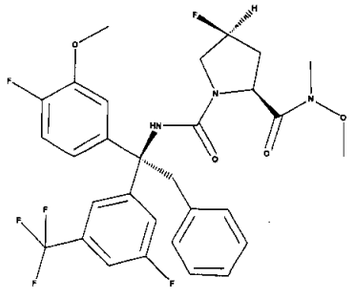

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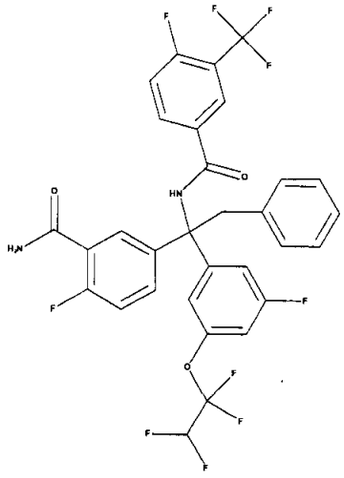

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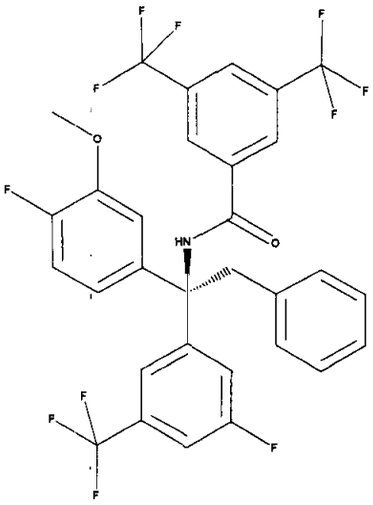

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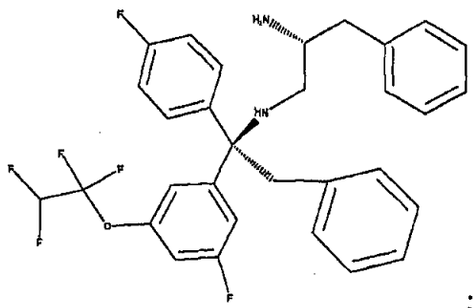

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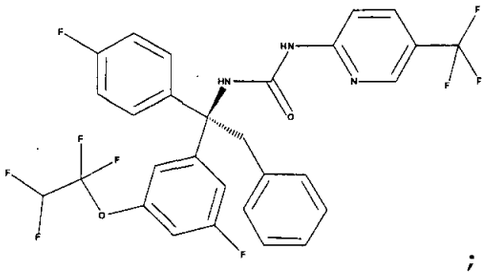

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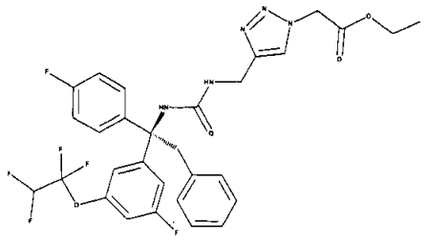
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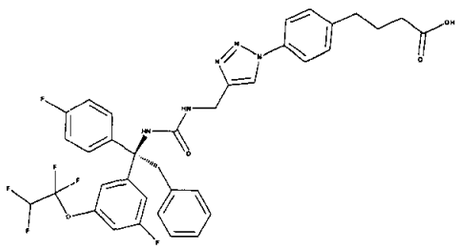
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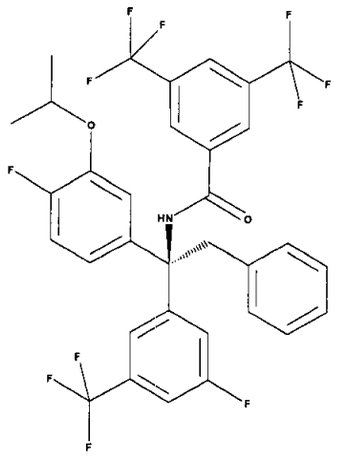
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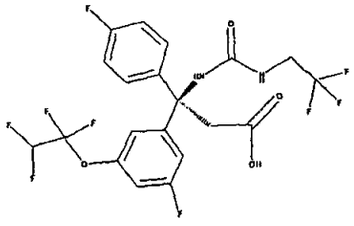
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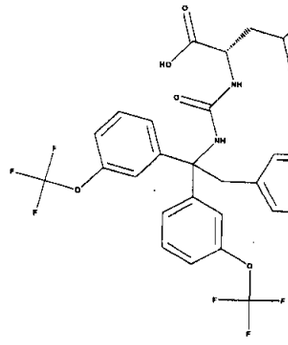
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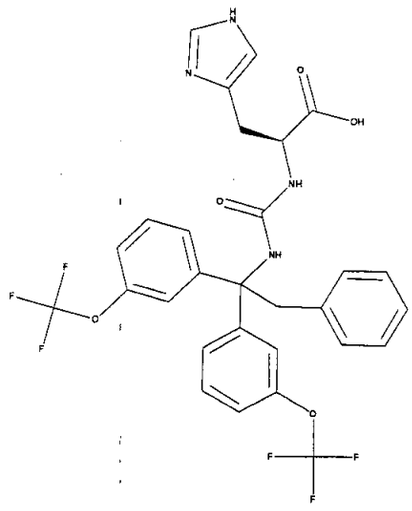


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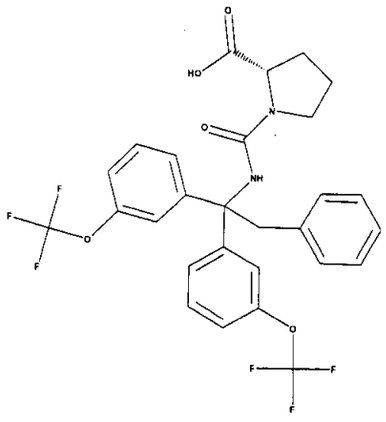


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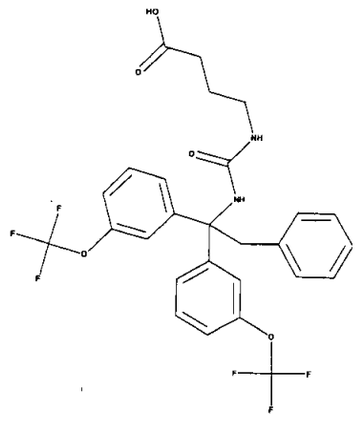
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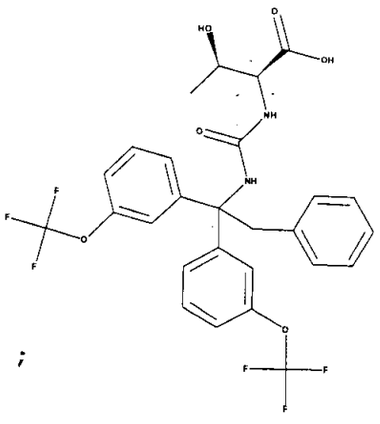
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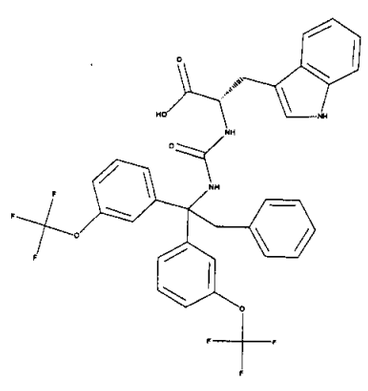
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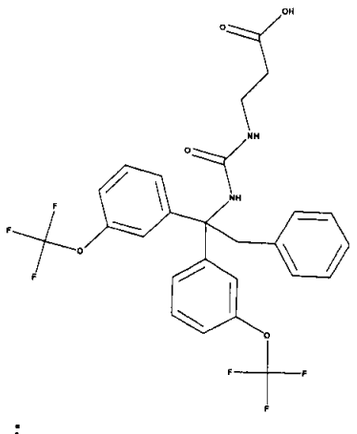
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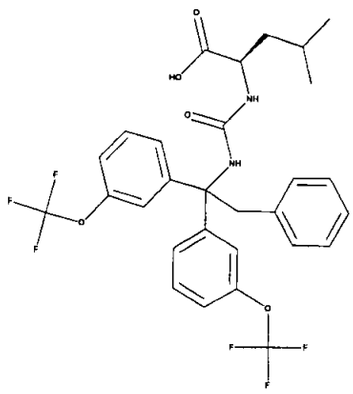


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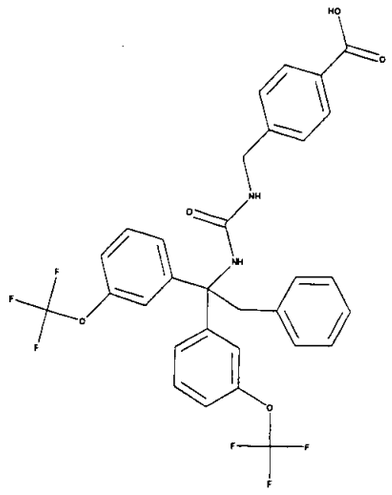


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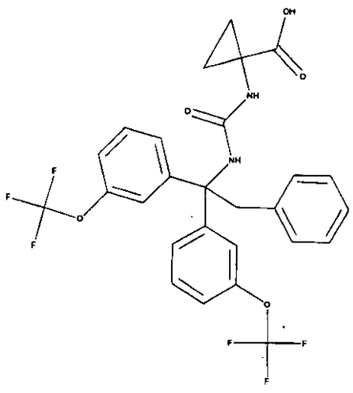
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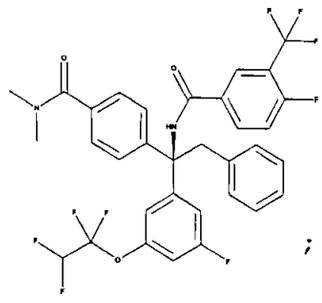
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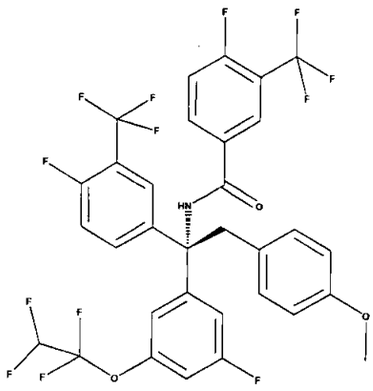
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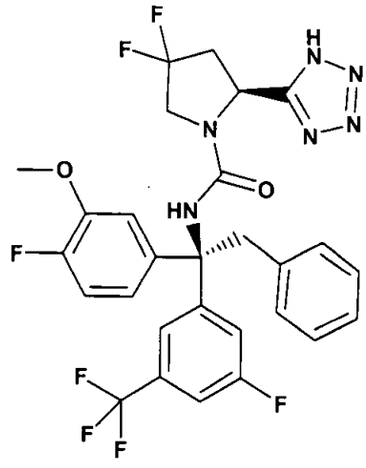
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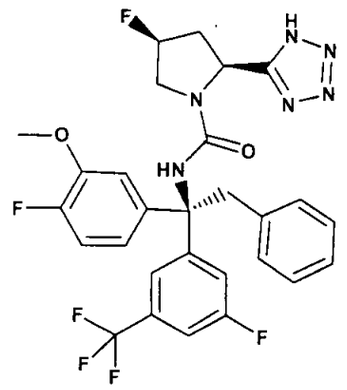
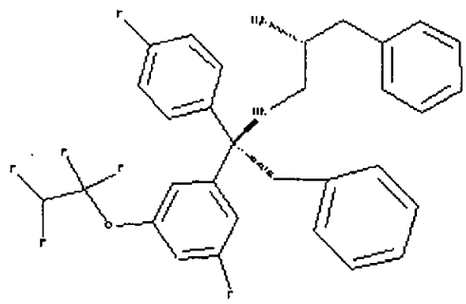


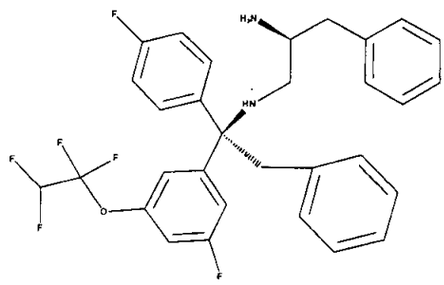
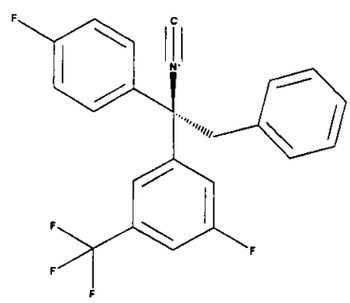
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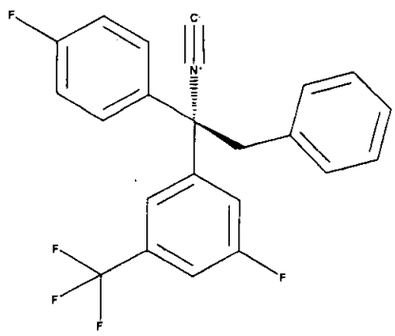
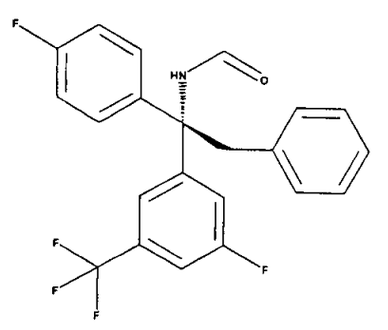


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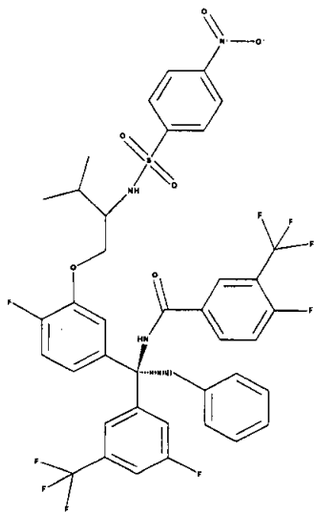
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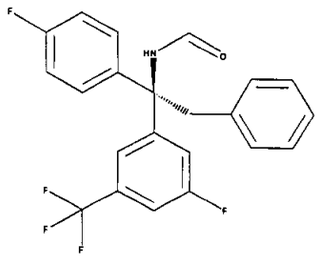

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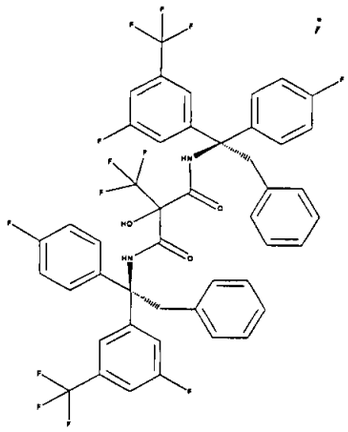
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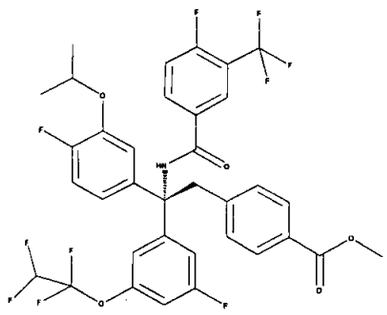
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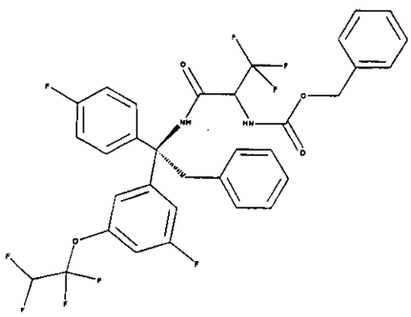
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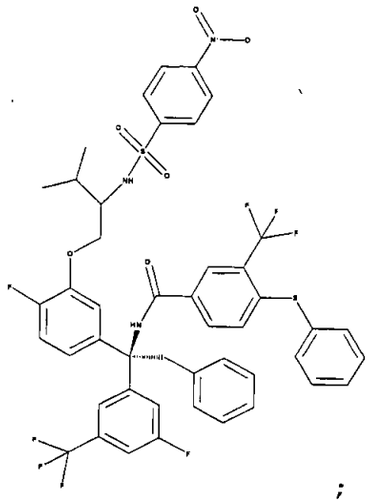
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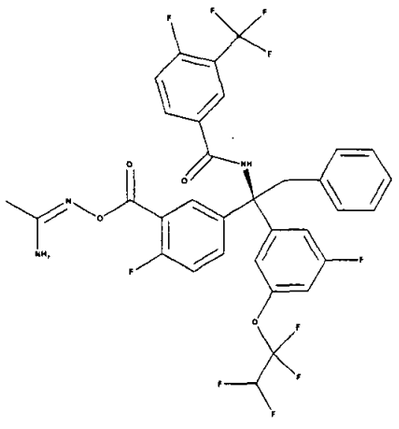
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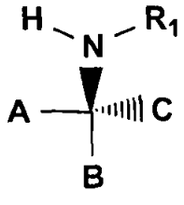
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2.- El compuesto de conformidad con la reivindicación 1, caracterizado porque es un compuesto de fórmula Ia.




Ia

3.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) $-S(O)_pR_6$, 18) $-SO_2NHR_6$, 19) $-COOR_6$, 20) $-NHC(CN)NHR_6$, 21) $-CONR_6R_6$, 22) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 23) alquenilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 24) $-OCOR_6$, 25) $-OCOOR_6$, o 26) $-OCONR_6R_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que

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puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, and 20) $-CONR_6R_6$; o

(b) heteroarilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, y 20) $-CONR_6R_6$;

C es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede

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substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, y 17) $-NHC(CN)NHR_6$;

(b) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$; o

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) $-S(O)_pR_6$, 15) $-SO_2NHR_6$, 16) $-COOR_6$, y 17) $-NHC(CN)NHR_6$;

$R_1$ es H, $-C(O)R_3$, $-C(O)NR_2R_3$, $-C(O)OR_4$, $-SO_2R_5$, $-C(S)NHR_7$, $-CR_8R_8R_8$, o $-C(S)R_3$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, y 19) $-NHC(CN)NHR_6$;

(c) alquenilo, que puede substituirse opcionalmente

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con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_6$, 19) -$S(O)_pR_6$, 20) -$SO_2NHR_6$, 21) -$COOR_6$, y 22) -$NHC(CN)NHR_6$; o

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$, 16) -COOH, 17) -$CO_2$alquilo de $C_1$-$C_6$, 18) -$CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, y 20) alquinilo de $C_2$-$C_6$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_6$, 16) -$S(O)_pR_6$, 17) -$SO_2NHR_6$, 18) -$COOR_6$, y 19) -$NHC(CN)NHR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o

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más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, 20) -$S(O)_pR_6$, 21) -$SO_2NHR_6$, 22) -$COOR_6$, y 23) -$NHC(CN)NHR_6$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11)

heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, 19) $-S(O)_pR_6$, 20) $-SO_2NHR_6$, 21) $-COOR_6$, y 22) $-NHC(CN)NHR_6$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4

heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_4$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23)

$-NHC(CN)NHR_6$;

(d) alquenilo de $C_2$-$C_6$; o

(e) alquinilo de $C_2$-$C_6$;

$R_5$ es arilalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_6$, 21) $-SO_2NHR_6$, 22) $-COOR_6$, y 23) $-NHC(CN)NHR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse

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opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13)

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heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente

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con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$S(O)_pR_{36}$, 20) -$SO_2NHR_{36}$, 21) -$COOR_{36}$, 22) -NHC(CN)$NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$S(O)_pR_{36}$, 20) -$SO_2NHR_{36}$, 21) -$COOR_{36}$, 22) -NHC(CN)$NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_7$ es arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

$R_8$ puede ser independientemente:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, 18) $-S(O)_pR_{26}$, 19) $-SO_2NHR_{26}$, 20) $-COOR_{26}$, y 21) $-NHC(CN)NHR_{26}$;

(c) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

(e) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$; o

(f) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, 20) $-S(O)_pR_{26}$, 21) $-SO_2NHR_{26}$, 22) $-COOR_{26}$, y 23) $-NHC(CN)NHR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4

heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$; (c) $-[(C=O)O_r]_s(C_2-C_8)$-alquenilo, en donde el alquenilo puede substituirse opcionalmente con uno o más de $R_{20}$; (d) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$; (e) heterociclilo substituido opcionalmente con uno o más $R_{20}$; (f) $-CONR_{26}R_{26}$; (g) alquinilo de $C_2$-$C_6$; (h) $-COR_{26}$; (i) $-S(O)_pR_{26}$; (j) $-SO_2NHR_{26}$; (k) $-COOR_{26}$; o (l) $-NHC(CN)NHR_{26}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) =O; (q) alquinilo de $C_2$-$C_6$; (r) -$COR_{26}$; (s) -$S(O)_pR_{26}$; (t) -$SO_2NHR_{26}$; (u) -$COOR_{26}$; (v) -$NHC(CN)NHR_{26}$; (w) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (x) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (y) -$CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) -$OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) -$NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) -$CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) =O; (r) alquinilo de $C_2$-$C_6$; (s) cicloalquilo; (t) cicloalquilalquilo; (u) -$COR_{26}$; (v) -$S(O)_pR_{26}$; (w) -$SO_2NHR_{26}$; (x) -$COOR_{26}$; o (y) -$NHC(CN)NHR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o

más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4)

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$-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$,

16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(f) hidrógeno;

(g) alquinilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5)

alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$; o

(h) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, 22) $-NHC(CN)NHR_{36}$, o 23) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido

opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, -$[(C=O)O_r]_s$arilo, -$[(C=O)O_r]_s$alquenilo, -$[(C=O)O_r]_s$alquilo, heterociclilo, $-CONR_{46}R_{46}$, alquinilo, $-COR_{36}$, $-S(O)_pR_{36}$, $-SO_2NHR_{36}$, $-COOR_{36}$, o $-C(CN)NHR_{36}$, en donde el arilo, alquilo, alquenilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$, $-S(O)_pR_{49}$, $-SO_2NHR_{49}$, $-COOR_{49}$, o $-NHC(CN)NHR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son

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independientemente hidrógeno, alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo;

r es 0 hasta 5;

s es 0 hasta 4; y

p es 1 ó 2.

4.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) =O, 17) -$COOR_6$, 18) -$CONR_6R_6$, 19) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 20) alquenilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 21) -$OCOR_6$, 22) -$OCOOR_6$, o 23) -$OCONR_6R_6$; o cualquiera de los dos substituyentes

adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-COOR_6$, y 17) $-CONR_6R_6$; o

(b) un heteroarilo que contiene nitrógeno, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

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arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-COOR_6$, y 17) $-CONR_6R_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) $-OR_6$, 3) $-NR_9R_{10}$, 4) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 5) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 6) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 7) $-CONR_6R_6$, y 8) $-COOR_6$;

$R_1$ es $-C(O)R_3$, $-C(O)NR_2R_3$, $-C(O)OR_4$ o $-CH_2R_8$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, y 16) $-COOR_6$;

(c) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, y 19) $-COOR_6$; o

(d) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$-, 16) -COOH, 17) -$CO_2$alquilo de $C_1$-$C_6$, 18) -$CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, y 20) alquinilo de $C_2$-$C_6$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_6$, y 16) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de

$C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de

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$C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con

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uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)$-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, y 19) $-COOR_6$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_4$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5)

alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$S(O)_pR_{36}$, 20) -$SO_2NHR_{36}$, 21) -$COOR_{36}$, y 22) -$NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) -$CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) -$COR_{36}$, 21) -$S(O)_pR_{36}$, 22) -$SO_2NHR_{36}$, 23) -$COOR_{36}$, y 24) -$NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse

opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_6$ se toman juntos para formar un anillo de 3

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hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, y 18) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4)

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alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$,

17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$; (c) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$; o (d) heterociclilo substituido opcionalmente con uno o más $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano, (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$,

13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más

de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$,

24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, $-[(C=O)O_r]_s$arilo, $-[(C=O)O_r]_s$alquilo, o heterociclilo, en donde

el arilo, alquilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$ o $-COOR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presentan, son independientemente hidrógeno, alquilo, arilo, heteroarilo o heterociclilo, diferente a heteroarilo;

r es 0 hasta 3;

s es 0 hasta 2; y

p es 1 ó 2.

5.- El compuesto de conformidad con la

reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) =O, 17) -$COOR_6$, 18) -$CONR_6R_6$, 19) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 20) -$OCOR_6$, 21) -$OCOOR_6$, o 22) -$OCONR_6R_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COOR_6$, y 16) $-CONR_6R_6$; o

(b) un heteroarilo que contiene nitrógeno de 6 hasta 10 miembros, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$,

15) $-COOR_6$, y 16) $-CONR_6R_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) $-OR_6$, 3) $-NR_9R_{10}$, 4) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 5) un heteroarilo que contiene nitrógeno, que puede substituirse opcionalmente con uno o más de $R_{20}$, 6) $-CONR_6R_6$, y 7) $-COOR_6$;

$R_1$ es $-C(O)R_3$, $-C(O)NR_2R_3$ o $-CH_2R_8$;

$R_2$ es:

(a) H;

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, y 16) $-COOR_6$; o

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4)

alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -COalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CO_2$alquilo de $C_1$-$C_6$, 18) $-CONR_6R_6$, 19) alquenilo de $C_2$-$C_6$, y 20) alquinilo de $C_2$-$C_6$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, y 16) $-COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste

de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_6$, y 20) -$COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(f) alquenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15)-$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_6$, y 19) $-COOR_6$;

o $R_2$ y $R_3$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4

heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) -$CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) -$COR_{36}$, 19) -$S(O)_pR_{36}$, 20) -$SO_2NHR_{36}$, 21) -$COOR_{36}$, y 22) -NHC(CN)$NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -$NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$,

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que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14)

heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_6$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, y 18) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste

de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno, (b) $-[(C=O)O_r]_s$arilo, en donde el arilo puede substituirse opcionalmente con uno o más de $R_{20}$, o (c) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h)

arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

o dos $R_{26}$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno, $-[(C=O)O_r]_s$arilo, o $-[(C=O)O_r]_s$alquilo, en donde el arilo o alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$ o $-COOR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo o heteroarilo;

r es 0 hasta 2;

s es 0 hasta 1; y

p es 1 ó 2.

6.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) =O, 17) -$COOR_6$, 18) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 19) -$OCOR_6$, y 20) -$OCOOR_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es:

(a) fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, y 15) $-COOR_6$; o

(b) un heteroarilo que contiene nitrógeno de 6 miembros, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con

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uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, y 15) $-COOR_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) fenilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, o 3) un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NR_2R_3$ o $-CH_2R_8$;

$R_2$ es:

(a) H; o

(b) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-COR_6$, 13) $-CONR_6R_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, y 16) $-COOR_6$;

$R_3$ es:

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(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) -$CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_6$, y 16) -$COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de

$C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que

puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) -$CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) -$COR_{26}$, y 18) -$COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o

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más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

o dos $R_8$ se toman juntos para formar un anillo de 3 hasta 9 miembros, que opcionalmente puede contener 1-4

heteroátomos seleccionados de N, O, y S y puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno, o (b) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

o $R_9$ y $R_{10}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o

(u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede

substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse

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opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7)

nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno o $-[(C=O)O_r]_s$alquilo, en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

o $R_{29}$ y $R_{30}$ se toman junto con el nitrógeno al cual ambos se enlazan para formar un anillo de 3 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, cicloalquilo, heteroarilo o heterociclilo puede substituirse

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opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, $-NR_{49}R_{50}$, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, $-CONR_{49}R_{50}$, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, cicloalquilalquilo, $-COR_{49}$, o $-COOR_{49}$;

$R_{49}$ y $R_{50}$, cada que se presenta, son independientemente hidrógeno, alquilo, arilo, o heteroarilo;

r es 0 hasta 2;

s es 0 hasta 1; y

p es 1 ó 2.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o

más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) =O, 17) alquinilo de $C_2$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 18) $-OCOR_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$;

C es alquilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1)

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fenilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, o 2) un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NHR_3$ o $-CH_2R_8$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, y 16) $-COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede

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substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14)

haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14)

heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) $-CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) $-COR_{26}$, y 18) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse

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opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; o (b) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{21}$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h)

arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-S(O)_pR_{36}$, 20) $-SO_2NHR_{36}$, 21) $-COOR_{36}$, y 22) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10)

arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-S(O)_pR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$,

24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$;

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{40}$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11)

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heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-S(O)_pR_{36}$, 23) $-SO_2NHR_{36}$, 24) $-COOR_{36}$, y 25) $-NHC(CN)NHR_{36}$; o

(f) hidrógeno;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno o $-[(C=O)O_r]_s$alquilo, en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo, heteroarilo o heterociclilo, diferente a heteroarilo, en donde el alquilo, arilo, heteroarilo o heterociclilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo o cicloalquilalquilo;

r es 0 hasta 2;

s es 0 hasta 1; y

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p es 1 ó 2.

8.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) =O, y 17) -$OCOR_6$; o cualquiera de los dos substituyentes adyacentes pueden unirse juntos para formar un anillo de 4 hasta 8 miembros, que opcionalmente puede contener 1-4 heteroátomos seleccionados de N, O, y S y está substituido opcionalmente con uno o más de $R_{20}$;

B es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) -$OR_6$, 4) alquiltio de

$C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$;

C es metilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) fenilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, o 2) un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NHR_3$ o $-CH_2R_8$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse

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opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) $-CONR_6R_6$, 13) alquenilo de $C_2$-$C_6$, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_6$, y 16) $-COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que

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puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con

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uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) $-CONR_6R_6$, 16) alquenilo de $C_2$-$C_6$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_6$, y 20) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-SO_2NHR_{36}$, 20) $-COOR_{36}$, y 21) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo,

que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-SO_2NHR_{36}$, 22) $-COOR_{36}$, y 23) $-NHC(CN)NHR_{36}$;

(c) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_9R_{10}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) $-CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) $-COR_{36}$, 22) $-SO_2NHR_{36}$, 23) $-COOR_{36}$, y 24) $-NHC(CN)NHR_{36}$; o

(d) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) arilalquinilo de $C_2$-$C_6$, 14) -$CONR_{26}R_{26}$, 15) =O, 16) alquinilo de $C_2$-$C_6$, 17) -$COR_{26}$, y 18) -$COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$,

15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) -$CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) -$COR_{26}$, y 20) -$COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12)

heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, 15) alquenilo de $C_2$-$C_6$, 16) $-CONR_{26}R_{26}$, 17) =O, 18) alquinilo de $C_2$-$C_6$, 19) $-COR_{26}$, y 20) $-COOR_{26}$;

$R_9$ y $R_{10}$ son independientemente: (a) hidrógeno; o (b) $-[(C=O)O_r]_s$alquilo ($C_1$-$C_8$), en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo, que puede substituirse opcionalmente con uno o más de

$R_{21}$; (i) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (n) haloalquilo de $C_1$-$C_6$; (o) alquenilo de $C_2$-$C_6$; (p) alquinilo de $C_2$-$C_6$; (q) $-COR_{26}$; (r) $-COOR_{26}$; (s) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (t) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (u) $-CONR_{26}R_{26}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) $-NR_{29}R_{30}$; (h) arilo; (i) arilalquilo; (j) heteroarilo; (k) heteroarilalquilo; (l) heterociclilo; (m) heterociclilalquilo; (n) haloalquilo de $C_1$-$C_6$; (o) $-CONR_{26}R_{26}$; (p) alquenilo de $C_2$-$C_6$; (q) alquinilo de $C_2$-$C_6$; (r) cicloalquilo; (s) cicloalquilalquilo; (t) $-COR_{26}$; o (u) $-COOR_{26}$;

$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9)

arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) haloalquilo de $C_1$-$C_6$, 13) alquenilo de $C_2$-$C_6$, 14) -COOH, 15) $-CONR_{36}R_{36}$, 16) =O, 17) alquinilo de $C_2$-$C_6$, 18) $-COR_{36}$, 19) $-SO_2NHR_{36}$, 20) $-COOR_{36}$, y 21) $-NHC(CN)NHR_{36}$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) $-NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) -COOH, 17) $-CONR_{36}R_{36}$, 18) =O, 19) alquinilo de $C_2$-$C_6$, 20) $-COR_{36}$, 21) $-SO_2NHR_{36}$, 22) $-COOR_{36}$, y 23) $-NHC(CN)NHR_{36}$;

(c) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) -

$NR_{29}R_{30}$, 9) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 12) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 13) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 14) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 15) haloalquilo de $C_1$-$C_6$, 16) alquenilo de $C_2$-$C_6$, 17) -COOH, 18) -$CONR_{36}R_{36}$, 19) =O, 20) alquinilo de $C_2$-$C_6$, 21) -$COR_{36}$, 22) -$SO_2NHR_{36}$, 23) -$COOR_{36}$, y 24) -NHC(CN)$NHR_{36}$; o

(d) hidrógeno;

$R_{29}$ y $R_{30}$ son independientemente hidrógeno o -$[(C=O)O_r]_s$alquilo, en donde el alquilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{36}$, cada que se presenta, es independientemente alquilo, arilo o heteroarilo, en donde el alquilo, arilo o heteroarilo puede substituirse opcionalmente con uno o más de $R_{40}$;

$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, alquenilo, arilalquiloxi, =O, alquinilo, cicloalquilo, o cicloalquilalquilo;

r es 0 hasta 2; y

s es 0 hasta 1.

9.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

A es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 14) haloalquilo de $C_1$-$C_6$, y 15) $-COR_6$;

B es fenilo, que está substituido con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede substituirse opcionalmente con uno o más de $R_{20}$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) $-NR_9R_{10}$, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 11) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$;

C es metilo, que es substituido con un heteroarilo que contiene nitrógeno de 5 ó 6 miembros, que puede substituirse opcionalmente con uno o más de $R_{20}$;

$R_1$ es $-C(O)R_3$, $-C(O)NHR_3$ o $-CH_2R_8$;

$R_3$ es:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) haloalquilo de $C_1$-$C_6$, 11) alquenilo de $C_2$-$C_6$, 12) alquinilo de $C_2$-$C_6$, 13) $-COR_6$, y 14) $-COOR_6$;

(b) arilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse

opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_6$, y 17) $-COOR_6$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_6$, y 17) $-COOR_6$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del

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grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_6$, y 17) -$COOR_6$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_6$, y

17) $-COOR_6$;

$R_6$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) $-OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) -COOH, 14) alquinilo de $C_2$-$C_6$, 15) $-COR_{36}$, y 16) $-COOR_{36}$; o

(b) hidrógeno;

$R_8$ puede ser independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) haloalquilo de $C_1$-$C_6$, 11) alquenilo de $C_2$-$C_6$, 12) alquinilo de $C_2$-$C_6$, 13) $-COR_{26}$, y 14) $-COOR_{26}$;

(b) arilo, que puede substituirse opcionalmente con

uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_{26}$, y 17) -$COOR_{26}$;

(c) cicloalquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) -$OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) -$COR_{26}$, y

17) $-COOR_{26}$;

(d) heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_{26}$, y 17) $-COOR_{26}$; o

(e) heterociclilo, diferente a heteroarilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, 3) $-OR_{26}$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) arilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 8) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 10) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 11) heterociclilo, que puede substituirse opcionalmente con uno o

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más de $R_{20}$, 12) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{20}$, 13) haloalquilo de $C_1$-$C_6$, 14) alquenilo de $C_2$-$C_6$, 15) alquinilo de $C_2$-$C_6$, 16) $-COR_{26}$, y 17) $-COOR_{26}$;

$R_{20}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) arilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (h) arilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (i) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (j) heteroarilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (k) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (l) heterociclilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; (m) haloalquilo de $C_1$-$C_6$; (n) alquenilo de $C_2$-$C_6$; (o) alquinilo de $C_2$-$C_6$; (p) $-COR_{26}$; (q) $-COOR_{26}$; (r) cicloalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$; o (s) cicloalquilalquilo, que puede substituirse opcionalmente con uno o más de $R_{21}$;

$R_{21}$ es: (a) halo; (b) alquilo de $C_1$-$C_6$; (c) $-OR_{26}$; (d) alquiltio de $C_1$-$C_6$; (e) ciano; (f) nitro; (g) arilo; (h) arilalquilo; (i) heteroarilo; (j) heteroarilalquilo; (k) heterociclilo; (l) heterociclilalquilo; (m) haloalquilo de $C_1$-$C_6$; (n) alquenilo de $C_2$-$C_6$; (o) alquinilo de $C_2$-$C_6$; (p) cicloalquilo; (q) cicloalquilalquilo; (r) $-COR_{26}$; o (s) $-COOR_{26}$;

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$R_{26}$, cada que se presenta, es independientemente:

(a) alquilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) -OH, 3) alquilo de $C_1$-$C_6$, 4) -$OR_{36}$, 5) alquiltio de $C_1$-$C_6$, 6) ciano, 7) nitro, 8) arilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 9) heteroarilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 10) heterociclilo, que puede substituirse opcionalmente con uno o más de $R_{40}$, 11) haloalquilo de $C_1$-$C_6$, 12) alquenilo de $C_2$-$C_6$, 13) -COOH, 14) alquinilo de $C_2$-$C_6$, 15) -$COR_{36}$, o 16) -$COOR_{36}$; o

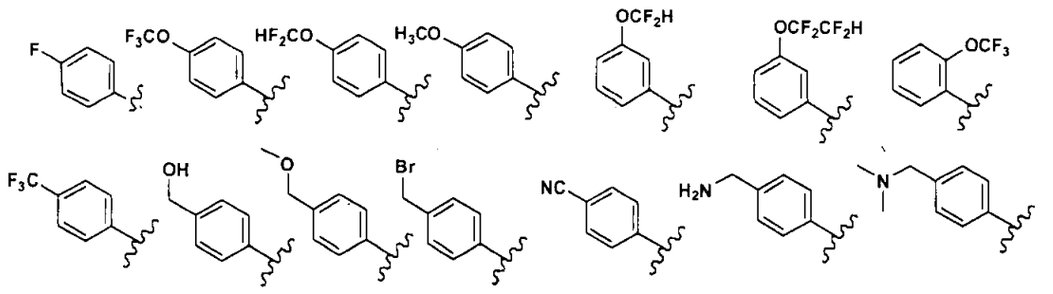
(b) hidrógeno;

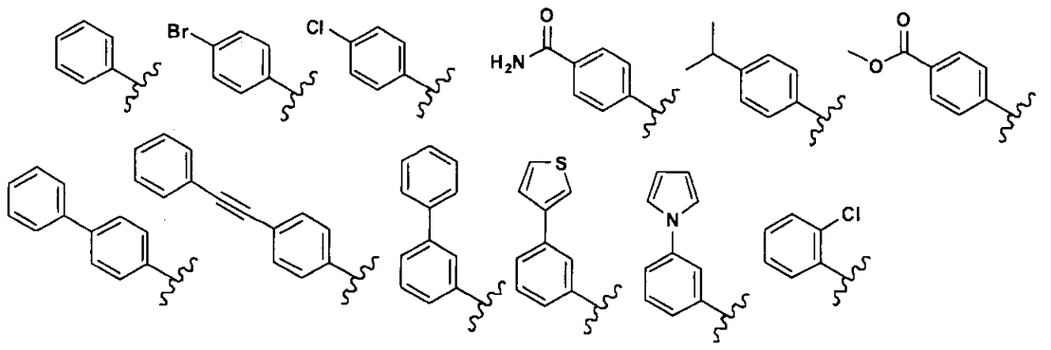
$R_{36}$, cada que se presenta, es independientemente alquilo, arilo o heteroarilo, en donde el alquilo, arilo o heteroarilo puede substituirse opcionalmente con uno o más de $R_{40}$; y

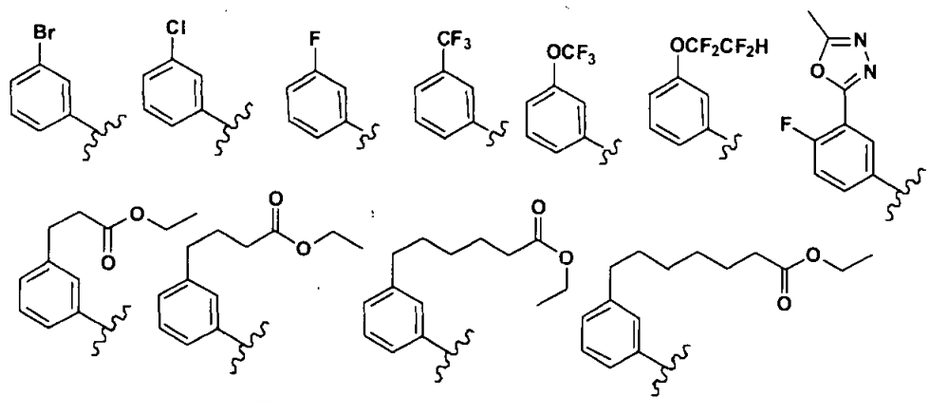
$R_{40}$ es halo, -OH, alquilo, alquiloxi, alquiltio, ciano, nitro, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclilalquilo, haloalquilo, haloalquiloxi, alquenilo, arilalquiloxi, alquinilo, cicloalquilo o cicloalquilalquilo.

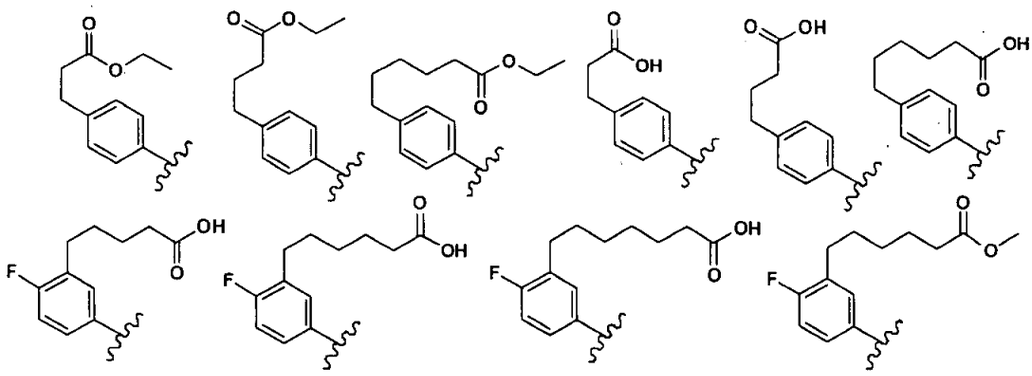
10.- El compuesto de conformidad con la reivindicación 1, caracterizado porque:

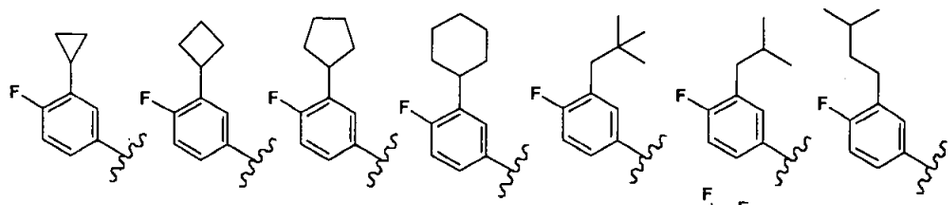
A es:

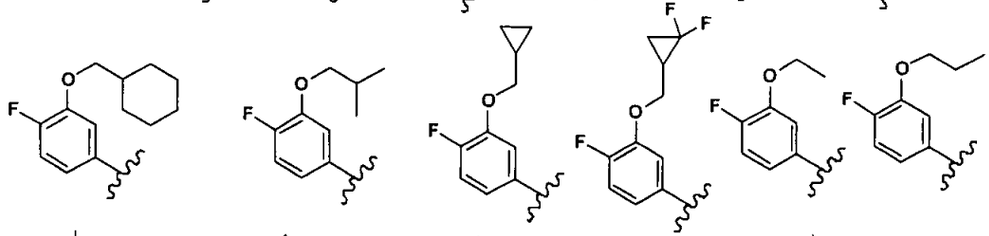

F
F3CO
HF2CO
H3CO
OCF2H
OCF2CF2H
OCF3
F3C
OH
O
Br
NC
H2N
N

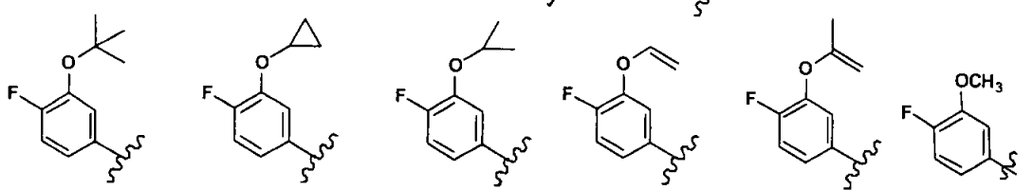

Br
Cl
O
H2N
O
O
S
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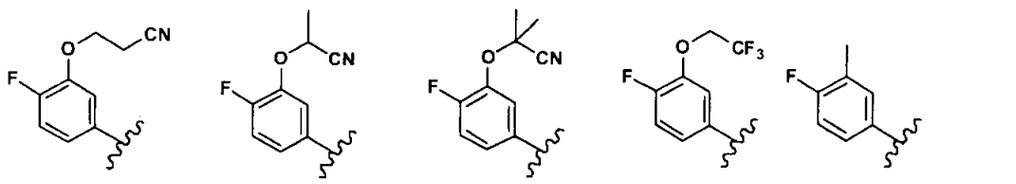

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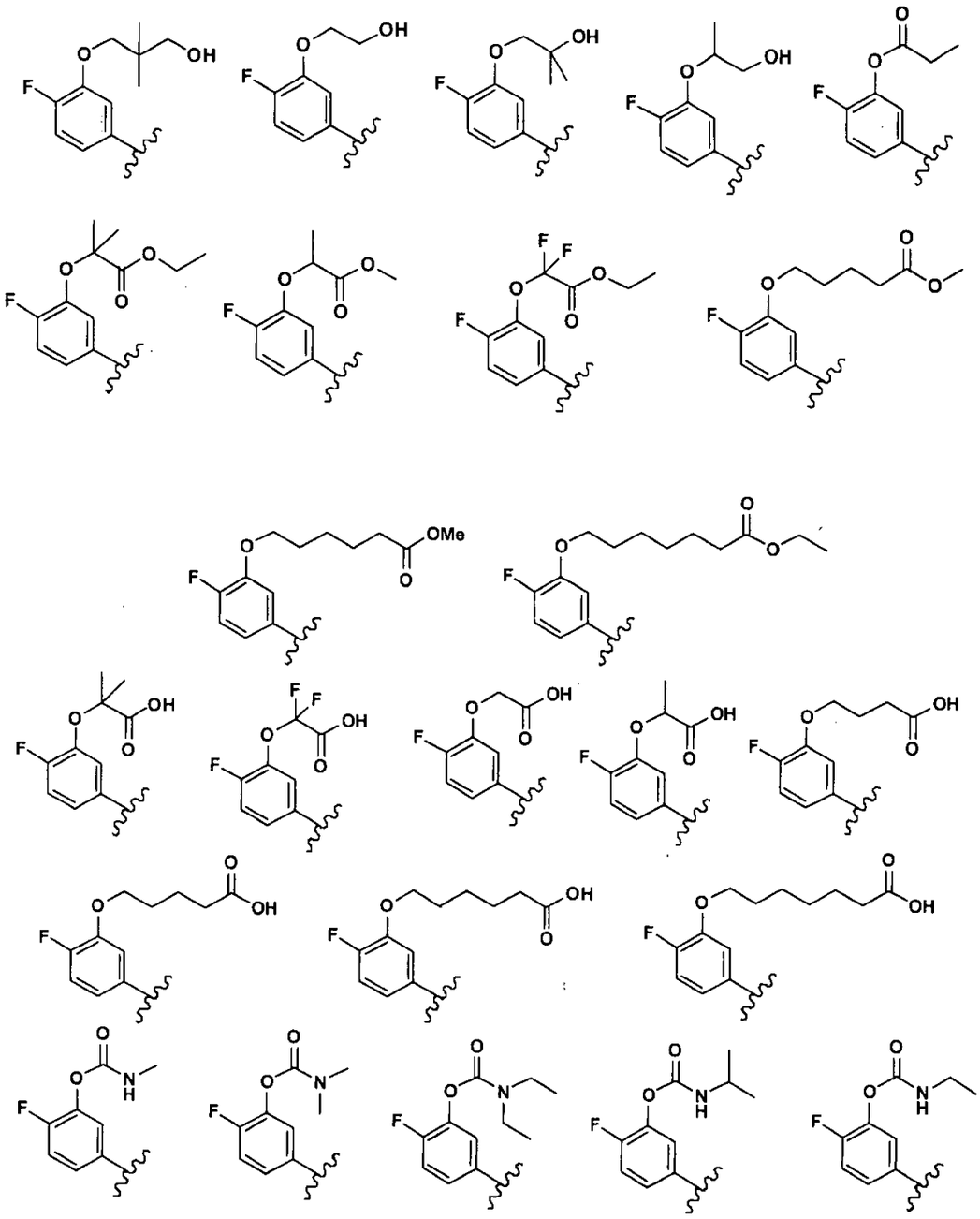


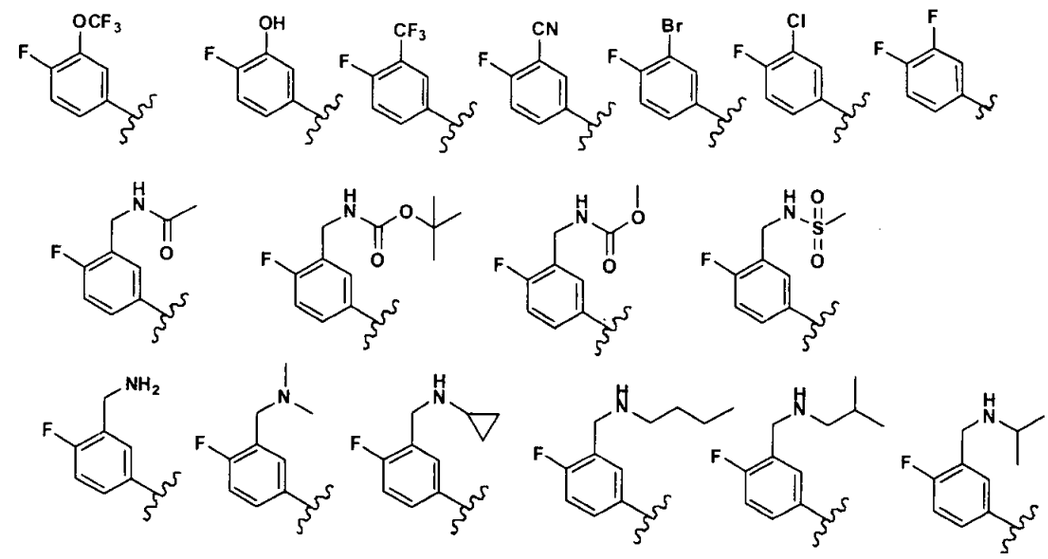


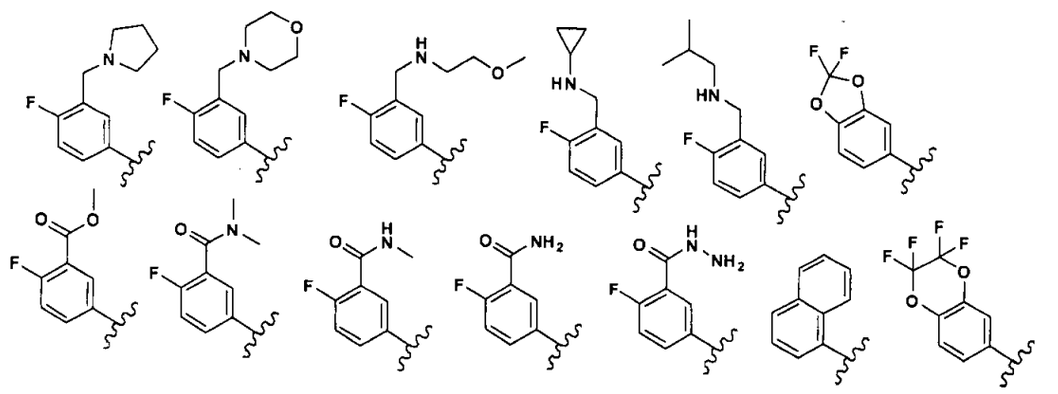


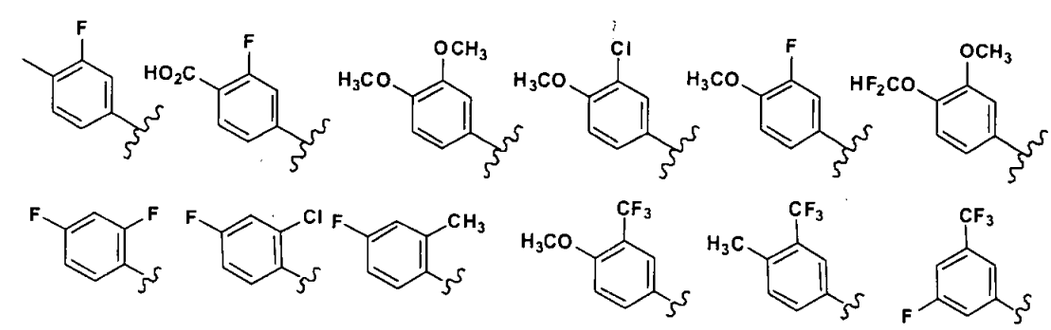


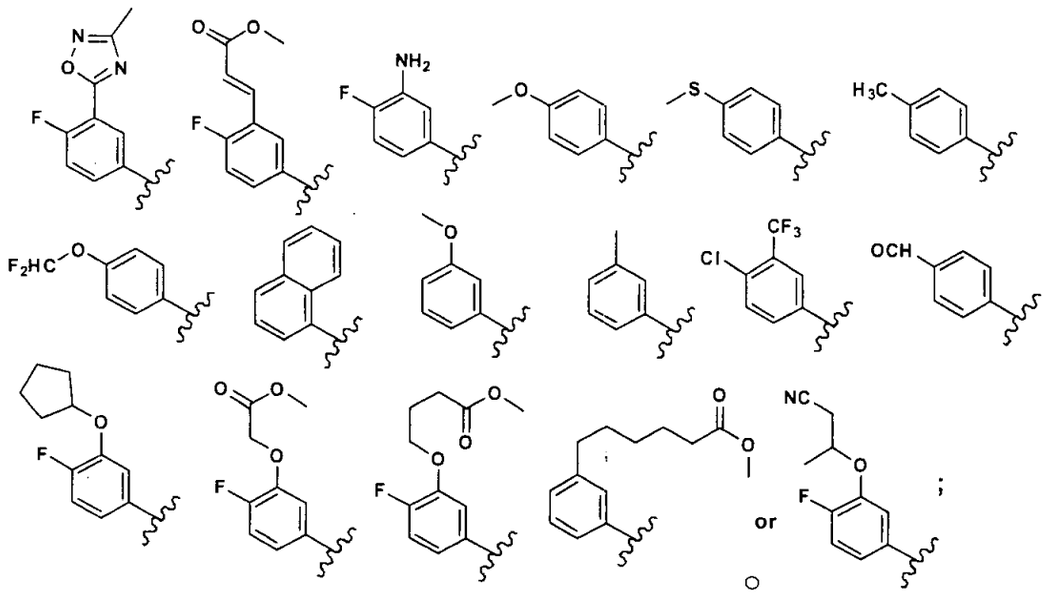










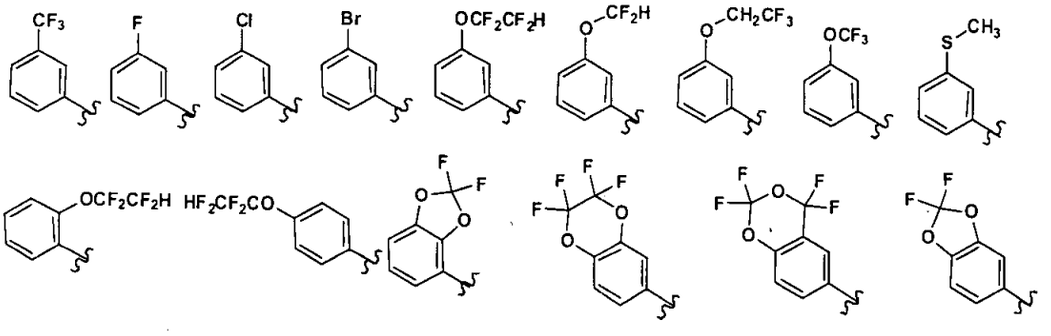


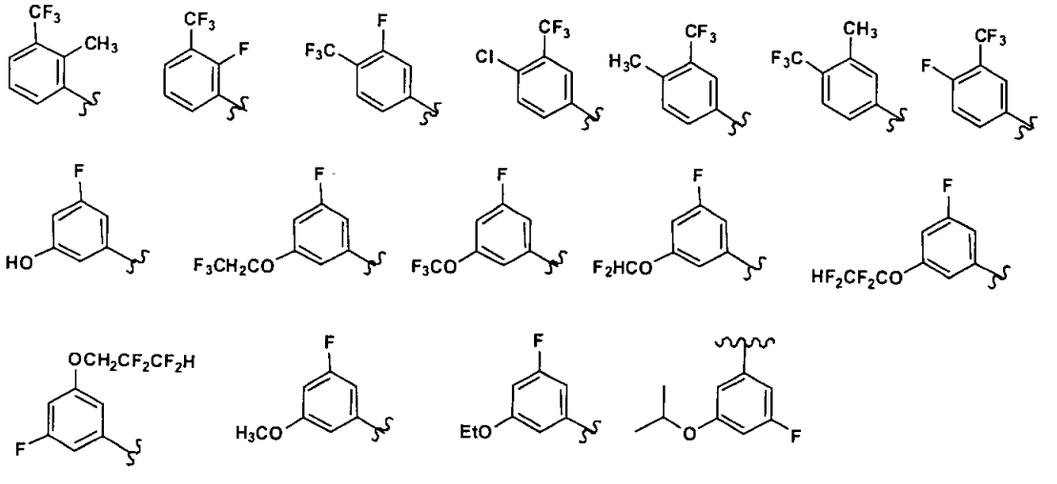
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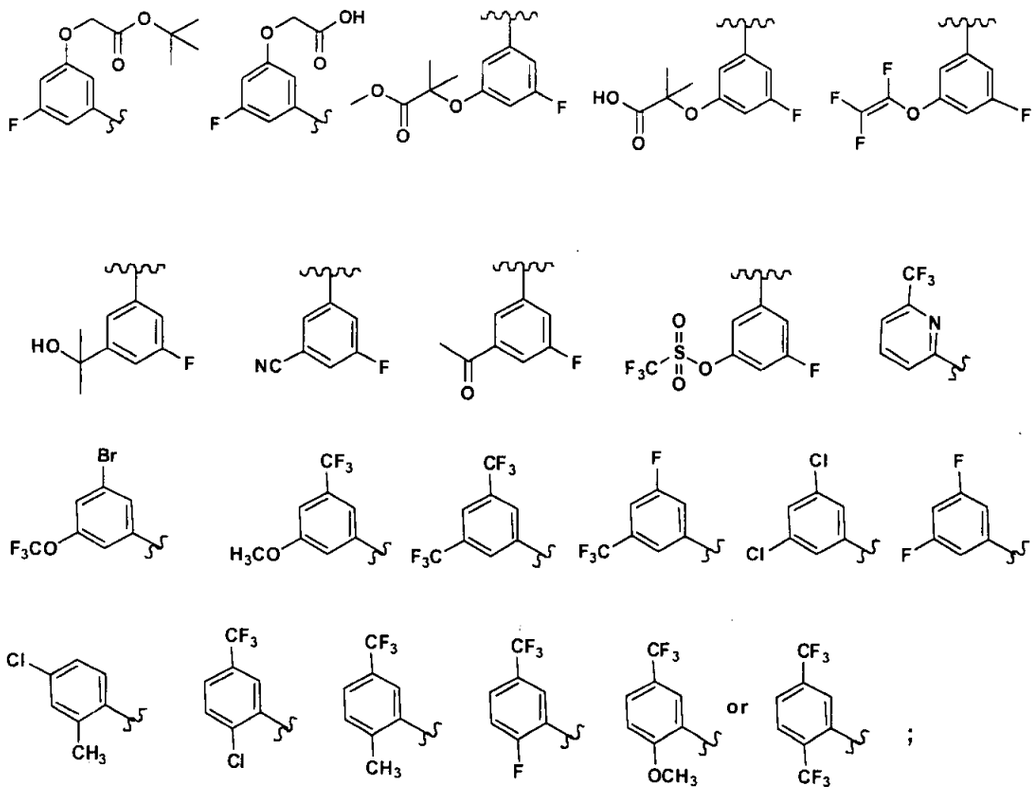


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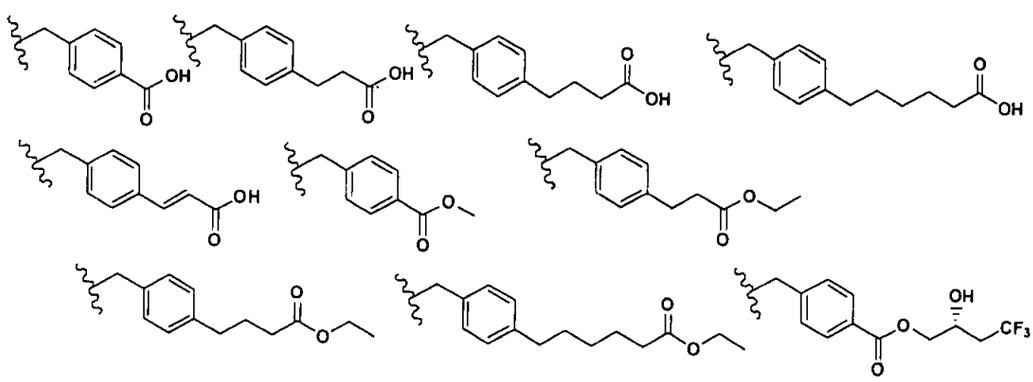
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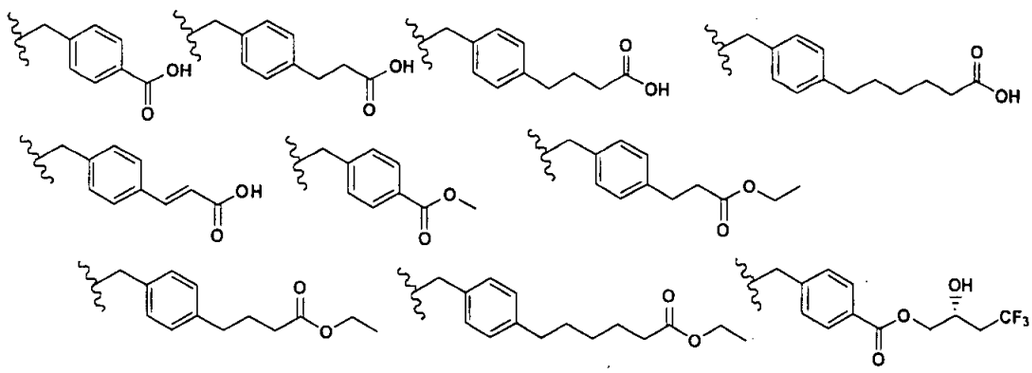


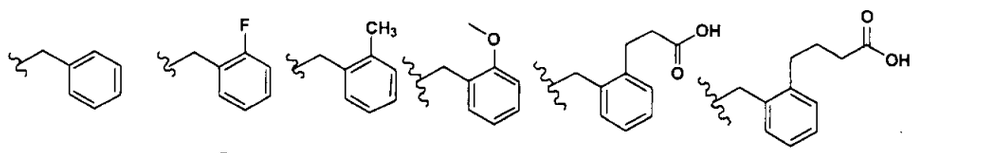


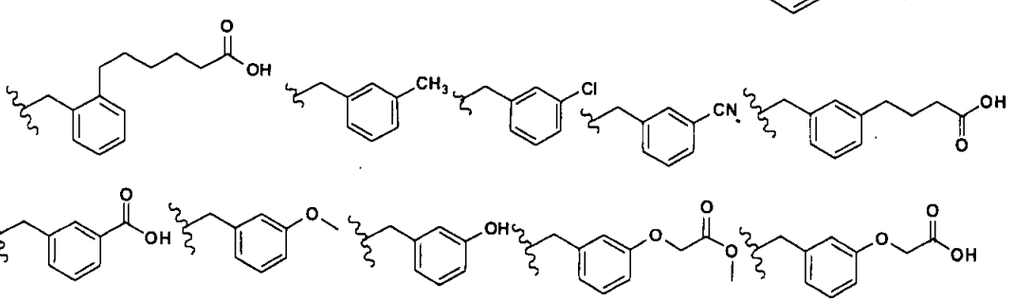
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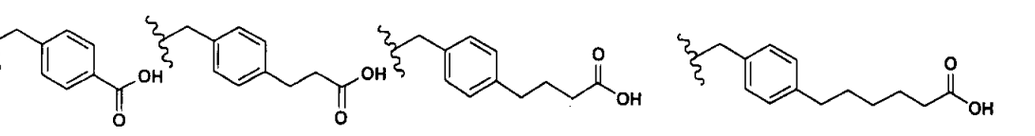


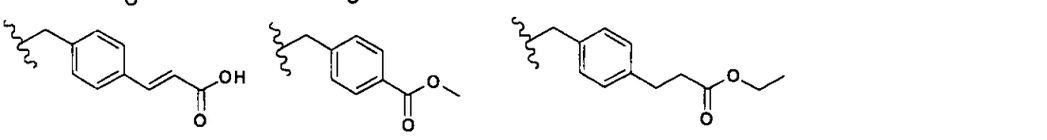


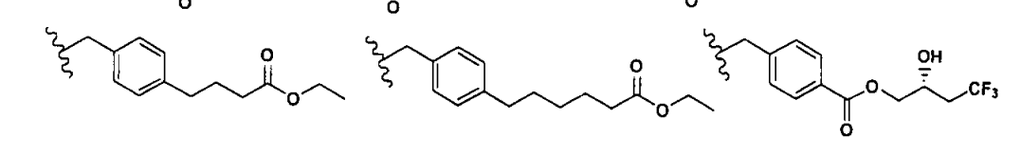






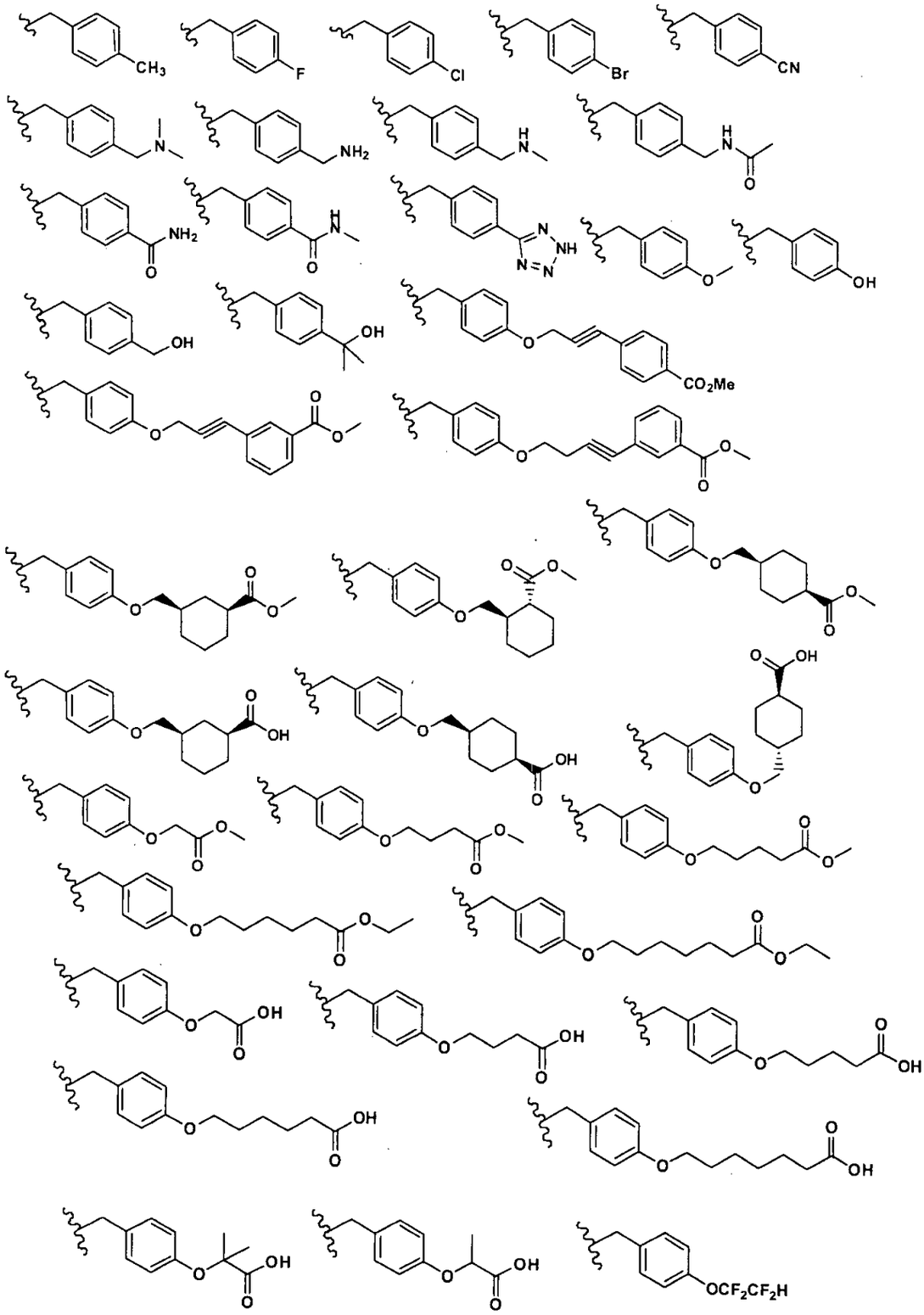


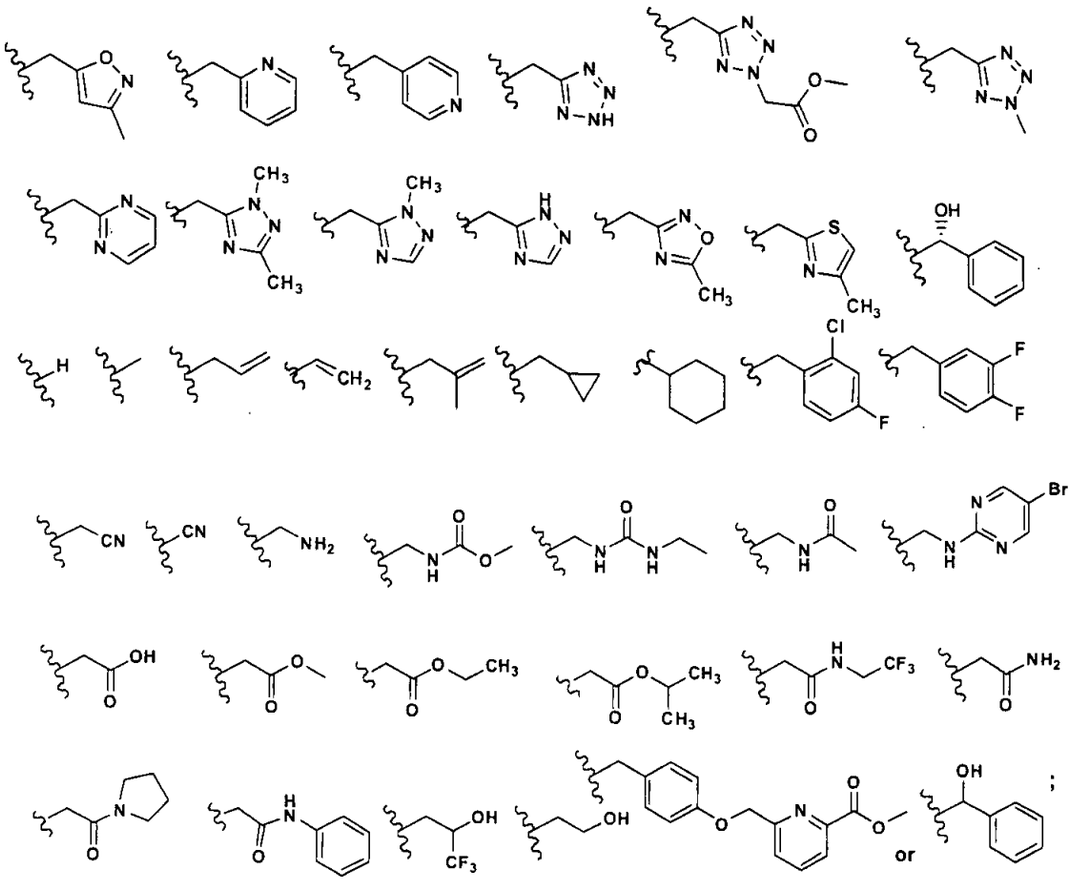






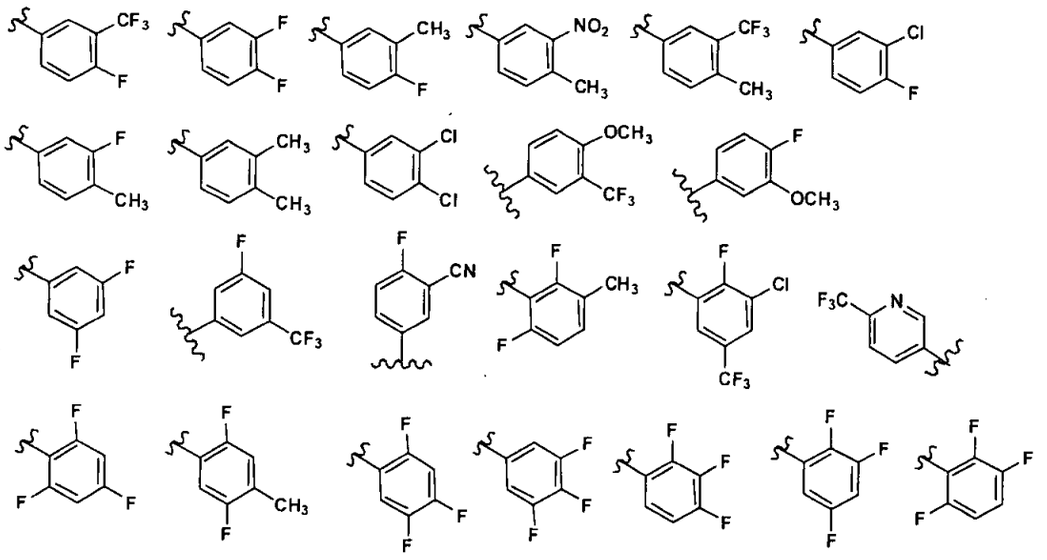
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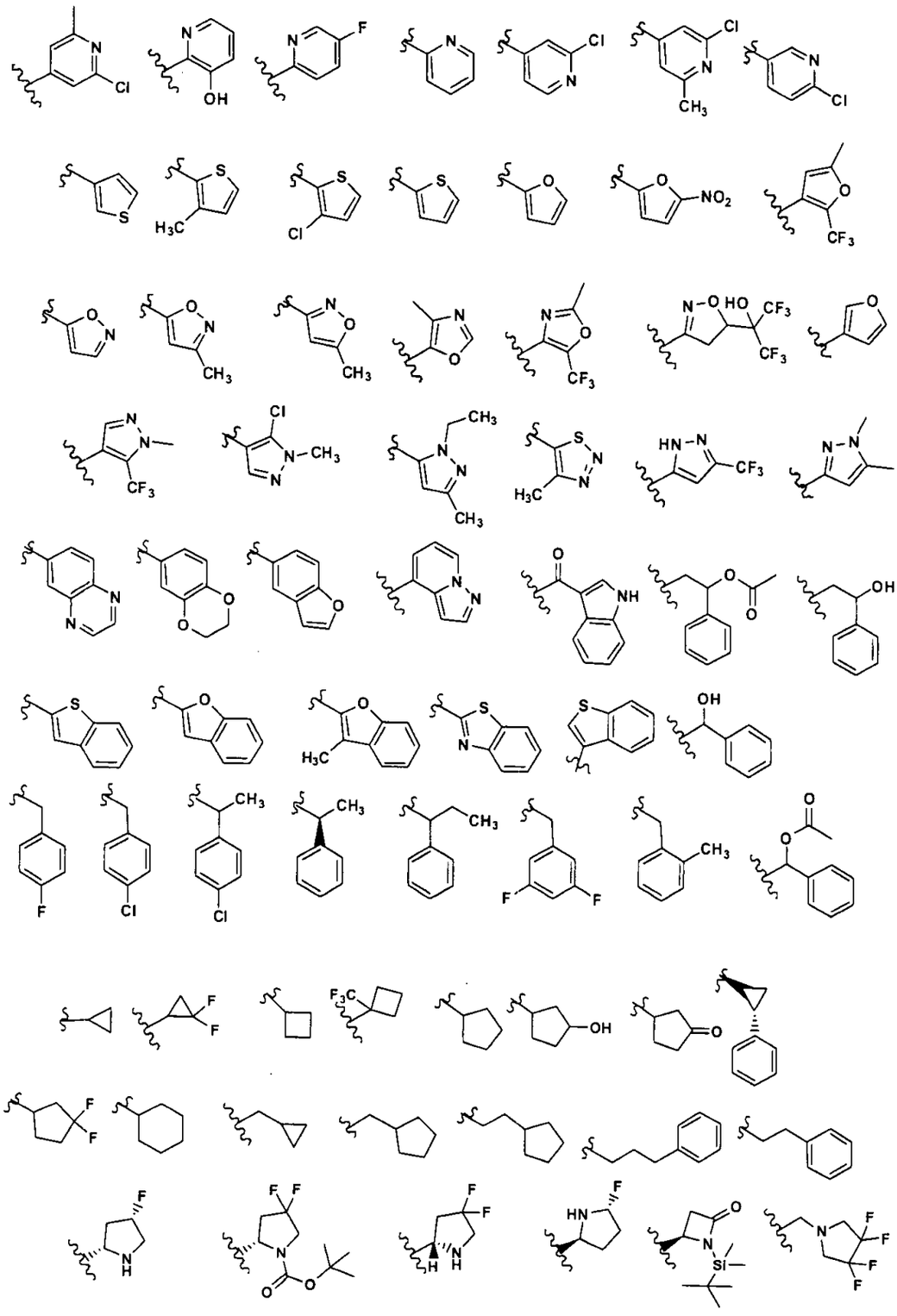


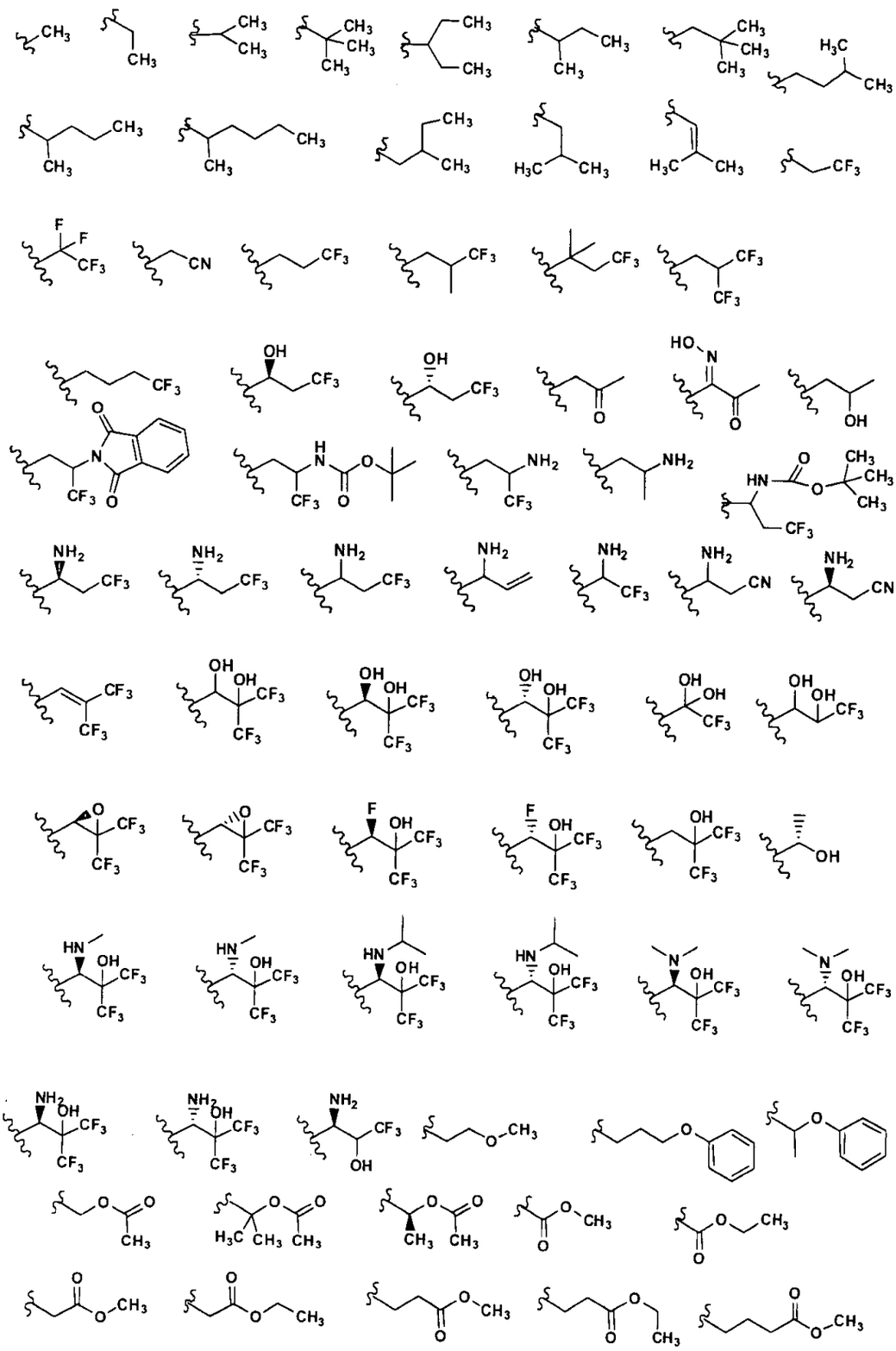


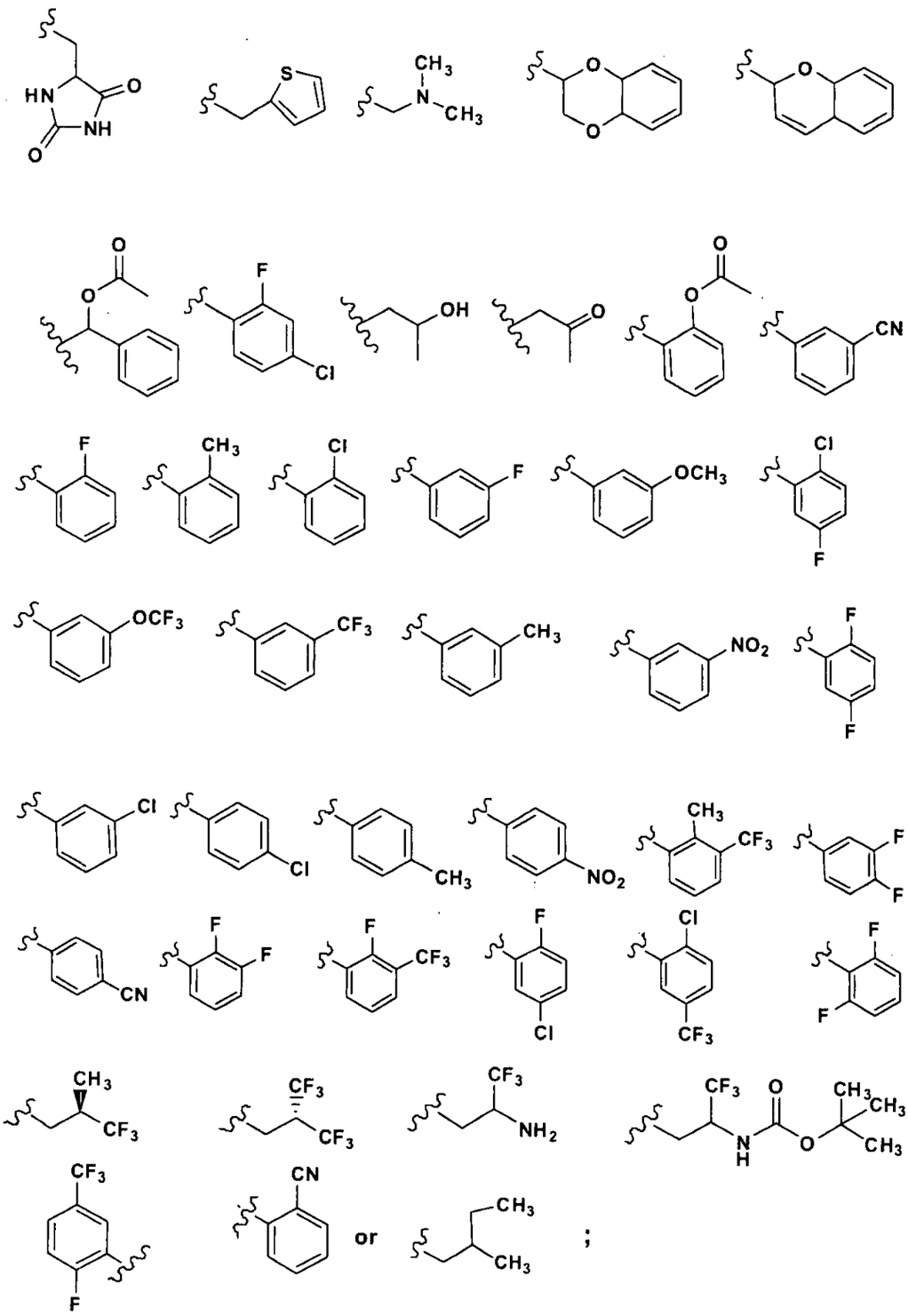
$R_1$ es:

(a) $-C(O)R_3$, en donde $R_3$:

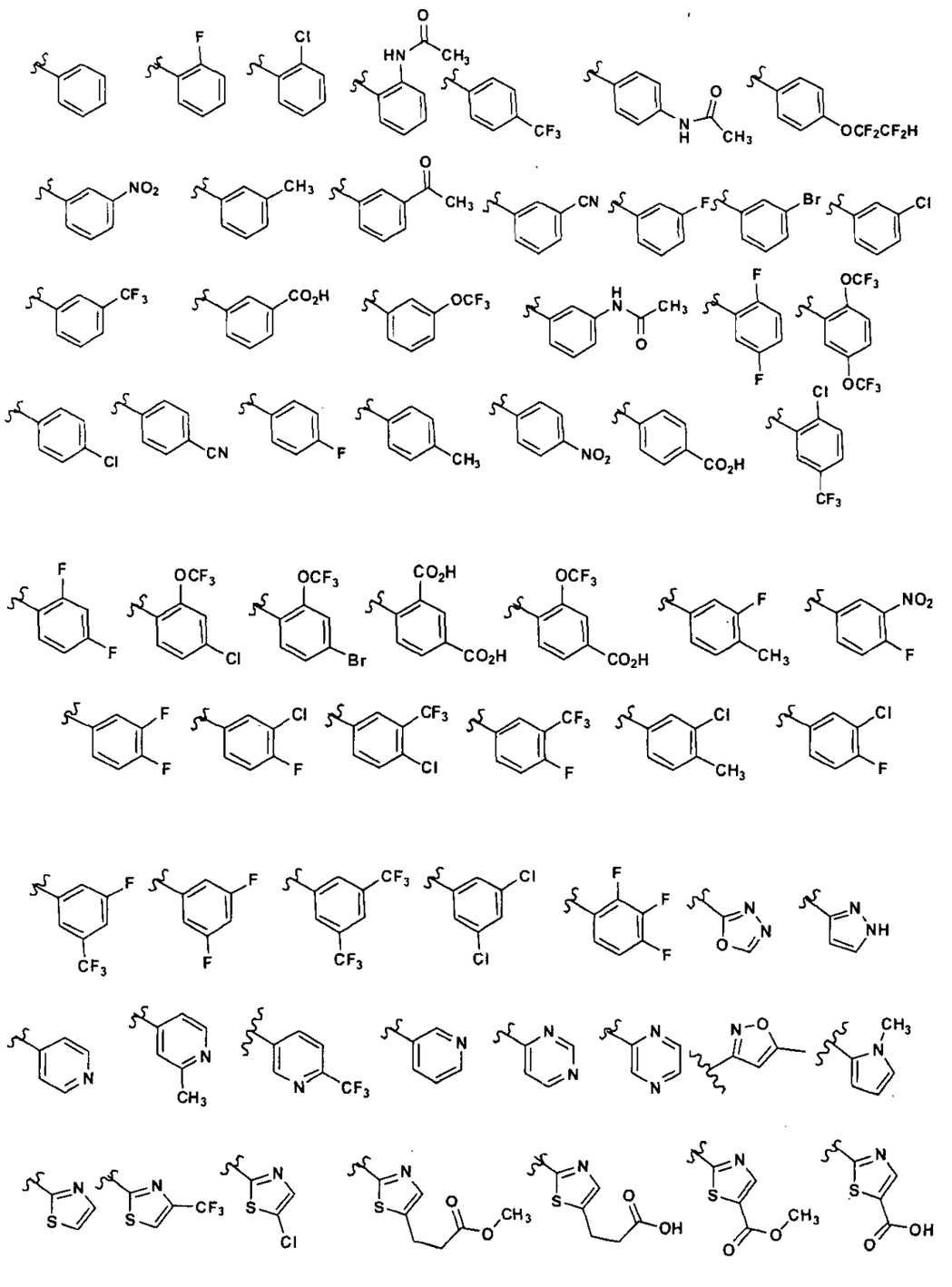




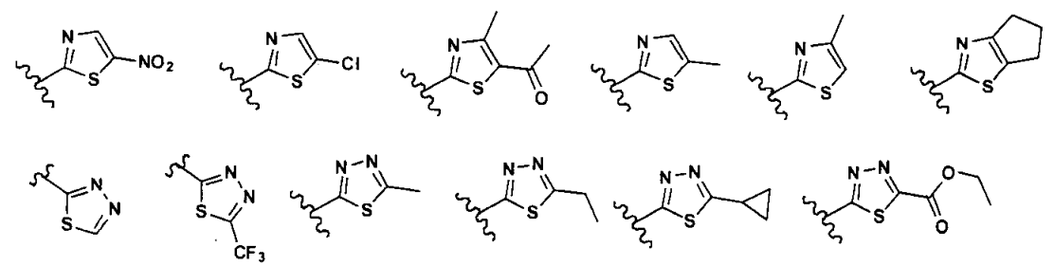


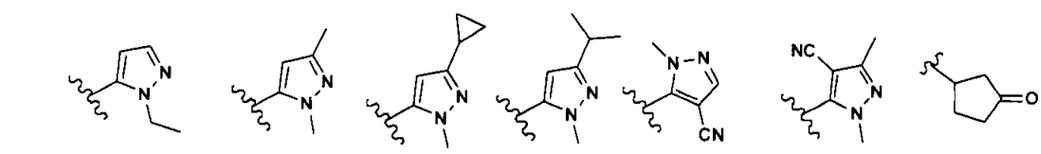

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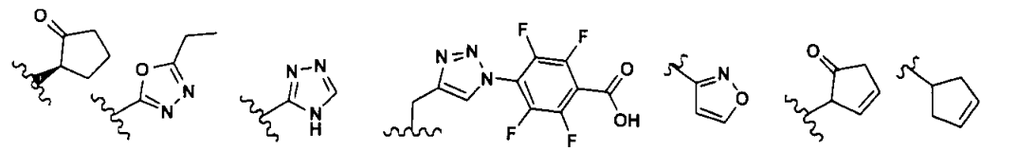
(b) $-C(O)NHR_3$, en donde el $R_3$ es:

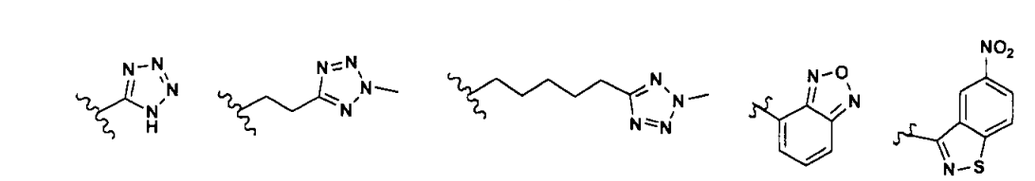


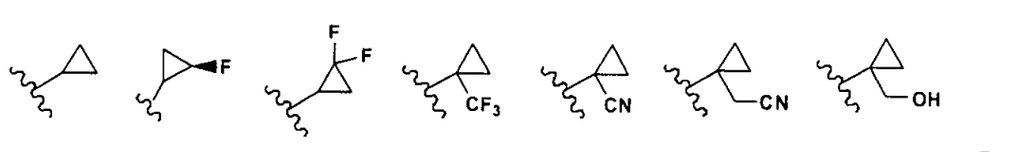
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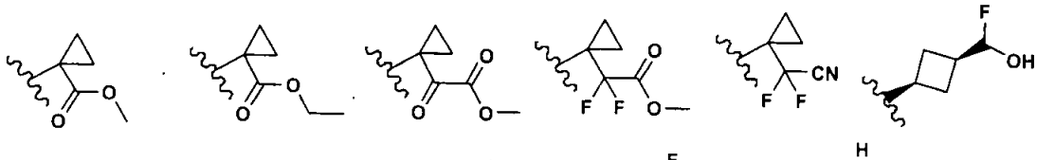


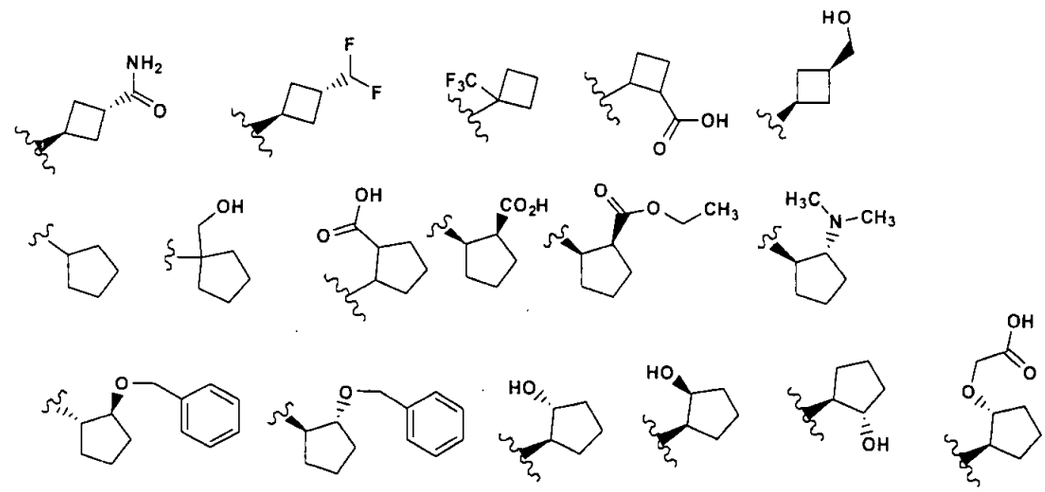


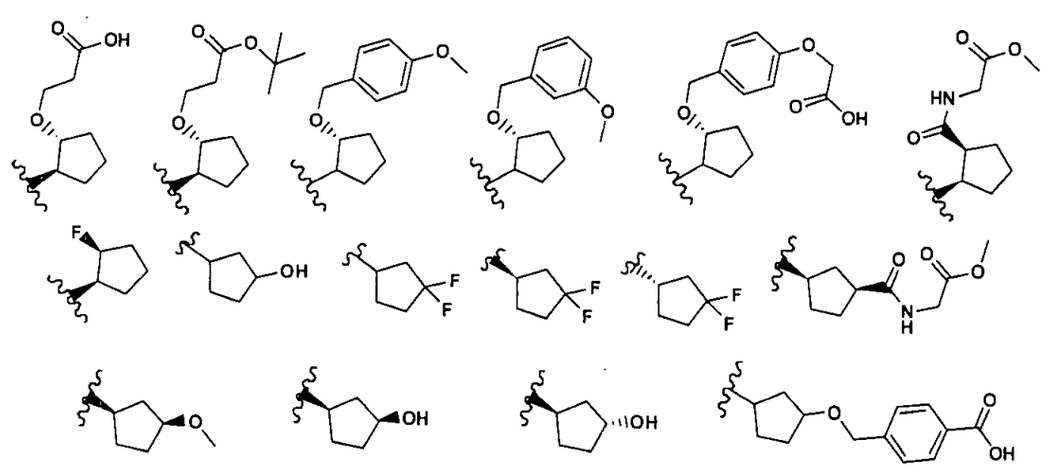


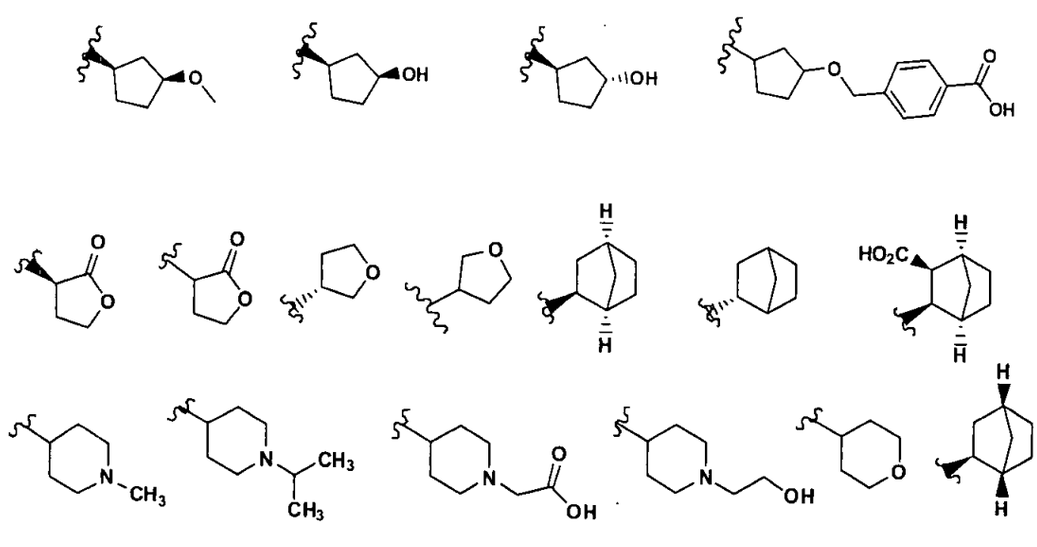


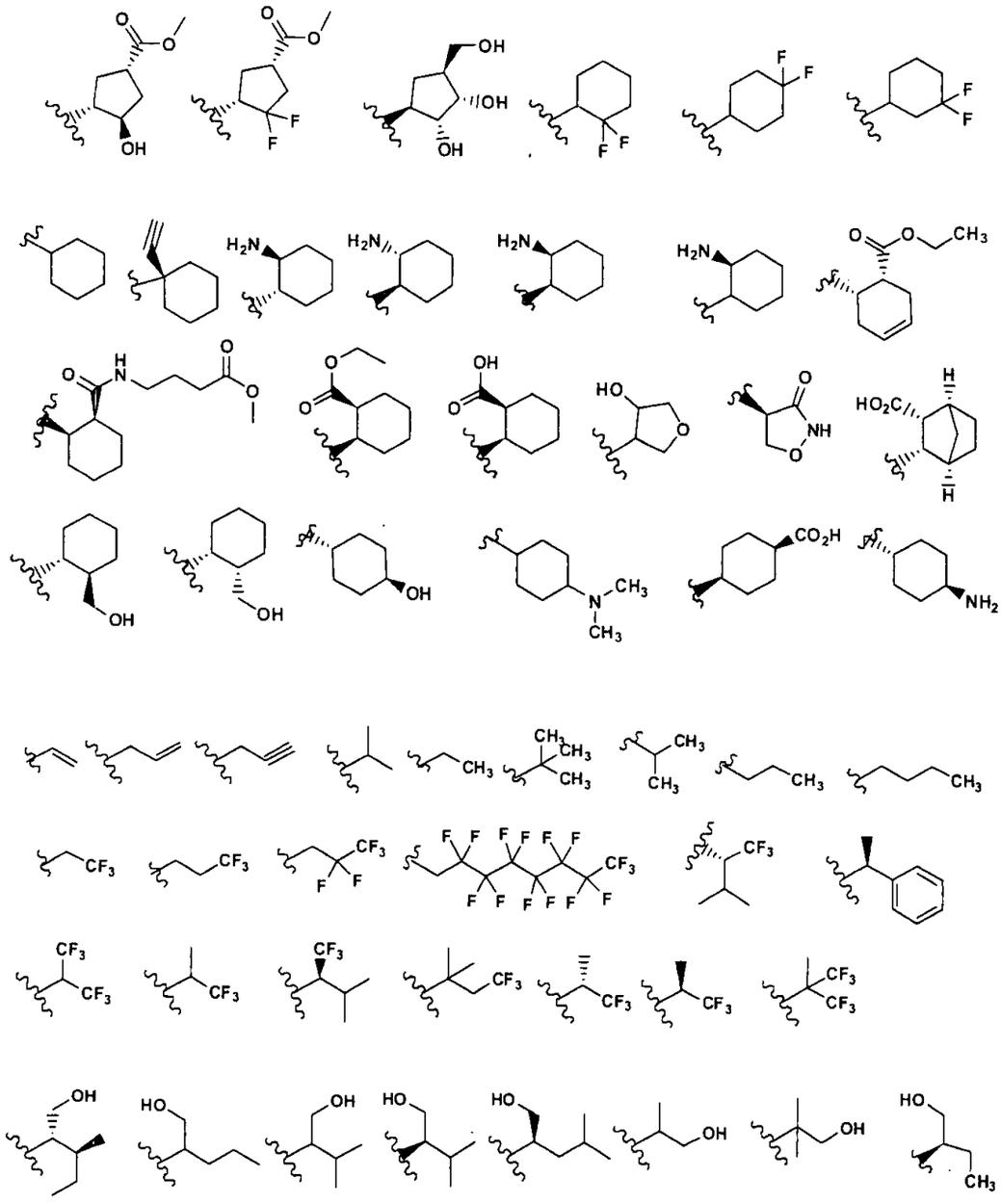


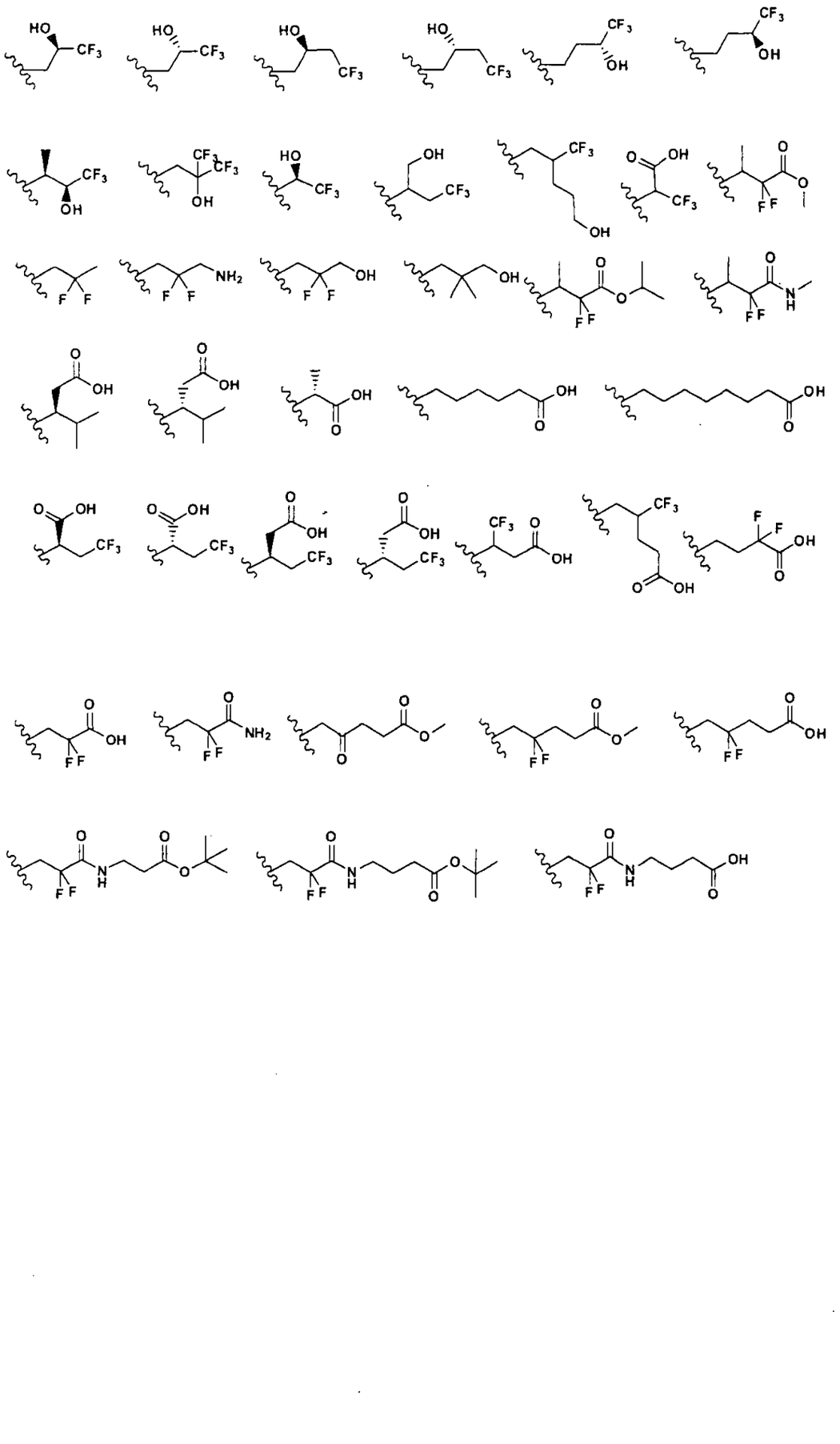


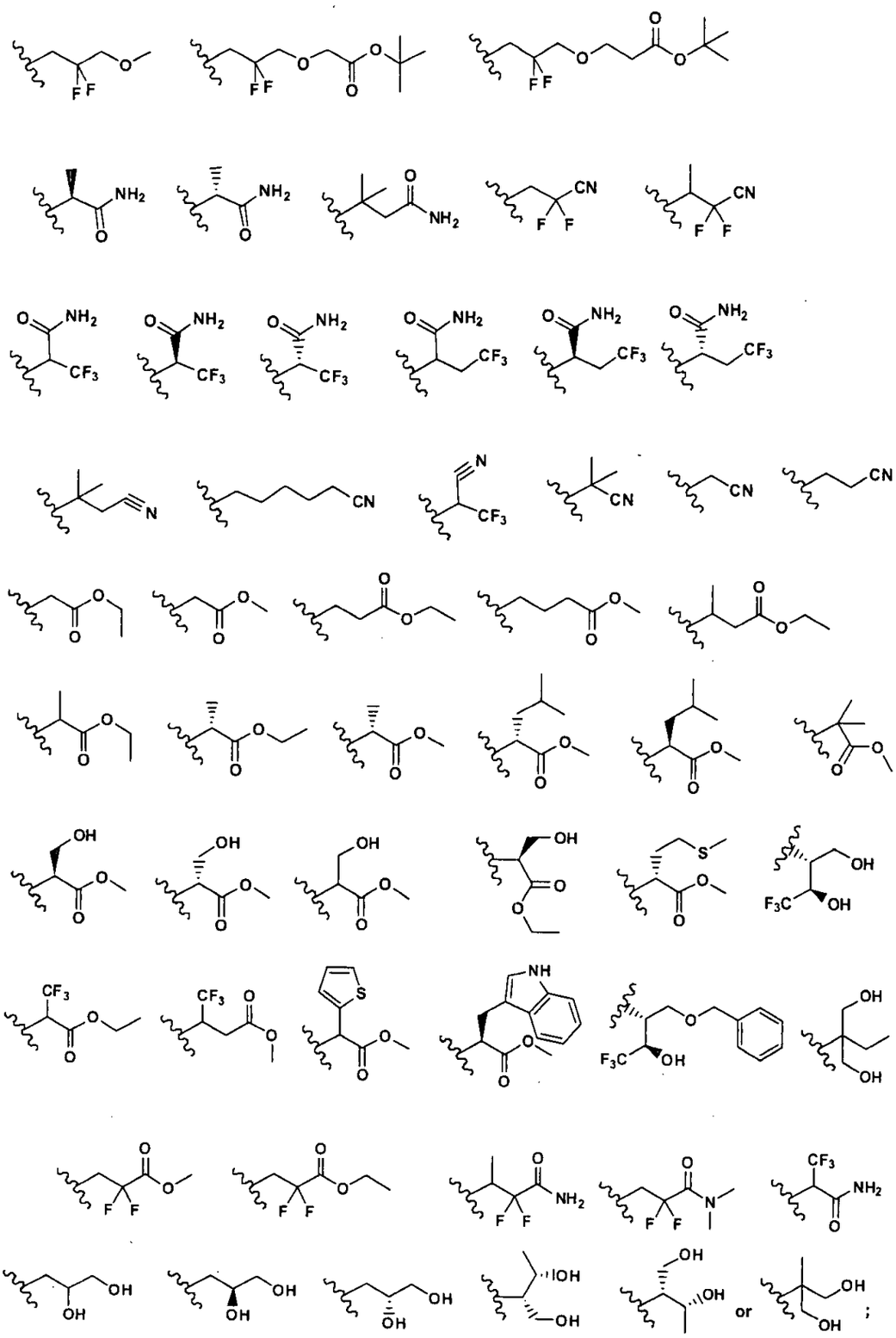






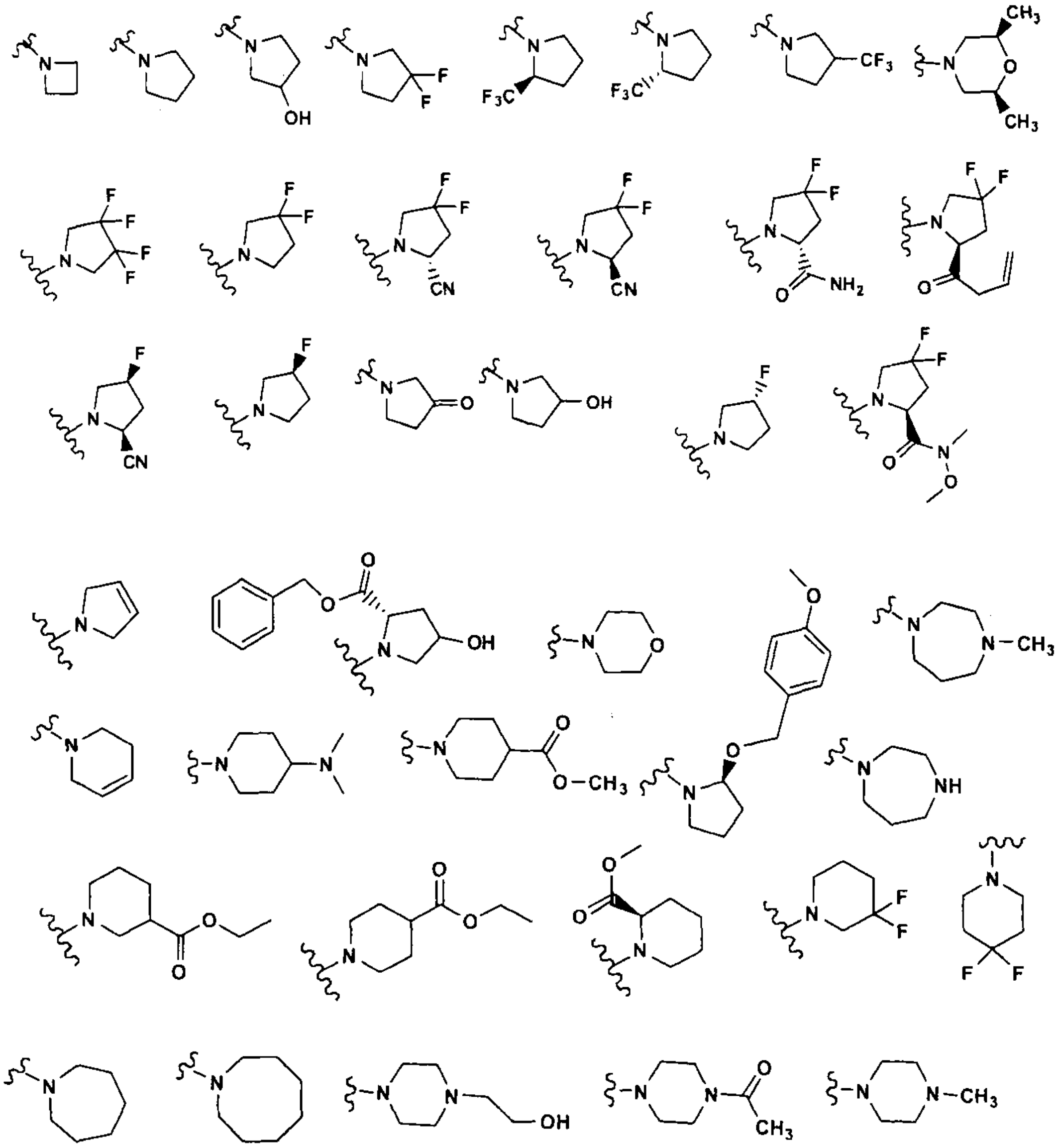




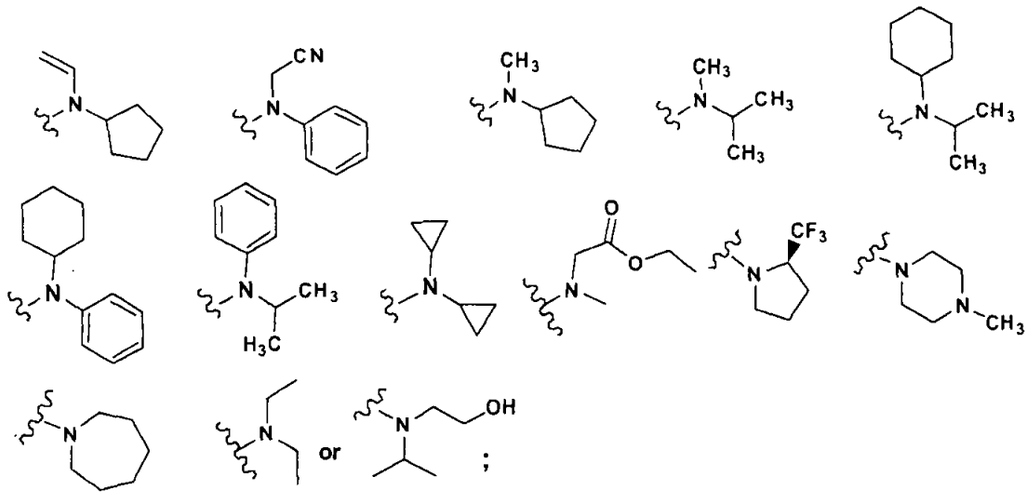


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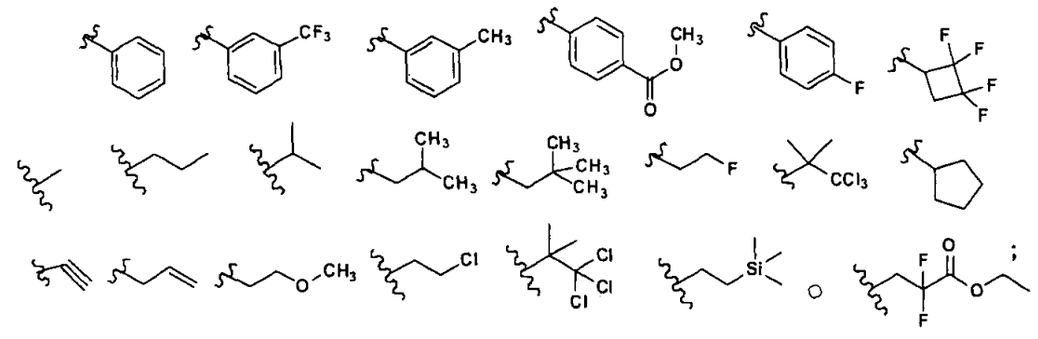
(c) $-C(O)NR_2R_3$, en donde el $NR_2R_3$ es:



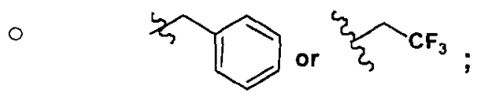
2026



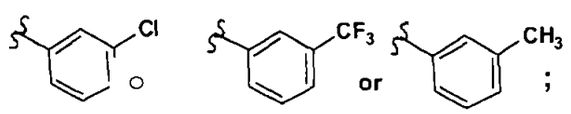
(d) $-C(O)OR_4$ en donde el $R_4$ es:



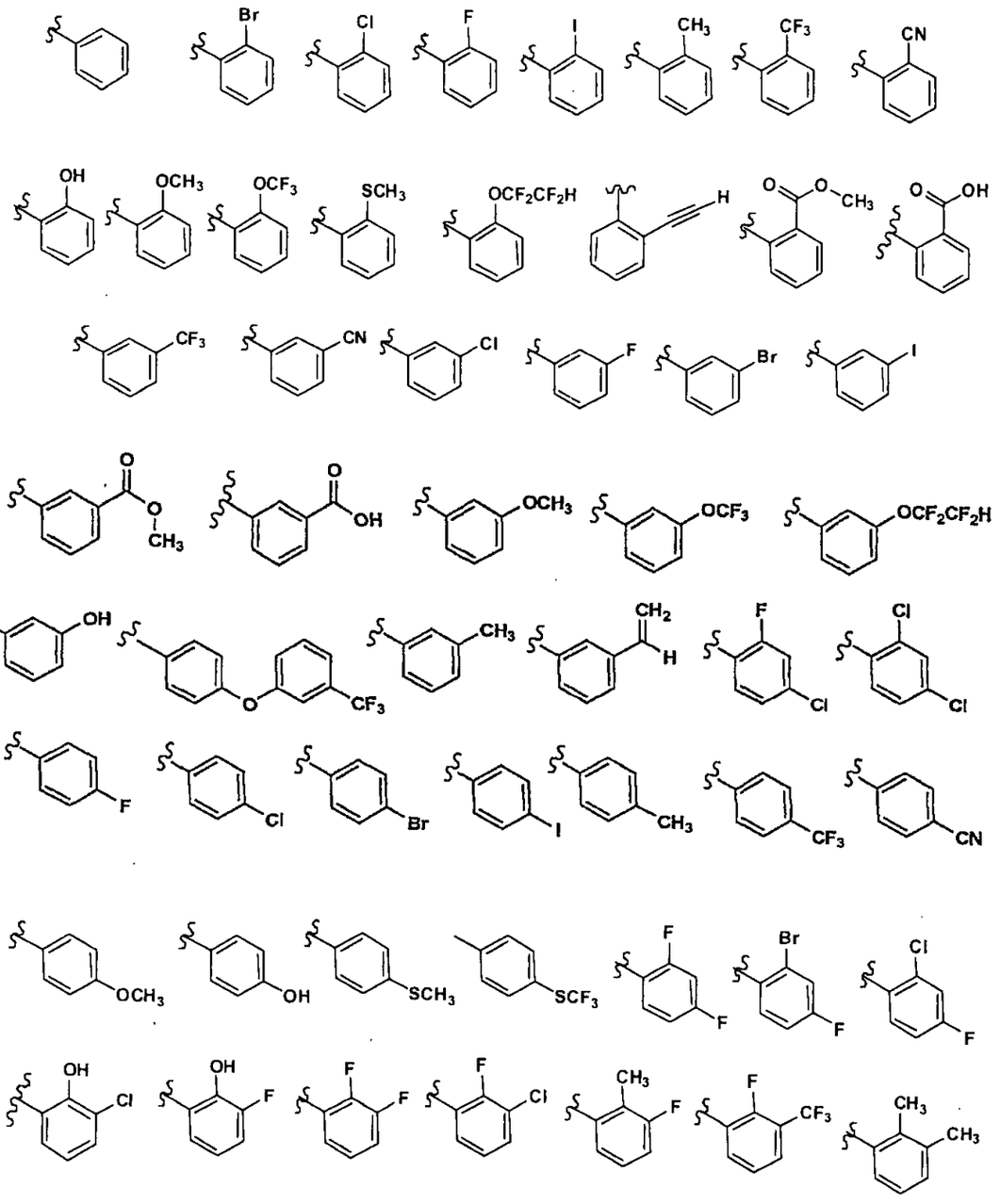
(e) $-SO_2R_5$ en donde el $R_5$ es:



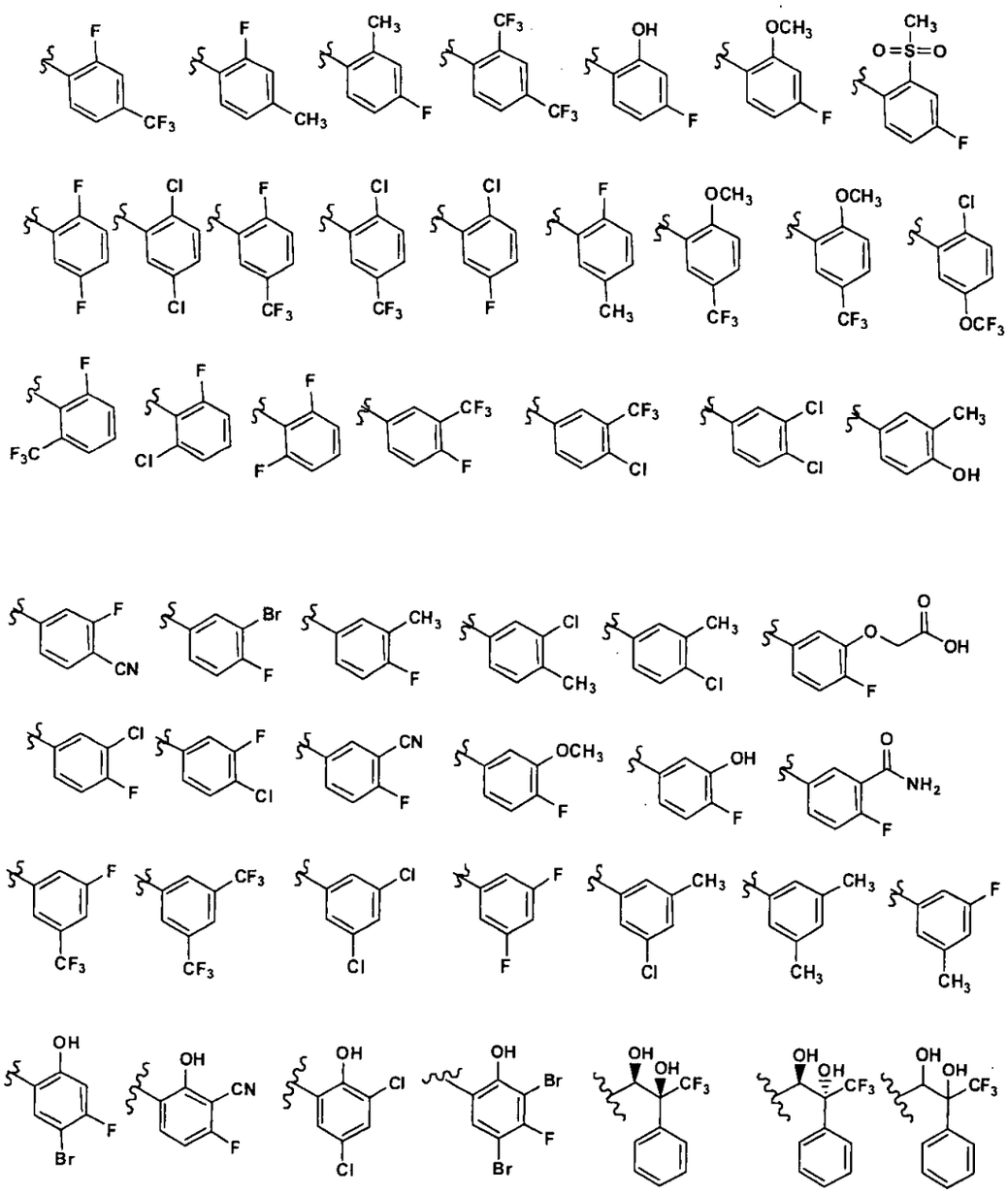
(f) $-CSNHR_7$ en donde el $R_7$ es:

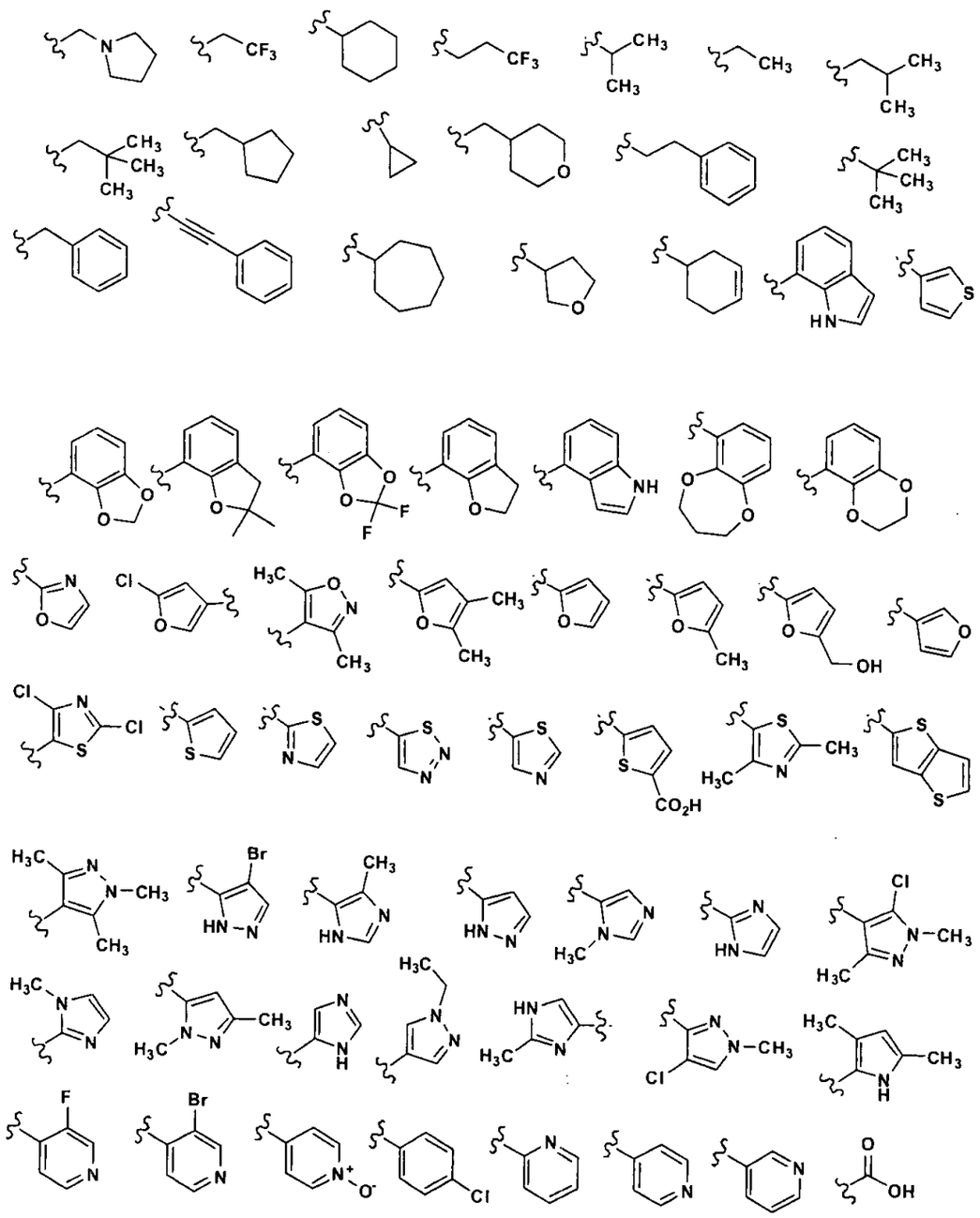


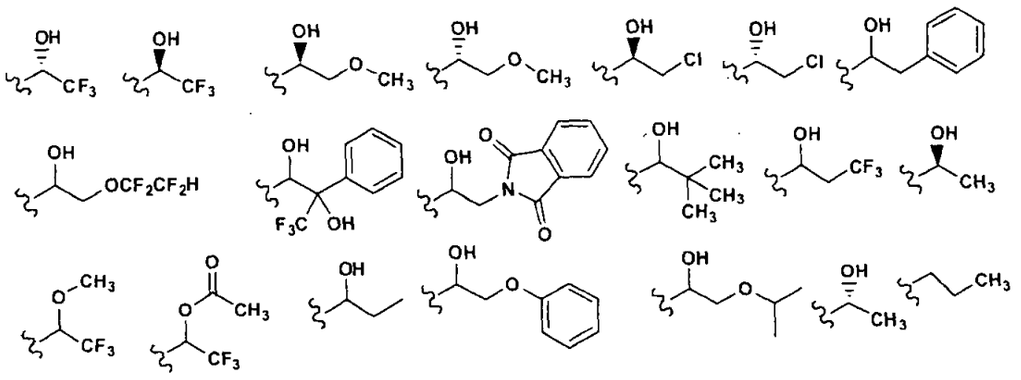
(g) $-CH_2R_8$ en donde el $R_8$ es:

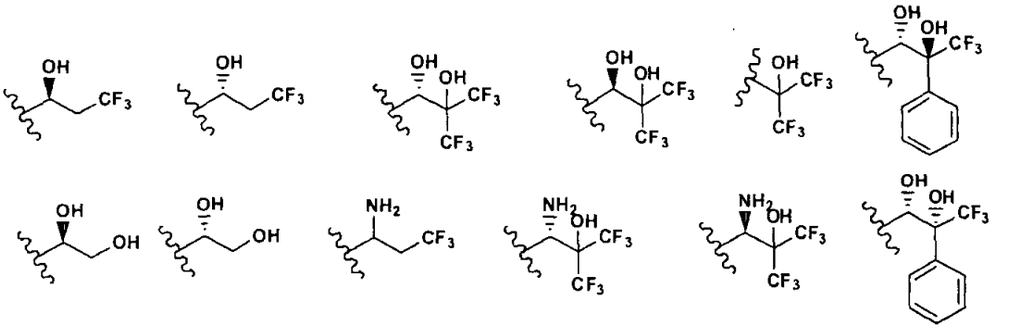


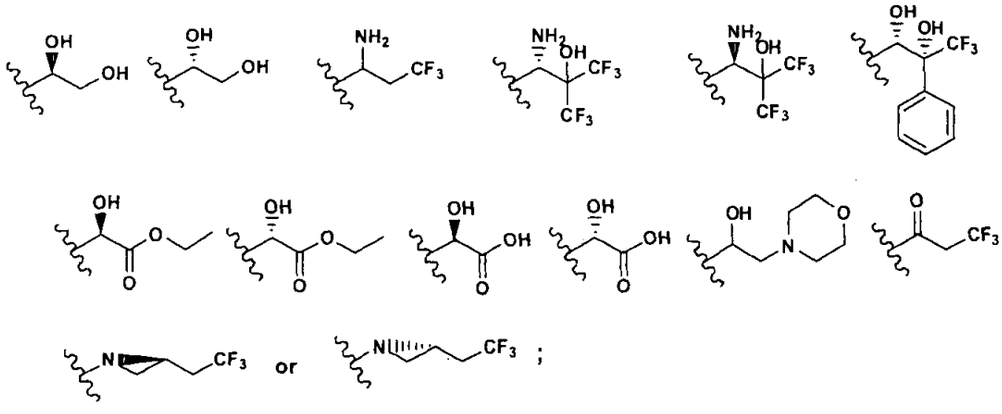
2028





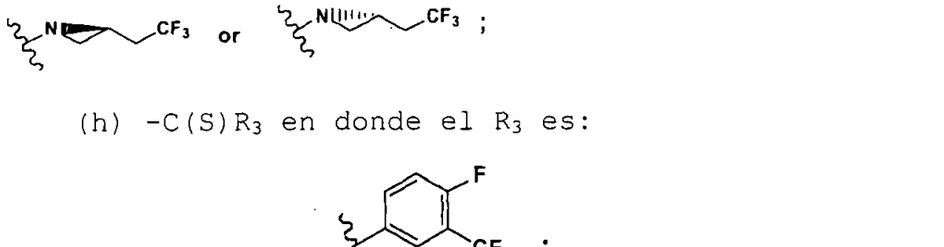




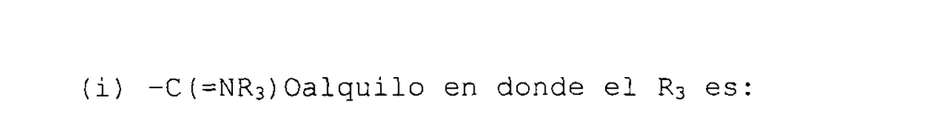




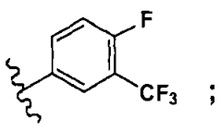




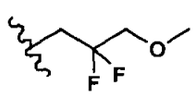




(h) -C(S)$R_3$ en donde el $R_3$ es:



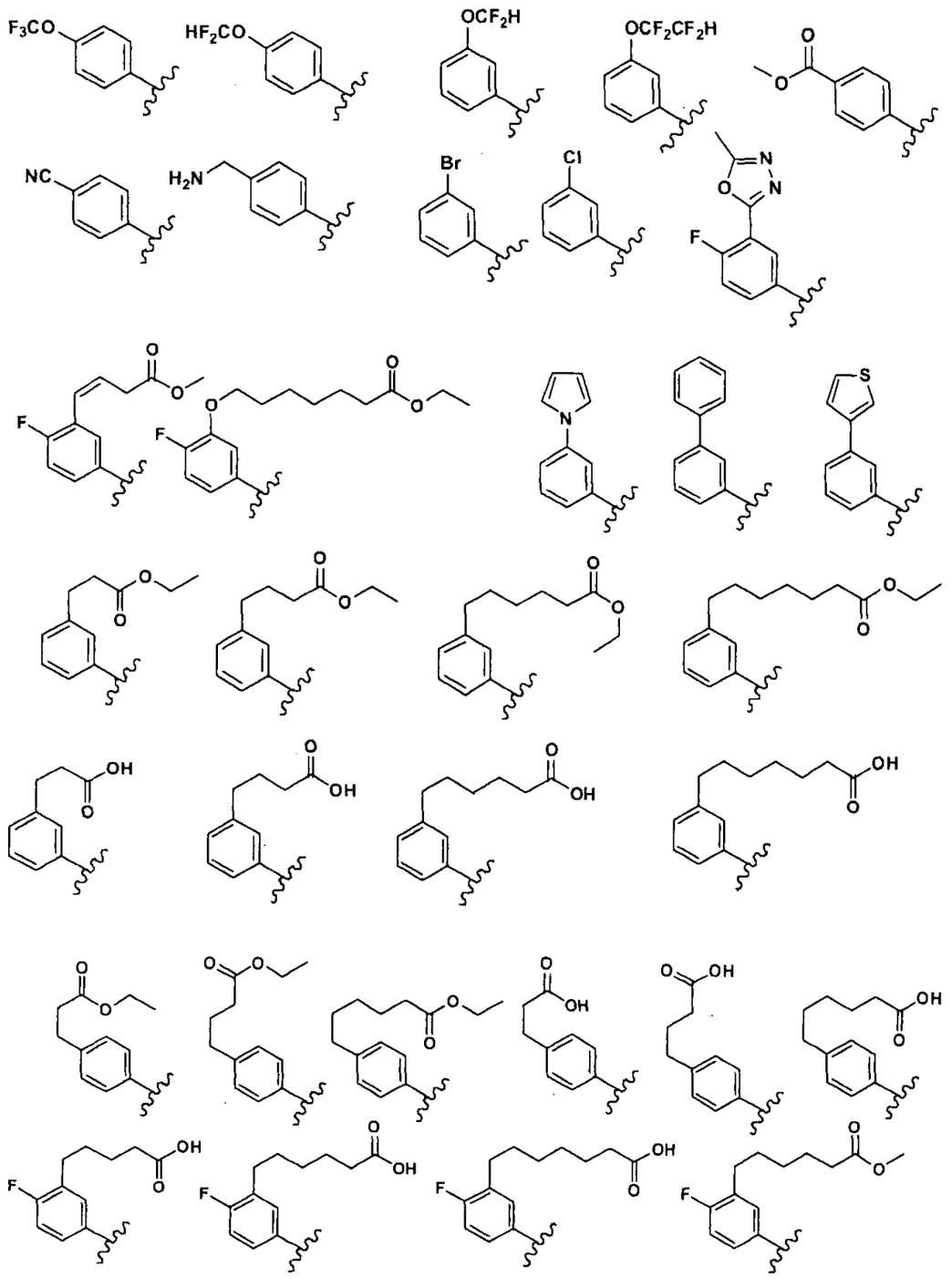
(i) -C(=N$R_3$)Oalquilo en donde el $R_3$ es:

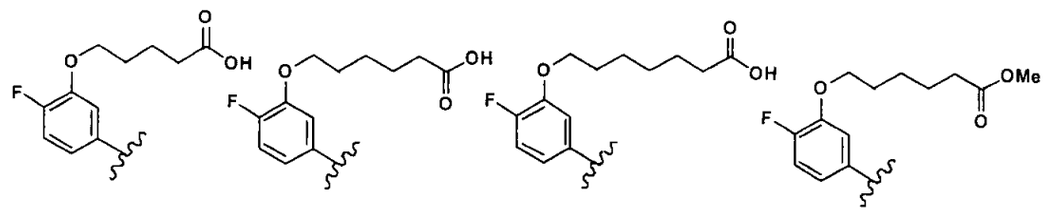


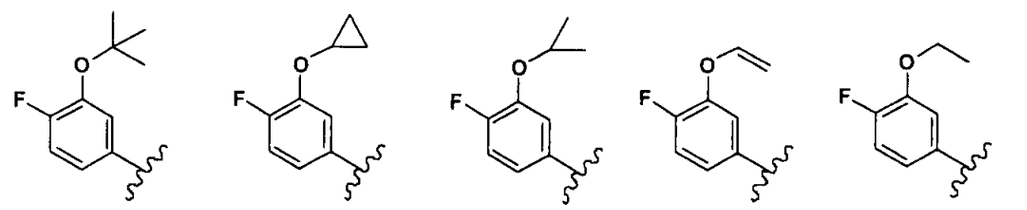
11.- El compuesto de conformidad con la

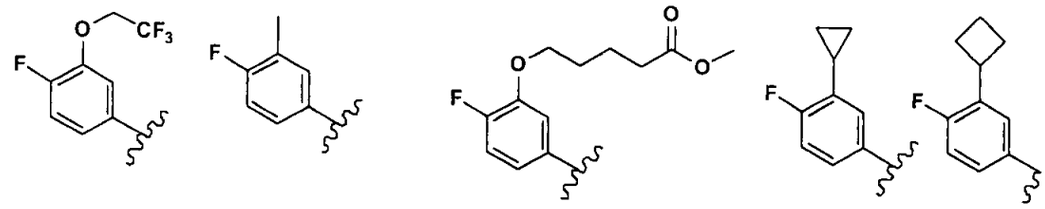
reivindicación 2, caracterizado porque:

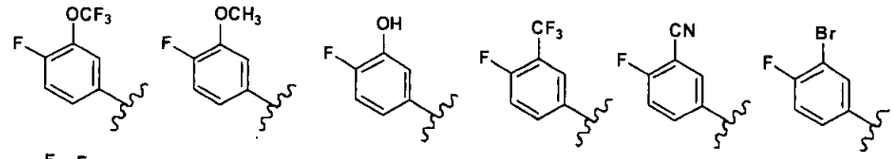
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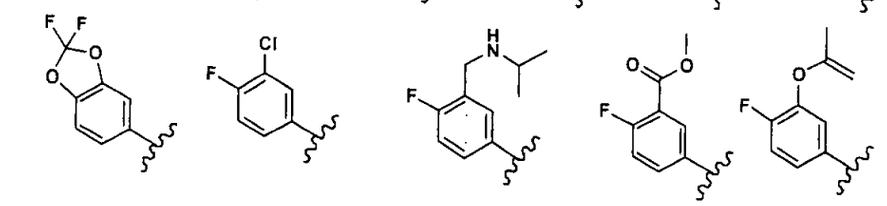


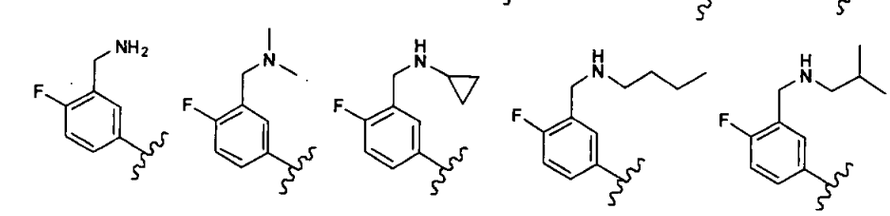


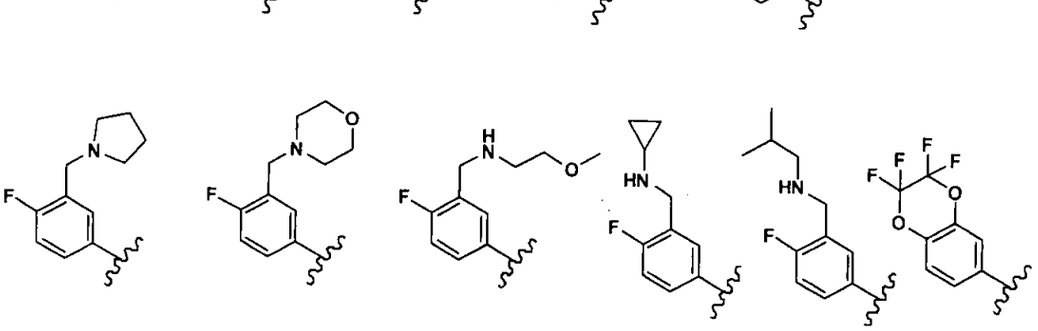


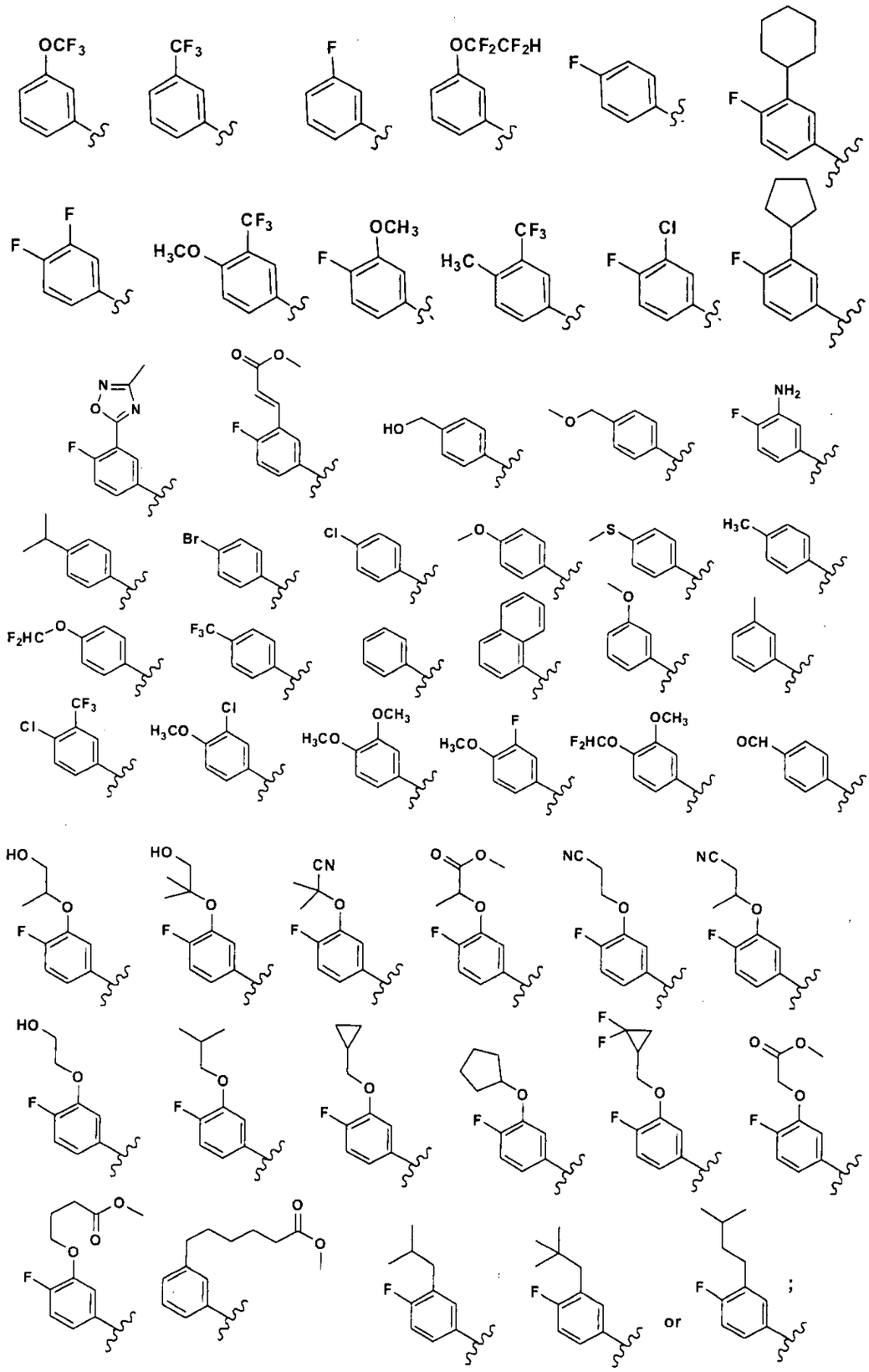






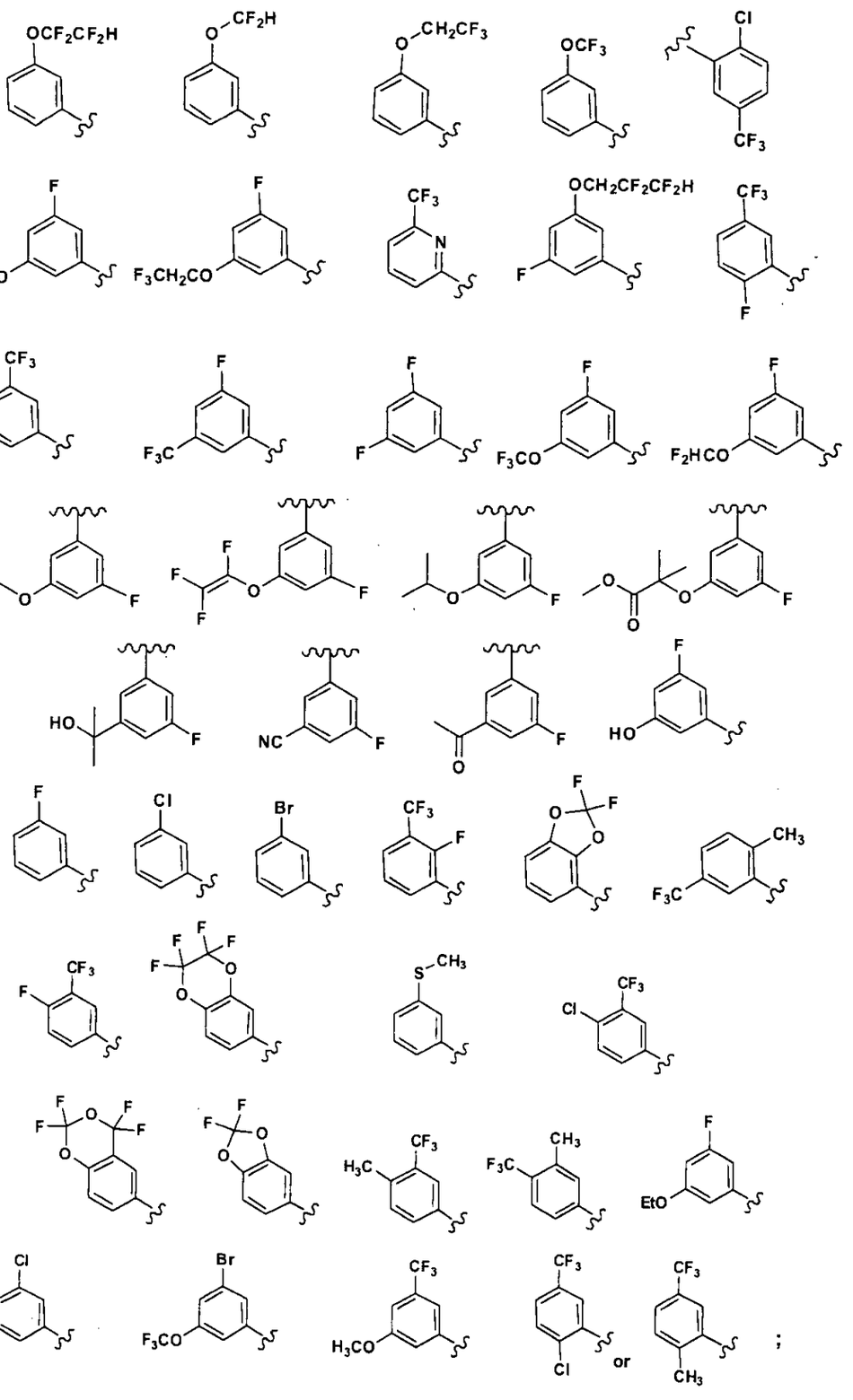





OCF3
CF3
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OCF2CF2H
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H3CO
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OCH3
H3C
CF3
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Cl
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N
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F
HO
O
NH2
F
Br
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S
H3C
F2HC
O
F3C
O
Cl
CF3
H3CO
Cl
H3CO
OCH3
H3CO
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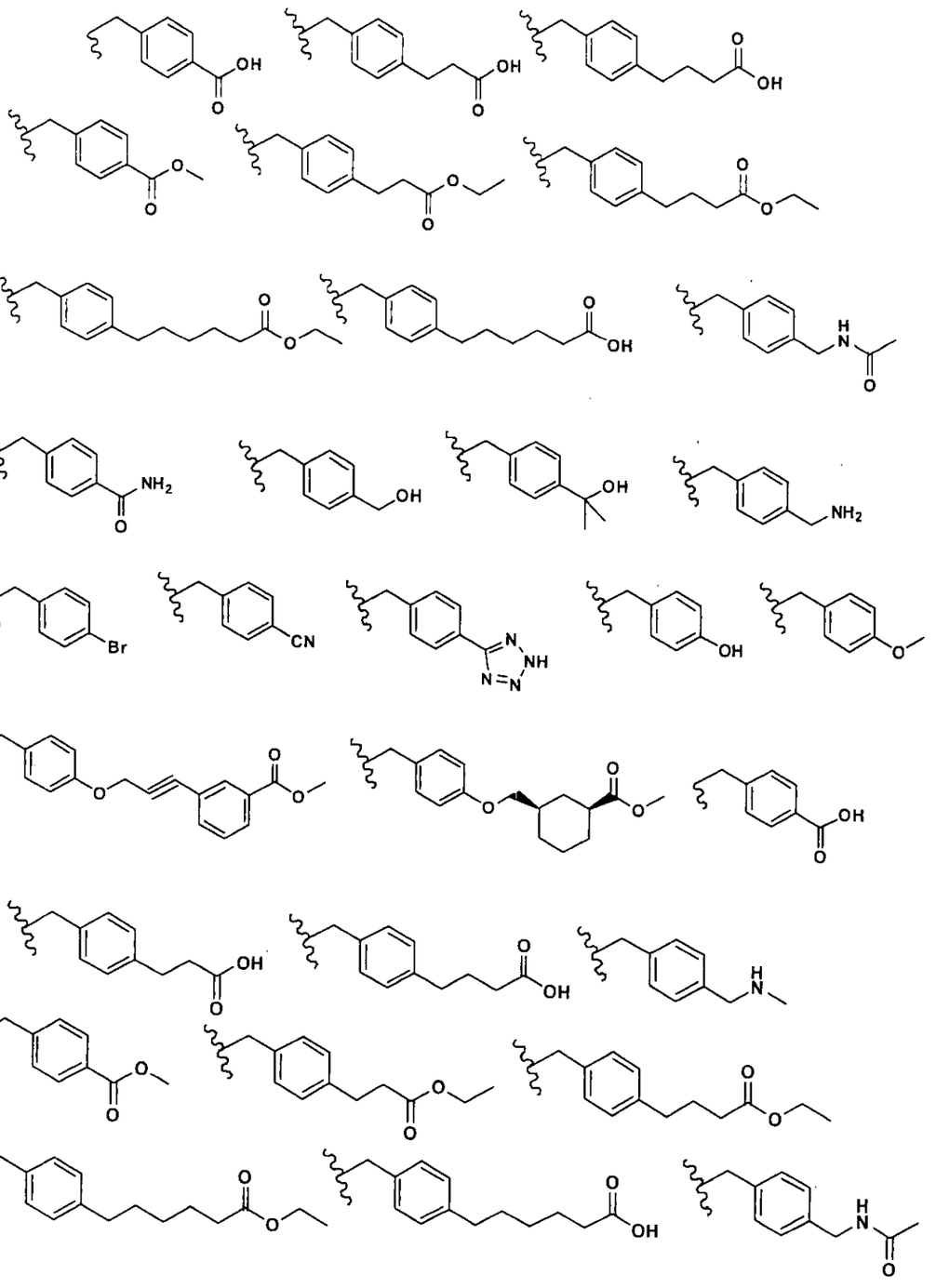
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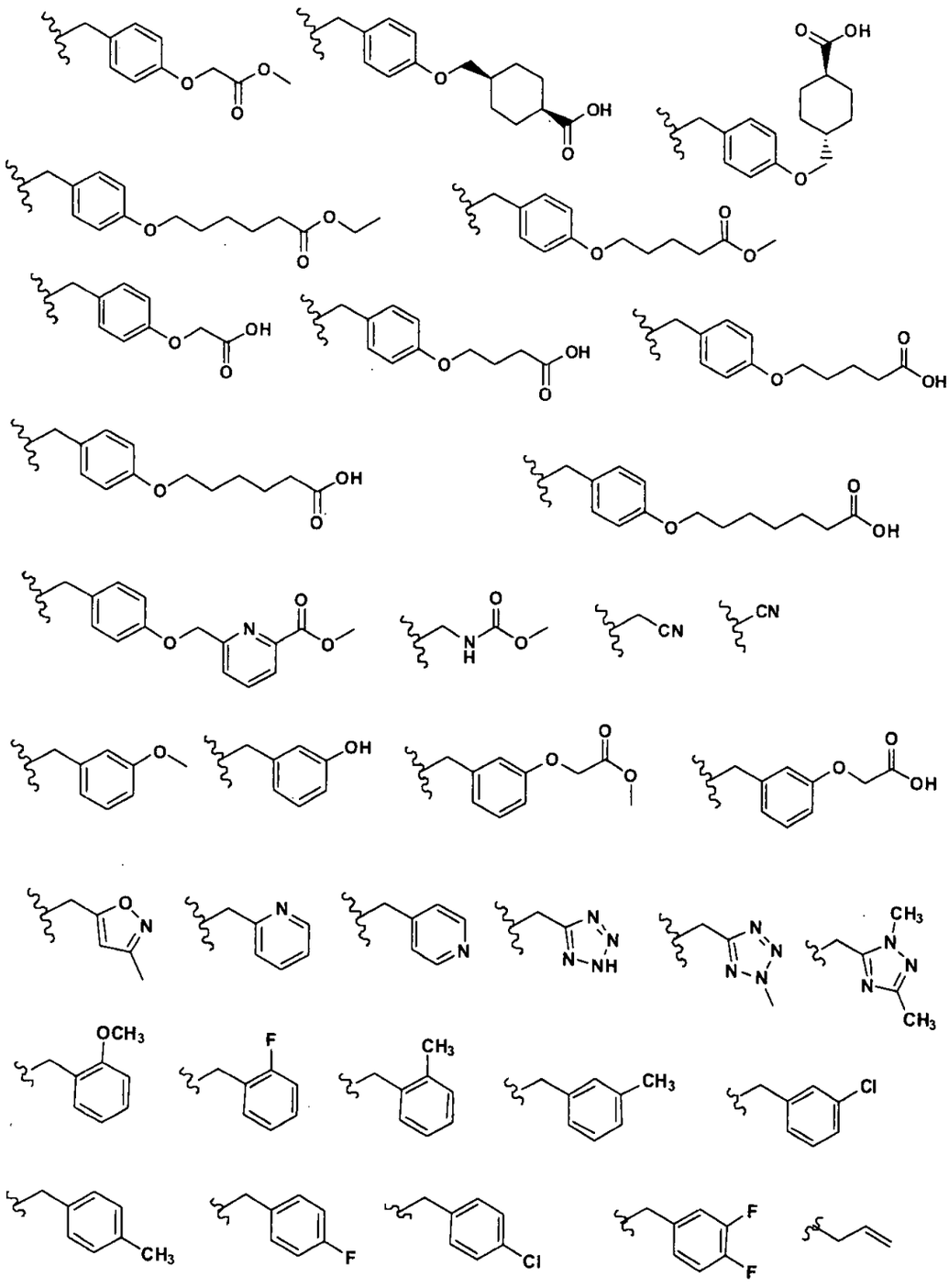
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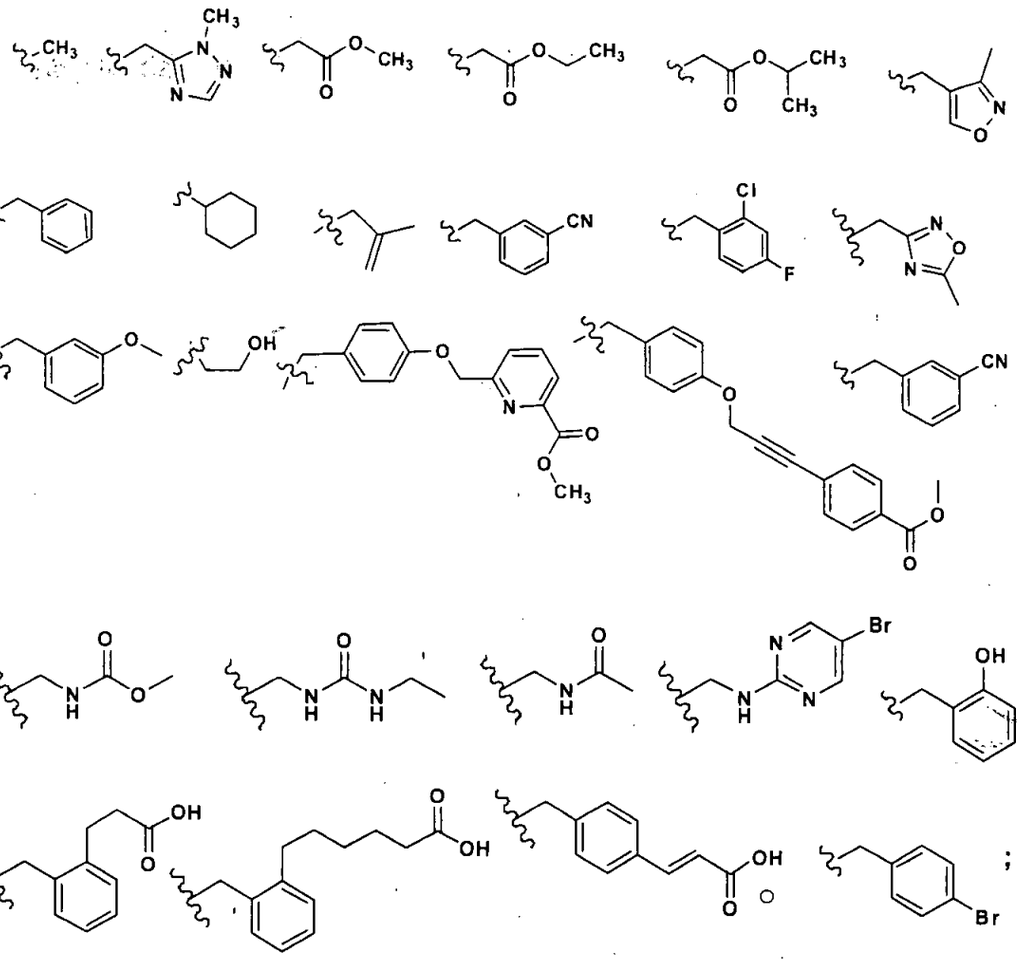


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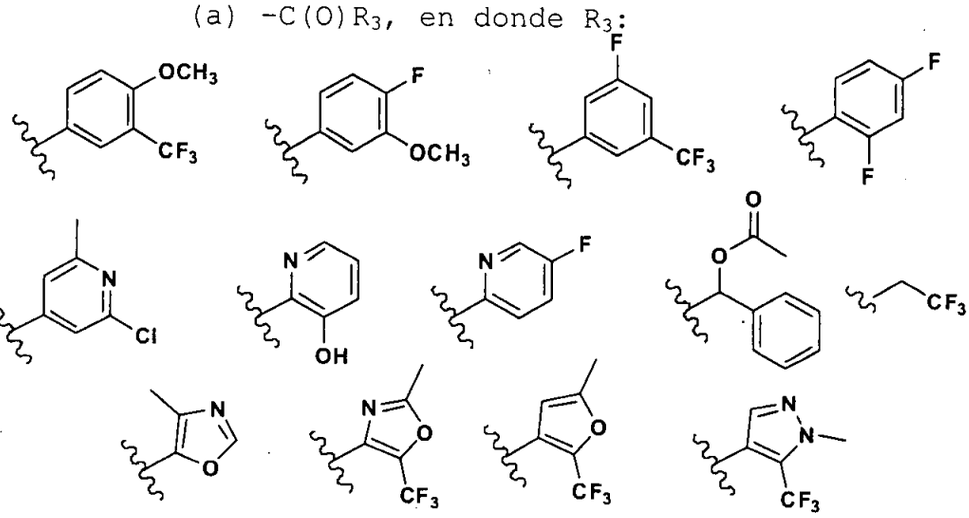


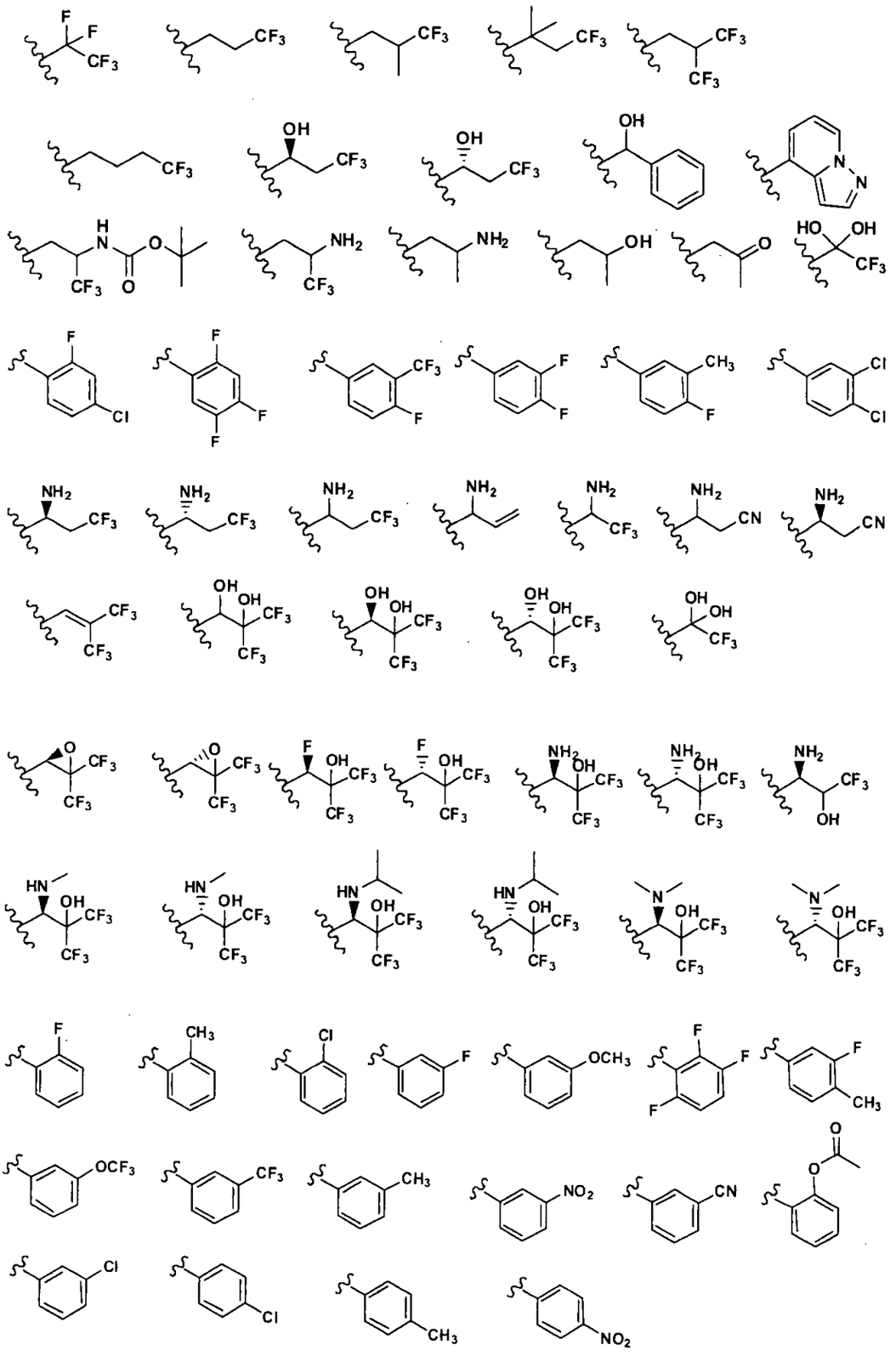


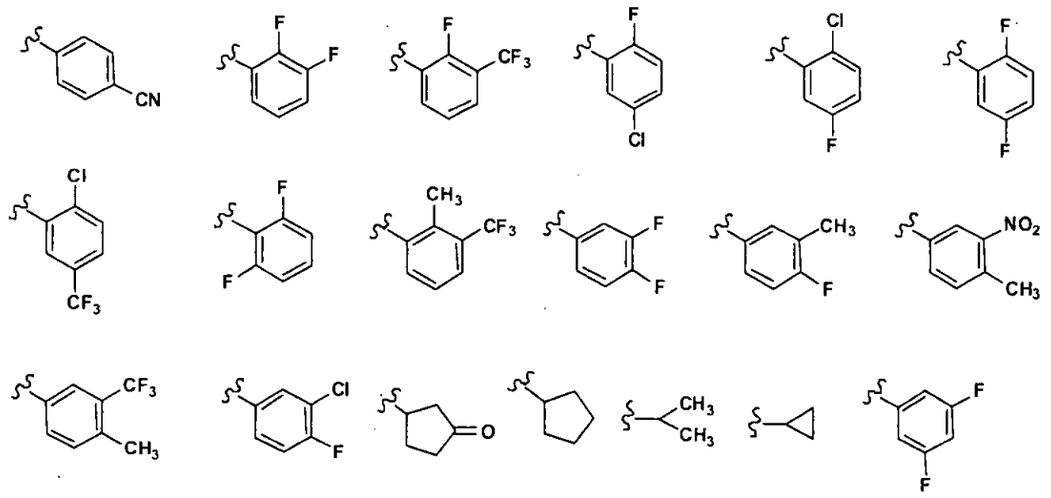


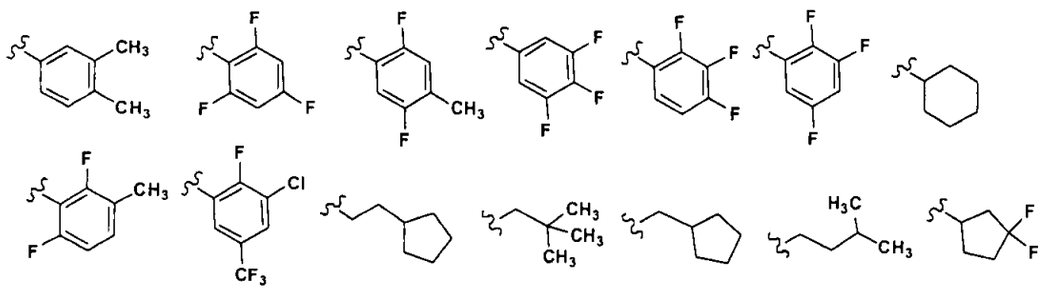
$R_1$ es H o:

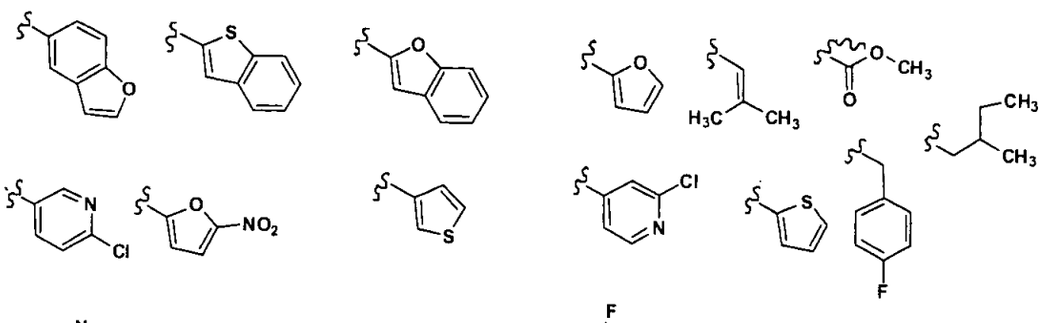
(a) $-C(O)R_3$, en donde $R_3$:



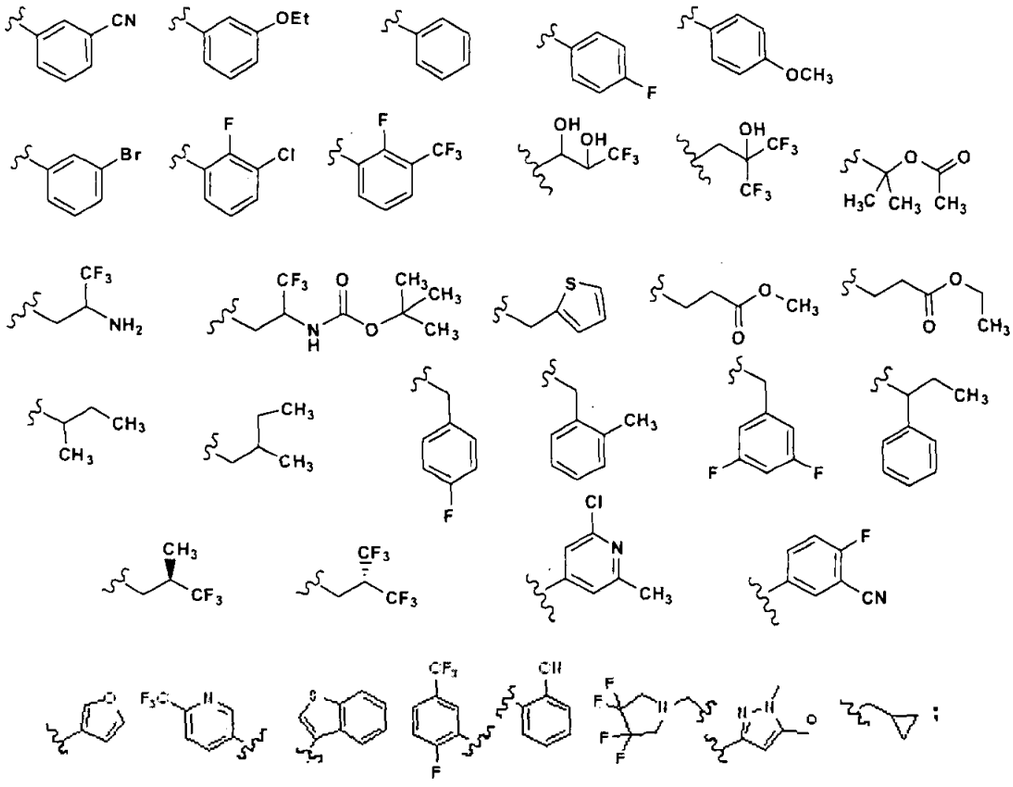



CN
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F
CF3
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Cl
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CF3
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CF3
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CH3
CH3
F
F

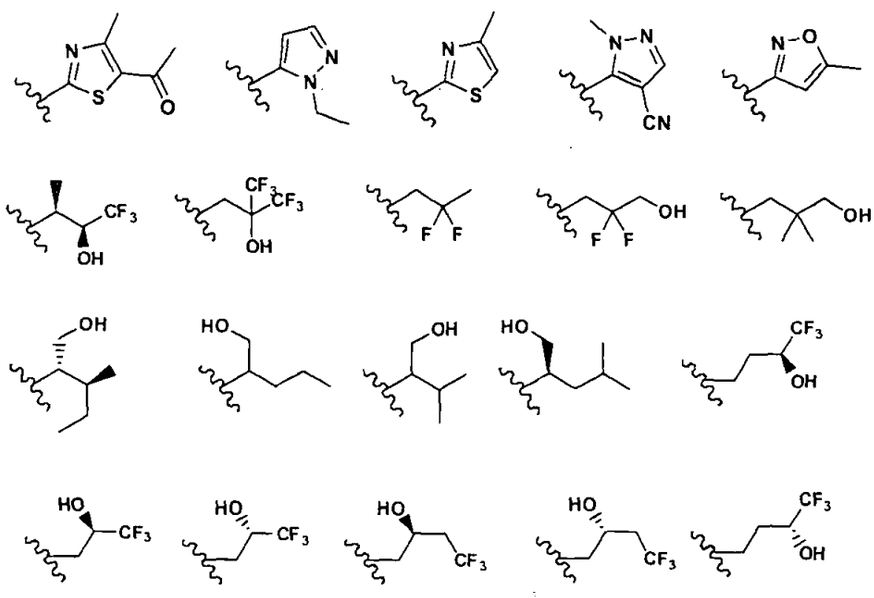

CH3
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F

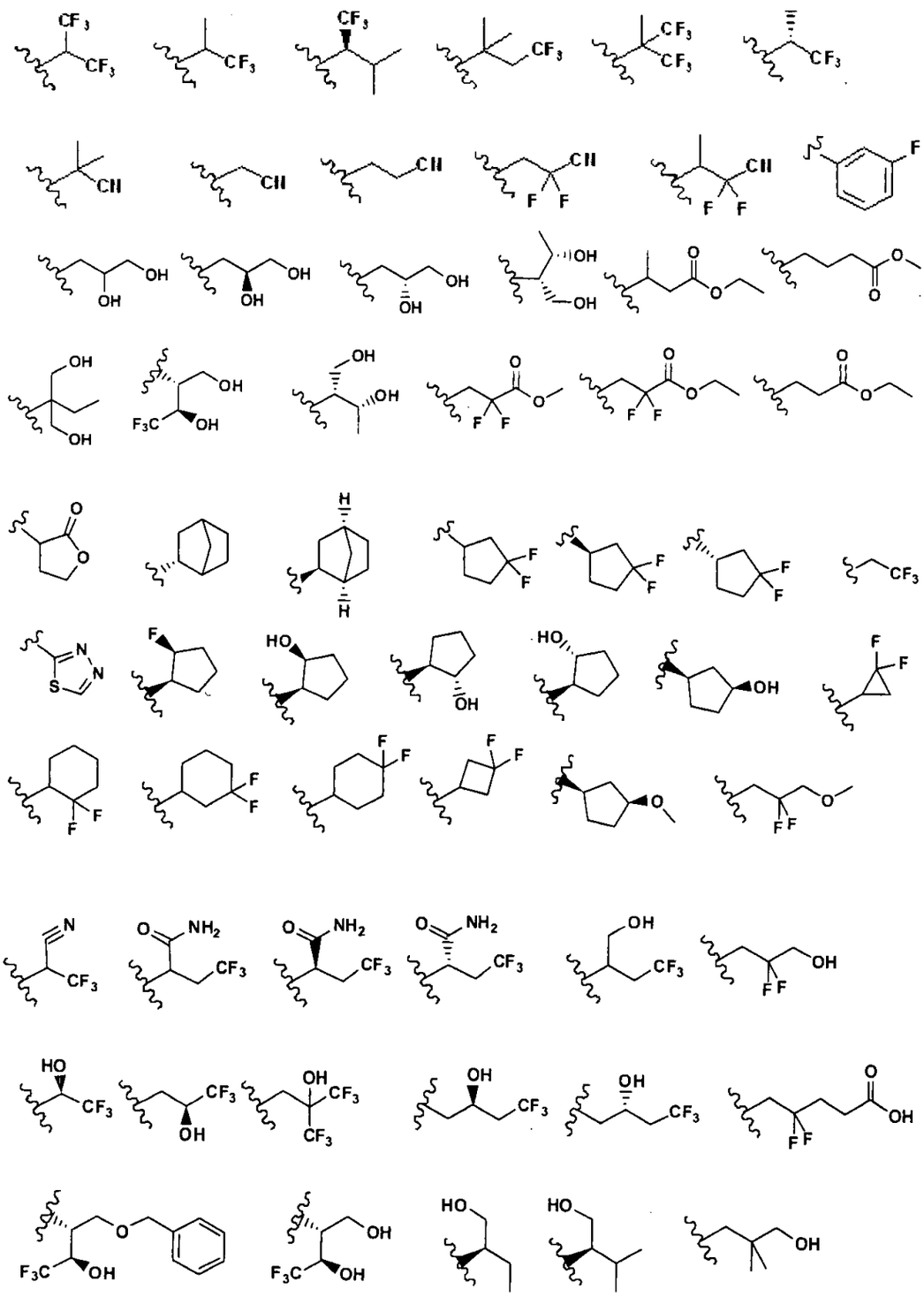

O
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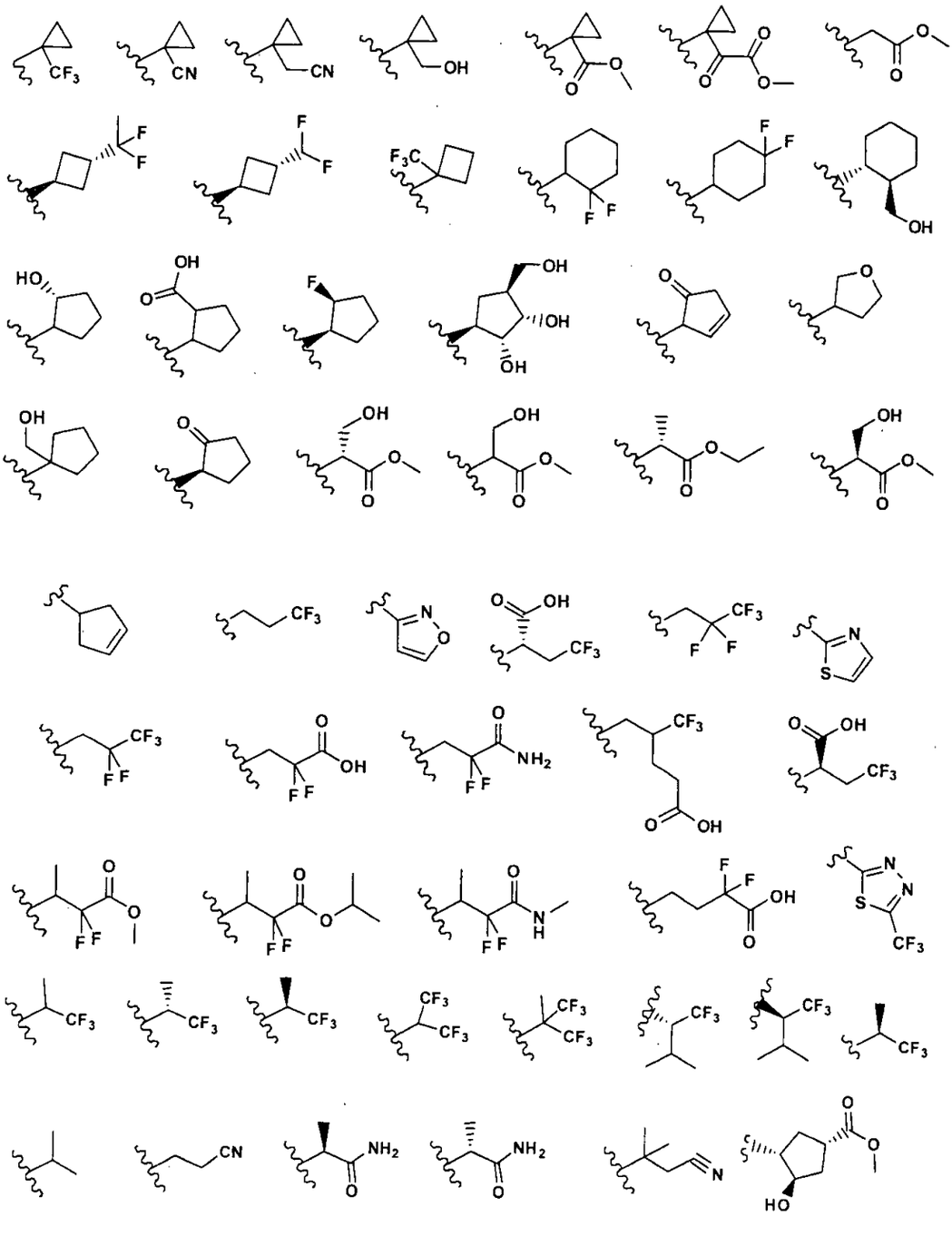

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CF3

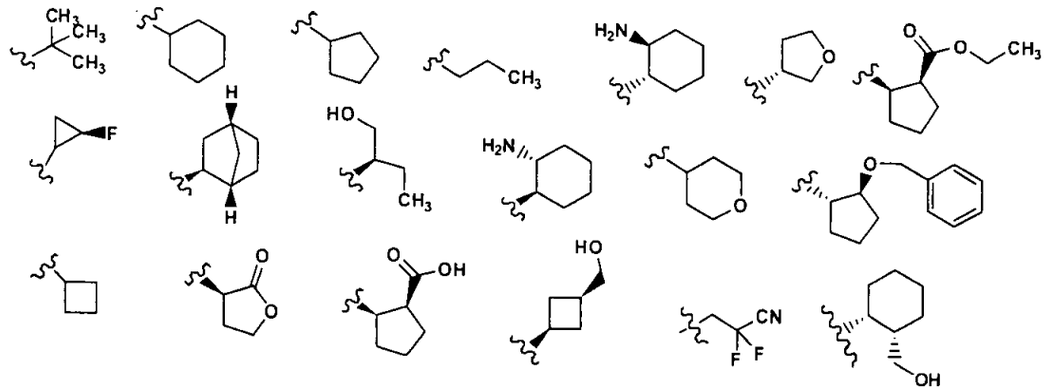


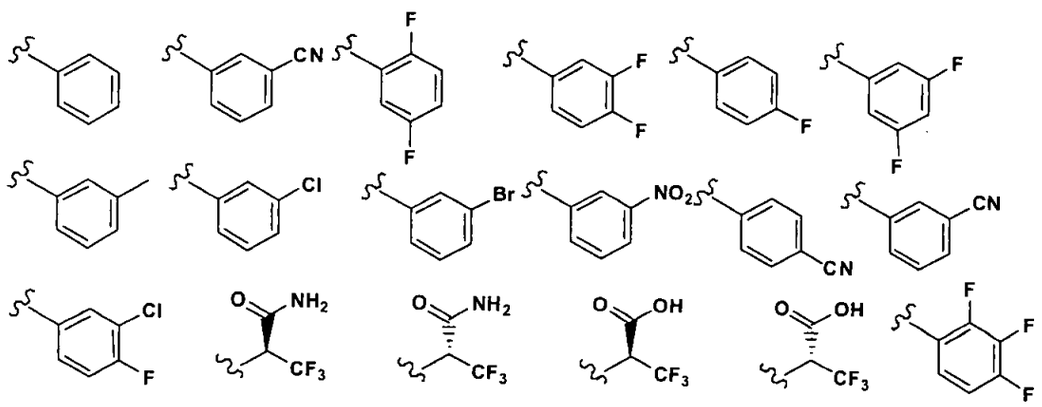
(b) $-C(O)NHR_3$, en donde el $R_3$ es:

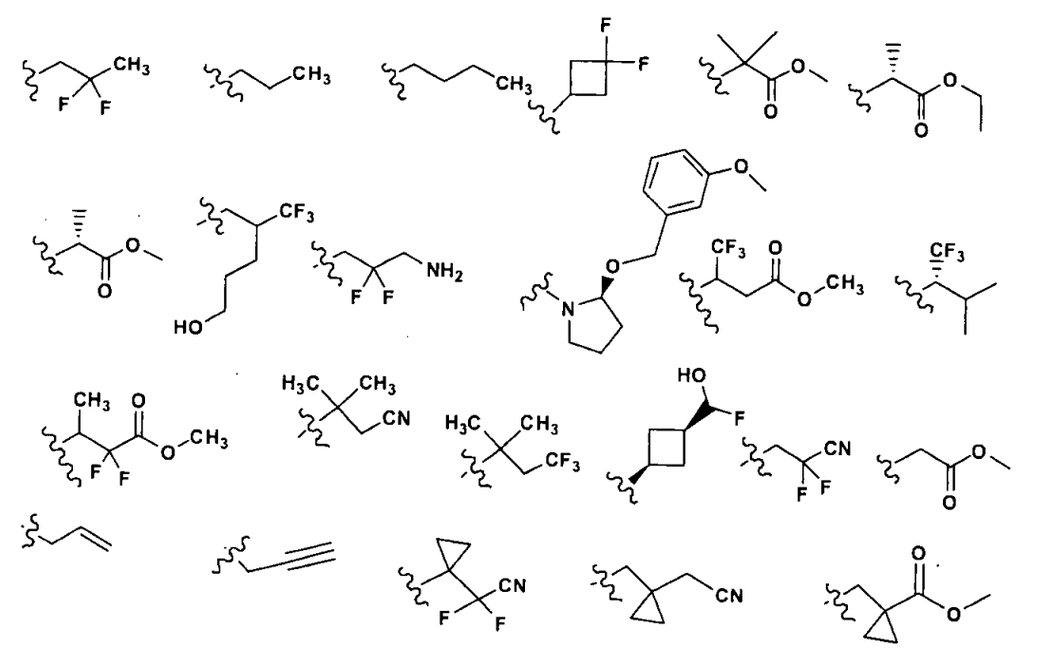




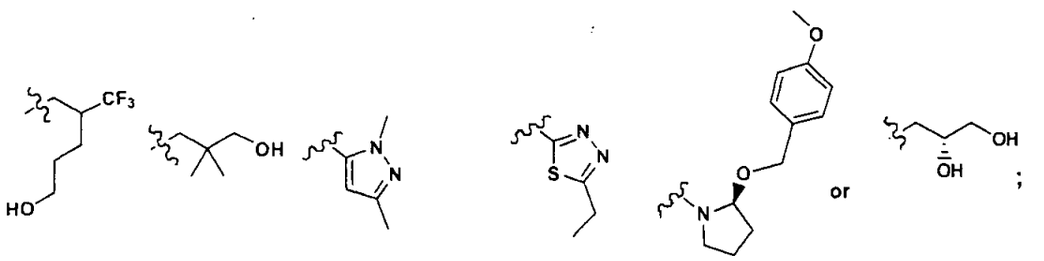




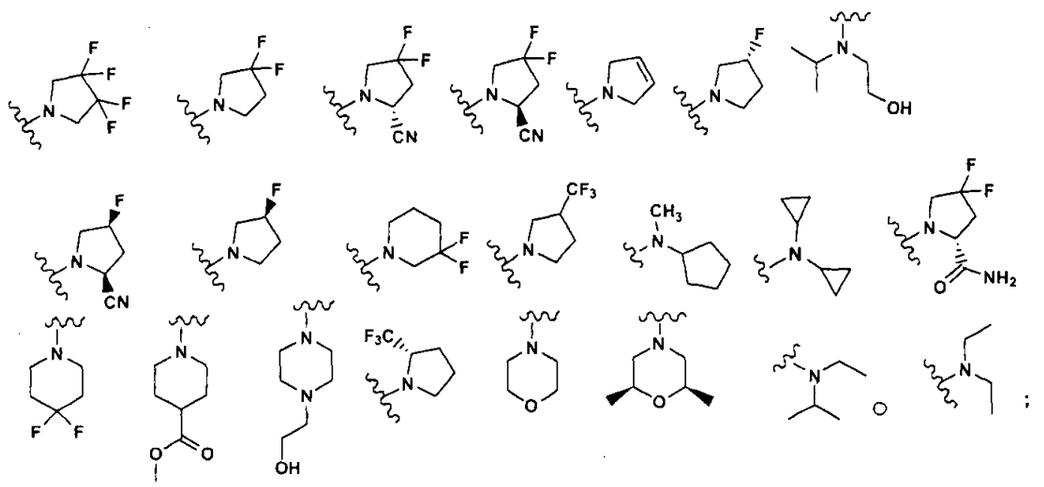




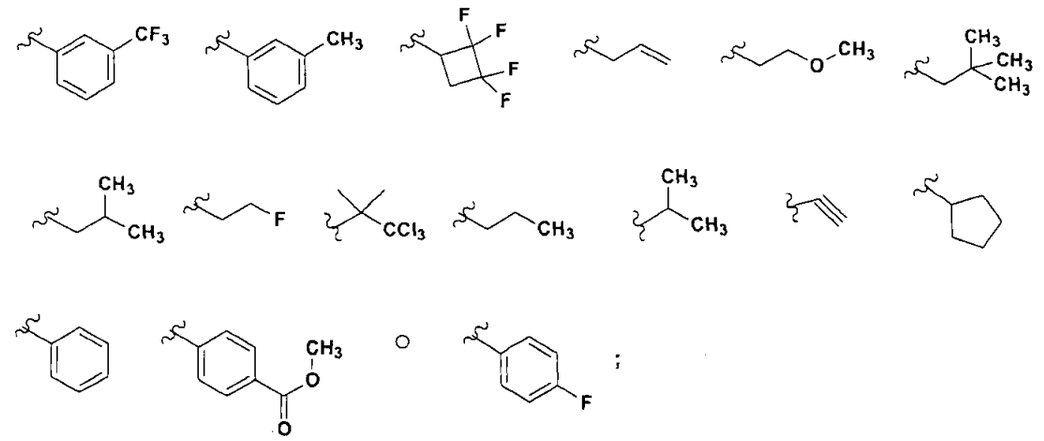
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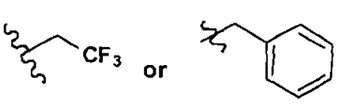

(c) $-C(O)NR_2R_3$, en donde el $NR_2R_3$ es:



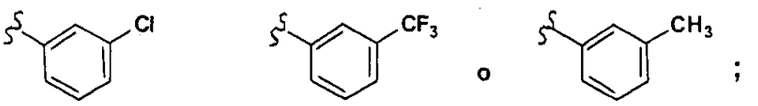

(d) $-C(O)OR_4$ en donde el $R_4$ es:



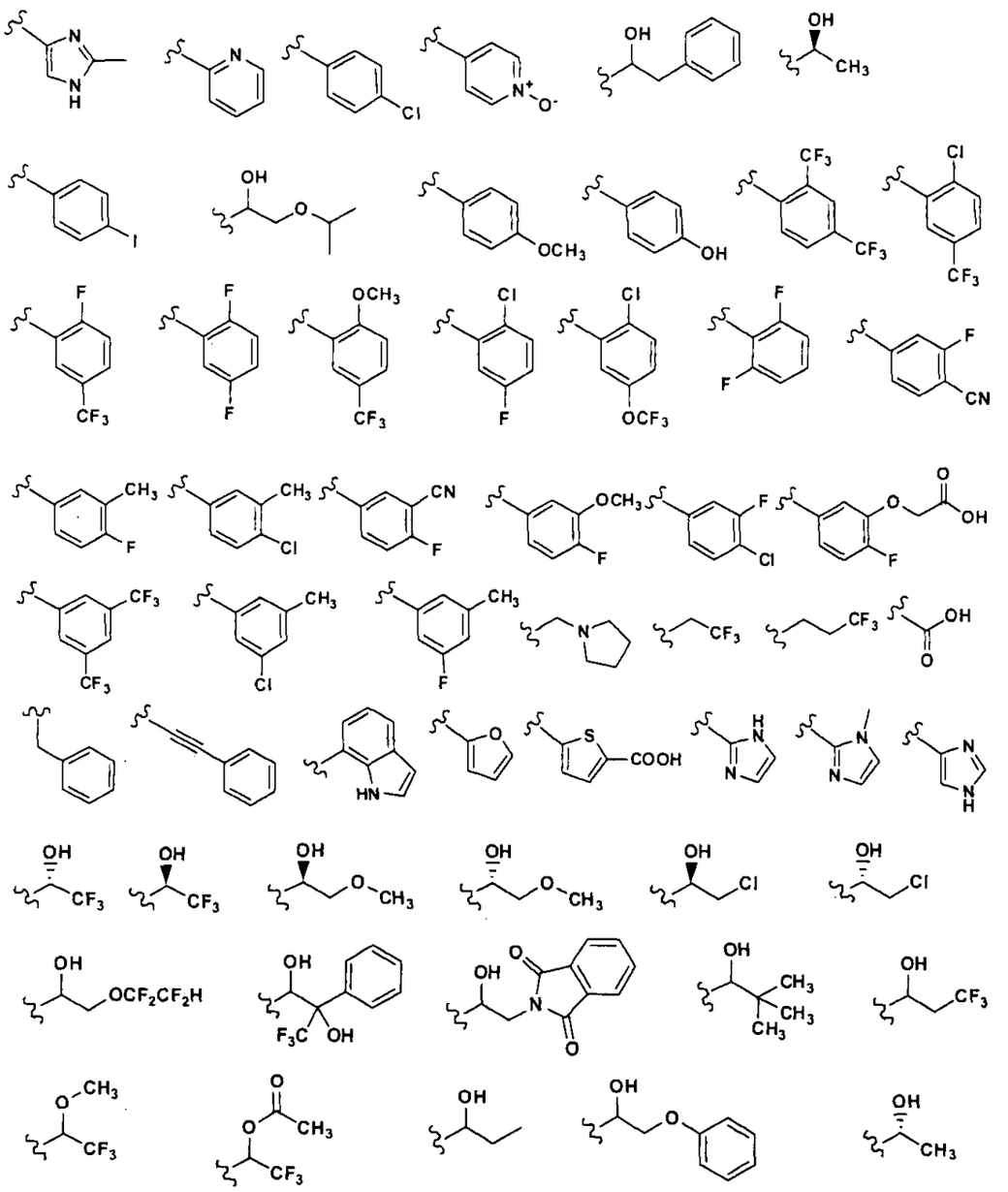

(e) $-SO_2R_5$ en donde el $R_5$ es:

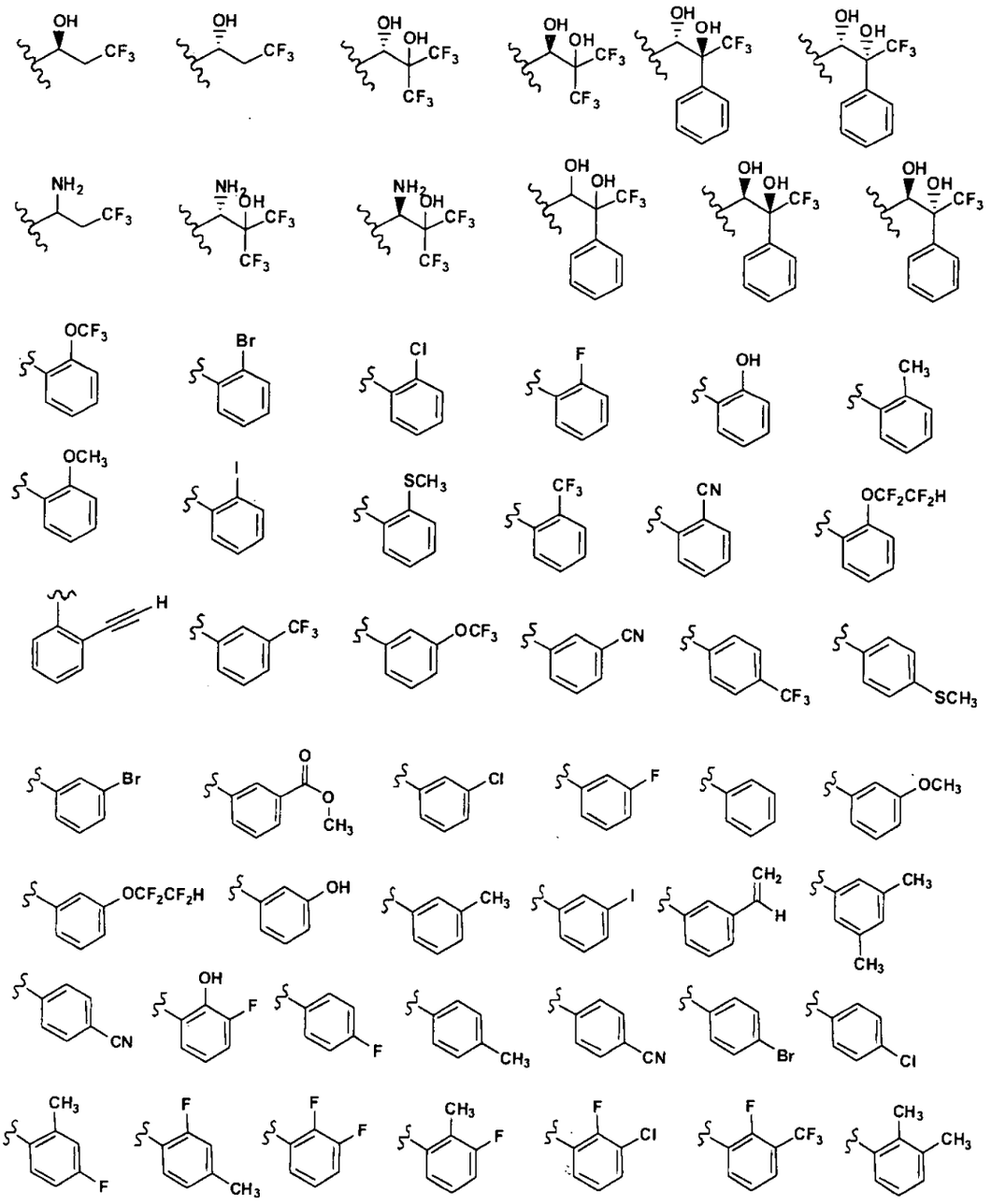


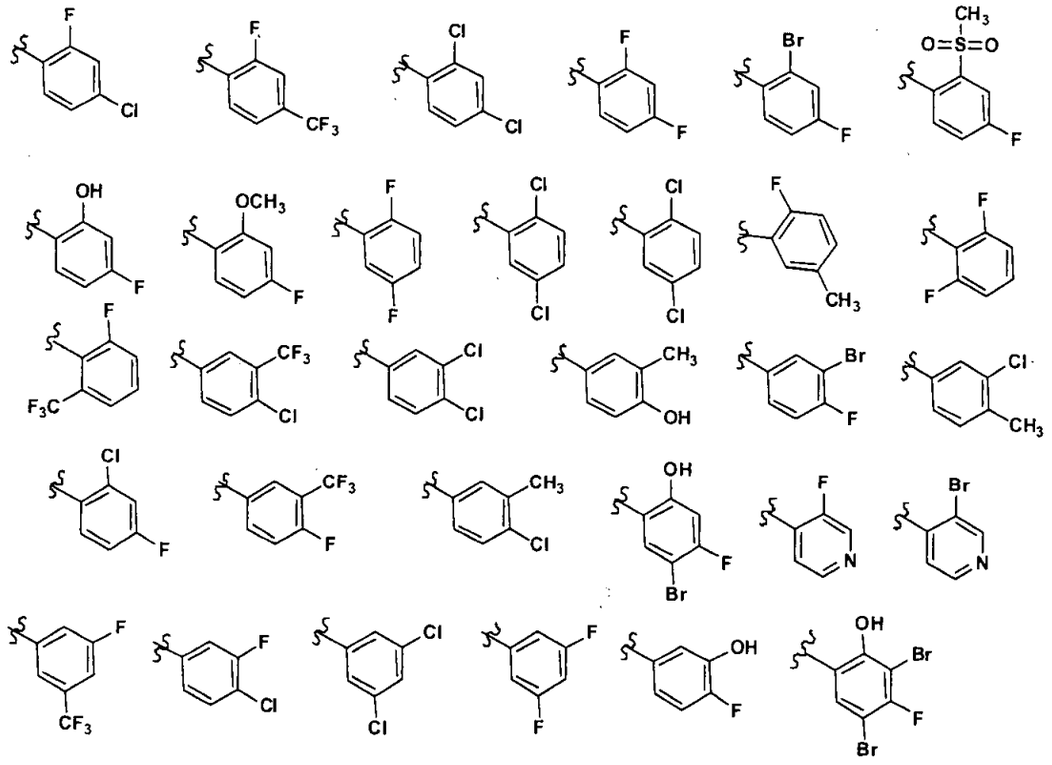
(f) $-CSNHR_7$ en donde el $R_7$ es:



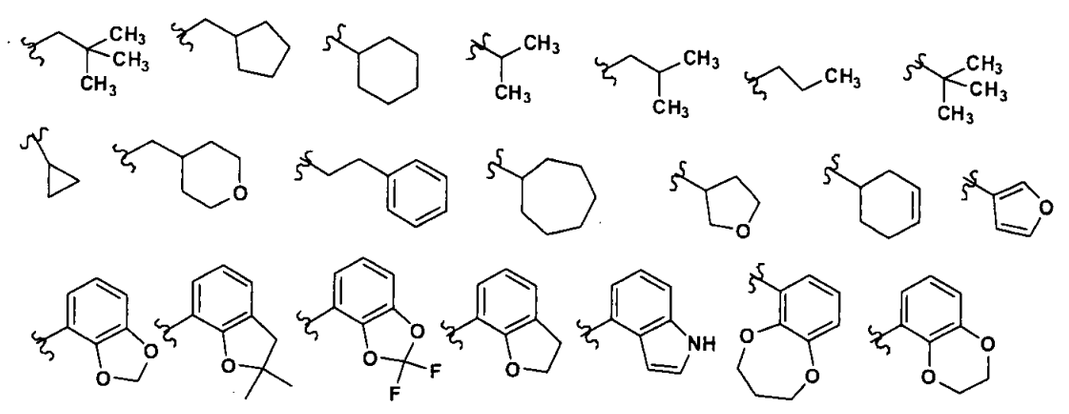
(g) $-CH_2R_8$ en donde el $R_8$ es:

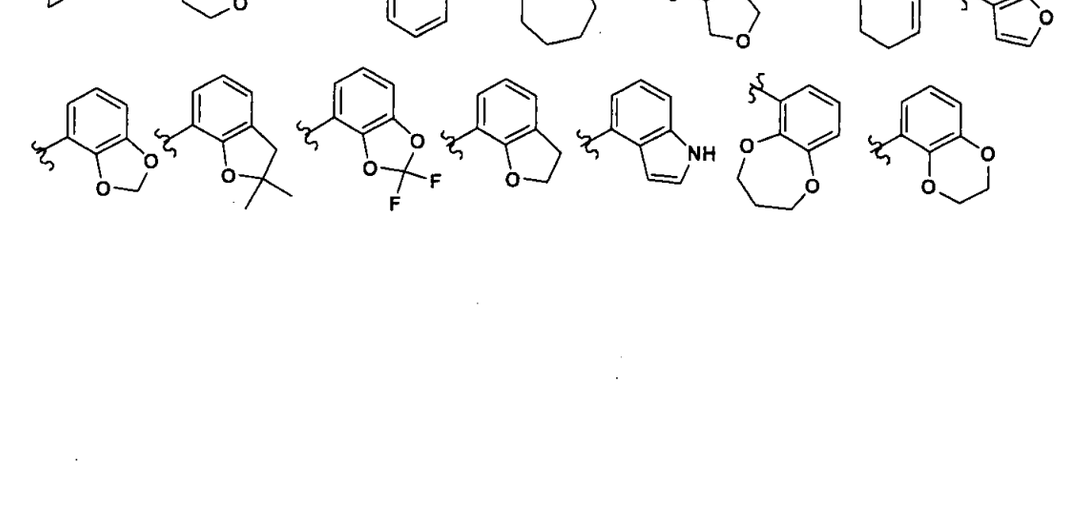


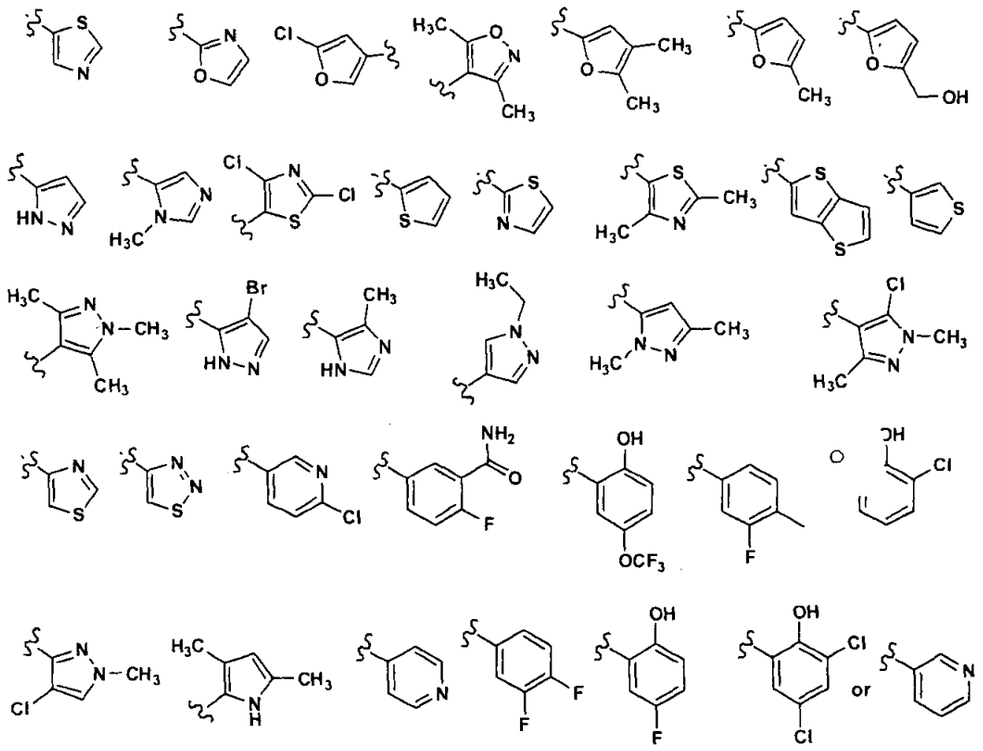

OH
CF3
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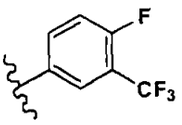








(h) $-C(S)R_3$, en donde $R_3$:



12.- Una composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con la reivindicación 1.

13.- La composición farmacéutica de conformidad con la reivindicación 12, caracterizada porque comprende además un portador farmacéuticamente aceptable.

14.- La composición farmacéutica de conformidad con la reivindicación 12 caracterizada porque comprende además al menos un agente terapéutico adicional.

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15.- Un método para inhibir la proteína de transferencia de éster de colesterilo, caracterizado porque comprende administrar a un mamífero que necesita del tratamiento una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1.

16.- Un método para tratar, prevenir o retardar el progreso del Alzheimer, ateroesclerosis, trombosis venosa, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, trastornos cardiovasculares, angina, isquemia, isquemia cardiaca, apoplejía, infarto al miocardio, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de diabetes, obesidad o endotoxemia en un mamífero, caracterizado porque se administra a un mamífero que necesita de tal tratamiento una cantidad, para tratar, prevenir o retardar la ateroesclerosis, enfermedad vascular periférica, dislipidemia, hiperbetalipoproteinemia, hipoalfalipoproteinemia, hipercolesterolemia, hipertrigliceridemia, hipercolesterolemia familiar, trastornos cardiovasculares, angina, isquemia, isquemia cardiaca, apoplejía, infarto al miocardio, lesión por reperfusión, restenosis angioplástica, hipertensión, complicaciones vasculares de diabetes, obesidad o

endotoxemia, de un compuesto de conformidad con la reivindicación 1.

17.- Un método para tratar, prevenir o retardar el progreso de una enfermedad que requiere de terapia del inhibidor de proteína de transferencia del éster de colesterilo, caracterizado porque comprende administrar, concurrente o secuencialmente, a un mamífero que necesita del tratamiento, prevención o retardo, una cantidad terapéuticamente efectiva de un compuestos de conformidad con la reivindicación 1 y al menos un agente terapéutico adicional.

18.- Un método para inhibir la producción de lipoproteína remanente, caracterizado porque comprende administrar a un mamífero un compuesto de conformidad con la reivindicación 1.

19.- Un método para elevar el colesterol HDL en un mamífero, caracterizado porque comprende administrar a un mamífero que necesita de tratamiento, un compuesto de conformidad con la reivindicación 1.

20.- El compuesto de conformidad con la reivindicación 1, caracterizado porque se ejemplifica en los ejemplos.

21.- Un proceso para la preparación de principalmente un compuesto de la fórmula WW, B-$OCF_2CF_2H$, caracterizado porque comprende reducir una mezcla comprendida

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de un compuesto de la fórmula WW y un compuesto de la fórmula YY, B-$OCF_2CF_2Br$, con polvo de zinc bajo condiciones ácidas, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 9) arilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 10) heteroarilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 11) heteroarilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 12) heterociclilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 13) heterociclilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) -$S(O)_pR_6$, 17) -$SO_2NHR_6$, 18) -$COOR_6$, 19) -$NHC(CN)NHR_6$, y 20) -$CONR_6R_6$ y $R_6$, $R_9$ y $R_{10}$ son como se definen de conformidad con la reivindicación 1.

22.- Un proceso para la preparación de una mezcla comprendida de un compuesto de la fórmula WW y un compuesto de la fórmula YY, B-$OCF_2CF_2Br$, caracterizado porque comprende hacer reaccionar un compuesto de la fórmula ZZ, B-OH, con 1,2-dibromotetrafluoroetano bajo condiciones básicas, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste

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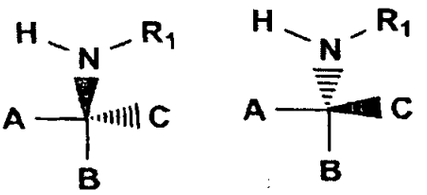
de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 9) arilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 10) heteroarilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 11) heteroarilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 12) heterociclilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 13) heterociclilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$, 15) -$COR_6$, 16) -$S(O)_pR_6$, 17) -$SO_2NHR_6$, 18) -$COOR_6$, 19) -$NHC(CN)NHR_6$, y 20) -$CONR_6R_6$ y $R_6$, $R_9$ y $R_{10}$ son como se definen de conformidad con la reivindicación 1.

23.- Un proceso para la preparación de un compuesto de la fórmula ZZ, caracterizado porque comprende hacer reaccionar un compuesto de la fórmula AAA, B-F, con trimetilsilanoato de potasio en un solvente diferente a THF, en donde B es fenilo, que puede substituirse opcionalmente con uno o más substituyentes seleccionados del grupo que consiste de: 1) halo, 2) alquilo de $C_1$-$C_6$, que puede opcionalmente substituirse con uno o más $R_{20}$, 3) -$OR_6$, 4) alquiltio de $C_1$-$C_6$, 5) ciano, 6) nitro, 7) -$NR_9R_{10}$, 8) arilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 9) arilalquilo, que puede opcionalmente substituirse con uno o

más $R_{20}$, 10) heteroarilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 11) heteroarilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 12) heterociclilo, que puede opcionalmente substituirse con uno o más $R_{20}$, 13) heterociclilalquilo, que puede opcionalmente substituirse con uno o más $R_{20}$, y 14) haloalquilo de $C_1$-$C_6$, 15) $-COR_6$, 16) $-S(O)_pR_6$, 17) $-SO_2NHR_6$, 18) $-COOR_6$, 19) $-NHC(CN)NHR_6$, y 20) $-CONR_6R_6$ y $R_6$, $R_9$ y $R_{10}$ son como se definen de conformidad con la reivindicación 1.

## RESUMEN DE LA INVENCION

Los compuestos de la fórmula Ia y IB




Ia y Ib

en donde A, B, C y $R_1$ son como se describen en la presente.

2055

# PATENT COOPERATION TREATY

PCT/US2006/060958

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BOGIE, Terence J.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>22 February 2007 (22.02.2007) | |
| Applicant's or agent's file reference<br>10761PCT | **IMPORTANT NOTIFICATION** |
| International application No.<br>PCT/US2006/060958 | International filing date *(day/month/year)*<br>16 November 2006 (16.11.2006) |
| International publication date *(day/month/year)*<br>**Not yet published** | Priority date *(day/month/year)*<br>23 November 2005 (23.11.2005) |
| Applicant<br>BRISTOL-MYERS SQUIBB COMPANY et al | |

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| Priority date | Priority application No. | Country or regional Office or PCT receiving Office | Date of receipt of priority document |
|---|---|---|---|
| 23 November 2005 (23.11.2005) | 60/739,374 | US | 19 January 2007 (19.01.2007) |
| 13 November 2006 (13.11.2006) | 11/558,979 | US | 19 January 2007 (19.01.2007) |

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer

Dorothée Mülhausen

Facsimile No. +41 22 338 82 70
Telephone No. +41 22 338 96 72

2056

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/060958

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C211/29 C07C215/08 C07C217/58 C07C229/36 C07C229/38
C07C233/09 C07C233/13 C07C233/18 C07C233/56 C07C233/60
C07C233/66 C07C233/73 C07C233/78 C07C235/20 C07C235/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2005/037796 A (LILLY CO ELI [US]; CAO GUOQING [US]; ESCRIBANO ANA MARIA [ES]; FERNAND) 28 April 2005 (2005-04-28) the whole document | 1-23 |
| A | US 2002/177708 A1 (SIKORSKI JAMES A [US] ET AL) 28 November 2002 (2002-11-28) the whole document | 1-23 |
| E | WO 2007/062342 A (SQUIBB BRISTOL MYERS CO [US]; YANG WU [US]; WANG YUFENG [US]) 31 May 2007 (2007-05-31) the whole document | 1-23 |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 July 2007 | 20/07/2007 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Fritz, Martin |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/060958

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 15-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is *restricted to the invention first mentioned in the claims; it is covered by claims Nos.:*

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/060958

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2005037796 A | 28-04-2005 | AU 2004282101 A1 | 28-04-2005 |
| | | BR PI0414186 A | 31-10-2006 |
| | | CA 2537942 A1 | 28-04-2005 |
| | | CN 1863778 A | 15-11-2006 |
| | | EP 1670768 A1 | 21-06-2006 |
| | | JP 2007508301 T | 05-04-2007 |
| | | KR 20060085675 A | 27-07-2006 |
| US 2002177708 A1 | 28-11-2002 | US 2003040545 A1 | 27-02-2003 |
| | | US 2003050317 A1 | 13-03-2003 |
| | | US 2003078264 A1 | 24-04-2003 |
| | | US 2003027826 A1 | 06-02-2003 |
| | | US 6521607 B1 | 18-02-2003 |
| WO 2007062342 A | 31-05-2007 | US 2007135467 A1 | 14-06-2007 |

# TRATADO DE COOPERACION EN MATERIA DE PATENTES

# PCT

## REPORTE DE BUSQUEDA INTERNACIONAL

**(Artículo 18 y Reglas 43 y 44 del PCT)**

| Referencia al expediente del solicitante o del agente | **PARA ACCION ADICIONAL** | véase Forma PCT/ISA/220 así como también, donde sea aplicable, el artículo 5 posterior. |
|---|---|---|
| 10493 PCT | | |
| No. de solicitud internacional | Fecha de presentación internacional *(día/mes/año)* | Fecha de prioridad (la más reciente) *(día/mes/año)* |
| PCT/US2006 /060958 | 16/11/2006 | 23/11/2005 |

Solicitante

BRISTOL-MYERS SQUIBB COMPANY

Este Reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y se transmite al solicitante de acuerdo con el Artículo 18. Una copia está siendo transmitida a la Oficina Internacional

Este Reporte de Búsqueda Internacional consiste de un total de 6 hojas.

☒ También está acompañado por una copia de cada documento de la técnica anterior citado en este reporte.

**I. Bases del reporte**

a. Con respecto al **idioma**, la búsqueda internacional se llevó a cabo en base de

☒ la solicitud internacional en el idioma en el cual se presentó

☐ una traducción de la solicitud internacional en _____, que es el idioma de una traducción E elaborada para los propósitos de la búsqueda internacional (Reglas 12.3(a) y 23.1(b)).

b. ☐ Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** descrita en la solicitud internacional, véase Cuadro No. I.

2. ☒ **Se encontró que ciertas reivindicaciones no son investigables** (véase Cuadro II).

3. ☐ **La unidad de la invención es deficiente** (véase Cuadro III).

4. Con respecto al **título**,

☐ el texto se aprueba como lo presentó el solicitante.

☒ esta Autoridad ha establecido que el texto se lee como sigue:

COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO

5. Con respecto al **resumen**,

☐ el texto se aprueba como lo presentó el solicitante

☒ esta Autoridad ha establecido que el texto es, de acuerdo con la Regla 38.2(b), tal como aparece en el Cuadro No. IV. El solicitante puede, dentro de un mes a partir de la fecha de envío por correo de este reporte de búsqueda internacional, proporcionar comentarios a esta Autoridad.

6. Con respecto a los **dibujos**,

a. la figura de los **dibujos** que se va a publicar con el resumen es la Figura No_____.

☐ como lo sugirió el solicitante.

☐ como lo seleccionó esta Autoridad, porque al solicitante le faltó sugerir una figura.

☐ como lo seleccionó esta Autoridad, porque esta figura caracteriza mejor la invención.

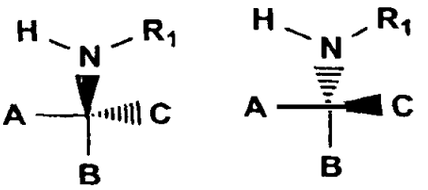
b. ☒ ninguna de las figuras debe publicarse con el resumen.

**REPORTE DE BUSQUEDA INTERNACIONAL**

No. de solicitud internacional
PCT/US2006/060958

**Cuadro No. IV** **Texto del resumen (Continuación del punto 5 de la primera hoja)**

Compuestos de la fórmula Ia y Ib




Ia y Ib

en donde A, B, C y R1 son como se decriben
en la presente. Los compuestos Ia y Ib son útiles como inhibidores CETP

# REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional

PCT/US2006/060958

**A. CLASIFICACIÓN DEL TEMA**

INV. C07D211/29 C07C215/08 C07C217/58 C07C229/36 C07C229/38
C07C233/09 C07C233/13 C07C233/18 C07C233/56 C07C233/60
C07C233/66 C07C233/73 C07C233/78 C07C235/20 C07C235/34

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

**B. CAMPOS BUSCADOS**

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):

C07C C07D A61K A619

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados:

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):

EPO-Interno, Datos WPI, Datos CHEM ABS

**C. DOCUMENTOS QUE SE CONSIDERAN QUE SON RELEVANTES**

| Categoría* | Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes | Relevante a la Reivindicación No. |
|---|---|---|
| A | WO 2005/037796 A (LILLY CO ELI [US]; CAO GUOQING [US]; ESCRIBANO ANA MARIA [ES]; FERNAND) Abril 28, 2005 (2005-04-28) | 1-23 |
| A | US 2002/177708 A1 (SIKORSKI JAMES A [US] Y OTROS) Noviembre 28, 2002 (2002.11.28) documento completo | 1-23 |
| E | WO 2007/062342 A (SQUIBB BRISTOL MYERS CO [US]; YANG WU [US]; WANG YUFENG [US]) Mayo 31, 2007 (2007-05-31) documento completo | 1-23 |

[X] Documentos adicionales se listan en la continuación del bloque C [X] Véase familia de patentes anexa.

* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.

"E" documento anterior publicado en o después de la fecha de presentación internacional.

"L" documento el cual puede arrojar dudas sobre la(s) reivindicación (es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.

"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.

"&" documento miembro de la misma familia de patentes.

| Fecha de la terminación real de la búsqueda internacional | Fecha de envío del reporte de búsqueda internacional |
|---|---|
| Julio 11, 2007 | 20/07/2007 |
| Nombre y dirección de correspondencia de la ISA/<br>Oficina Europea De Patentes, P.B. 5818 Patentlaan 2<br>NL- 2280 HV Rijswijk,<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Funcionario Autorizado<br><br>Fritz, Martin |

# REPORTE DE BUSQUEDA INTERNACIONAL
## Información sobre miembros de la familia

No. de solicitud internacional

PCT/US2006/060958

**C. (Continuación) DOCUMENTOS CONSIDERADOS COMO RELEVANTES**

| Categoría | Cita del documento, con indicación, cuando sea apropiado, de los pasajes relevantes | Relevante para reivindicación No. |
|---|---|---|
| | | |

# REPORTE DE BUSQUEDA INTERNACIONAL
## Información sobre miembros de la familia

No. de solicitud internacional
PCT/US2006/060958

**Recuadro II Observaciones en donde no se encontraron ciertas reivindicaciones (Continuación del punto 2 de la primera página)**

El Reporte de Búsqueda Internacional no ha sido establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2) por las siguientes razones:

1. ☒ Reivindicaciones Nos.:
   porque se refieren al contenido no requerido a ser buscado por esta Autoridad, principalmente:
   Aunque las reivindicaciones 15-19 están dirigidas a un método para el tratamiento del cuerpo del ser humano/animal, la búsqueda se ha llevado a cabo y basado en los efectos alegados del compuesto/composición

2. ☒ Reivindicaciones Nos.:
   porque se refieren a partes de la Solicitud Internacional que no condescienden con los requerimientos prescritos a tal grado que no se puede llevar a cabo ninguna Búsqueda Internacional significativa, específicamente:
   véase hoja de INFORMACION ADICIONAL PCT/ISA/210

3. ☐ Reivindicaciones Nos.:
   porque son reivindicaciones dependientes y no se han redactado de acuerdo con la segunda y tercera frases de la Regla 6.4(a).

**Recuadro III Observaciones en donde falta la unidad de la invención (Continuación del punto 3 de la primera página)**

La Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

1. ☐ Cuando todas las cuotas de búsqueda adicionales requeridas sean pagadas a tiempo por el solicitante, este Reporte de Búsqueda Internacional cubre todas las reivindicaciones que se pueden buscar.

2. ☐ Cuando se puedan buscar todas las reivindicaciones investigables sin esfuerzo justificando una cuota adicional, esta Autoridad no solicitará el pago de ninguna cuota adicional.

3. ☐ Cuando solamente se paguen a tiempo algunas de las cuotas de búsqueda adicionales por el solicitante, este Reporte de Búsqueda Internacional cubre solamente esas reivindicaciones para las cuales se pagaron las cuotas, específicamente las reivindicaciones Nos.:

4. ☐ No se pagaron a tiempo las cuotas adicionales requeridas por el solicitante. En consecuencia, este Reporte de Búsqueda Internacional está restringido a la primera invención mencionada en las reivindicaciones; está cubierto por las reivindicaciones Nos.:

Observaciones sobre la protesta

☐ Las cuotas de búsqueda adicionales estuvieron acompañadas por la protesta del solicitante
☐ Ninguna protesta acompañó el pago de cuotas de búsqueda adicionales.

# REPORTE DE BUSQUEDA INTERNACIONAL

## Información sobre miembros de la familia

No. de solicitud internacional
PCT/US2006/060958

| Documento de patente citado en el reporte de búsqueda | | Fecha de publicación | Miembro(s) de la familia de la patente | | Fecha de publicación |
|---|---|---|---|---|---|
| WO 2005037796 | A | 28-04-2005 | AU | 2004282101 A1 | 28-04-2005 |
| | | | BR | PI0414186 A | 31-10-2006 |
| | | | CA | 2537942 A1 | 28-04-2005 |
| | | | CN | 1863778 A | 15-11-2006 |
| | | | EP | 1670768 A1 | 21-06-2006 |
| | | | JP | 2007508301 T | 05-04-2007 |
| | | | KR | 20060085675 A | 27-07-2006 |
| US 2002177708 | A1 | 28-11-2002 | US | 2003040545 A1 | 27-02-2003 |
| | | | US | 2003050317 A1 | 13-03-2003 |
| | | | US | 2003078264 A1 | 24-04-2003 |
| | | | US | 2003027826 A1 | 06-02-2003 |
| | | | US | 6521607 B1 | 18-02-2003 |
| WO 2007062342 | A | 31-05-2007 | US | 2007135467 A1 | 14-06-2007 |

# TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

Remitente: ADMINISTRACIÓN DE LA BÚSQUEDA INTERNACIONAL

Destinatario:

ver forma PCT/ISA/210

# PCT

## OPINIÓN ESCRITA DE LA ADMINISTRACIÓN ENCARGADA DE LA BÚSQUEDA INTERNACIONAL

(Regla 43*bis*.1 del PCT)

Fecha de expedición *(día/mes/año)*
ver forma PCT/ISA/210

Referencia del expediente del solicitante o del mandatario
ver forma PCT/ISA/220

PARA CONTINUAR LA TRAMITACIÓN
ver párrafo 2 siguiente

| Solicitud internacional N° | Fecha de presentación internacional *(día/mes/año)* | Fecha de prioridad *(día/mes/año)* |
|---|---|---|
| PCT/US2006/060958 | 16.11.2006 | 23.11.2005 |

Clasificación Internacional de Patentes (CIP) o a la vez clasificación nacional y CIP
INV. C07D211/29 C07C215/08 C07C217/58 C07C229/36 C07C229/38 C07C233/09 C07C233/13 C07C233/18 C07C233/56 C07C233/60 C07C233/66 C07C233/73 C07C233/78 C07C235/20 C07C235/34 C07C235/48

Solicitante
BRITOL-MYERS SQUIBB COMPANY

1. La presente opinión contiene indicaciones relativas a los puntos siguientes:

| | | |
|---|---|---|
| ☒ | Recuadro I | Base de esta opinión |
| ☐ | Recuadro II | Prioridad |
| ☒ | Recuadro III | No formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial |
| ☐ | Recuadro IV | Falta de unidad de invención |
| ☒ | Recuadro V | Declaración motivada según la Regla 43*bis*.1(.a)i) sobre la novedad, la actividad inventiva y la aplicación industrial: citas y explicaciones en apoyo de esta declaración |
| ☐ | Recuadro VI | Ciertos documentos citados |
| ☐ | Recuadro VII | Defectos en la solicitud internacional |
| ☐ | Recuadro VIII | Observaciones relativas a la solicitud internacional |

2. **CONTINUACIÓN DE LA TRAMITACIÓN**

Si se hace una petición de examen preliminar internacional, esta opinión se considerará como una opinión escrita de la Administración encargada del examen preliminar internacional ("IPEA") salvo en aquellos casos en los que el solicitante elija una Administración a ésta y, la IPEA elegida haya notificado a la Oficina Internacional según lo previsto en la Regla 66.1bis(b) que las opiniones escritas de esta Administración encargada de la búsqueda internacional no serán consideradas como tales.

Si esta opinión es, como se indica más arriba, considerada como una opinión escrita de la IPEA, se invita al solicitante a que presente ante la IPEA una respuesta por escrito junto con modificaciones, en su caso, antes de la expiración del plazo de 3 meses a contar desde la fecha de envío del formulario PCT/ISA/220 o antes de la expiración del plazo de 22 meses a contar desde la fecha de prioridad, aplicándose el plazo que expire más tarde.

Para otras opciones, consultar el formulario PCT/ISA/220.

3. Para más detalles, ver las notas del formulario PCT/ISA/220.

| Nombre y dirección postal de ISA: | Fecha de terminación de esta opinión | Funcionario autorizado |
|---|---|---|
| Oficina Europea De Patentes, P.B. 5818 Patentlaan 2<br>NL- 2280 HV Rijswijk, Pays Bas<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | ver forma PCT/ISA/210 | Fritz, Martin<br>Teléfono No. +31 70 340-3024 |

## Recuadro No. I Bases de la opinión

1. Con respecto al **idioma**, esta opinión se ha establecido sobre las bases de:
   - ☒ la solicitud internacional en el idioma en cual se presentó
   - ☐ una traducción de la solicitud internacional en _____, que es el idioma de una traducción elaborada para los propósitos de la búsqueda internacional (bajo las Reglas 12.3(a) y 23.1 (b)).

2. Con respecto a cualquier **secuencia de nucleótido y/o aminoácido** descrita en la solicitud internacional y necesaria para la invención reclamada, esta opinión se ha establecido sobre las bases de:
   a. tipo de material:
      - ☐ una lista de secuencias
      - ☐ el (los) cuadro(s) relacionado(s) con la lista de secuencias

   b. formato del material:
      - ☐ en papel
      - ☐ en forma electrónica

   c. hora de presentación/preparación:
      - ☐ contenida en la solicitud internacional según presentada
      - ☐ presentada junto con la solicitud internacional en forma electrónica.
      - ☐ preparada subsiguientemente a esta Autoridad para los propósitos de la búsqueda.

3. ☐ Además, en el caso de más de una versión o copia de una lista de secuencias y/o cuadro relacionado con la misma que se ha presentado o elaborado, se prepararon las declaraciones requeridas de que la información en las copias subsiguientes o adicionales son es idéntica a aquella de la solicitud según presentada o no va más allá de la solicitud según presentada, según sea apropiado.

4. Comentarios adicionales:

**OPINION ESCRITA DE LA AUTORIDAD DE BUSQUEDA INTERNACIONAL**

**Solicitud Internacional No.** PCT/US2006/060958

**Recuadro No. III No establecimiento de opinión con respecto a la novedad, paso inventivo y aplicabilidad industrial**

Las preguntas de si la invención reclamada parece que es novedosa, para involucrar un paso inventivo (para ser no obvio), o para ser industrialmente aplicable no se han examinado con respecto a:

☐ la solicitud internacional completa,

☒ reivindicaciones Nos. 1-9(parte); 12-19(parte);21-23;15-19 con respecto a la aplicabilidad industrial

porque:

☒ dicha solicitud internacional, o dichas reivindicaciones Nos. 15-19 con respecto a la aplicabilidad industrial se refieren al siguiente tema que no requiere de un examen preliminar internacional (*especificar*):
**ver hoja aparte**

☒ la descripción, reivindicaciones o dibujos (*indicar elementos particulares a continuación)* o dichas reivindicaciones Nos. 21-23 son tan poco claras que no se puede formar ninguna opinión significativa. *(especificar)*:
**ver hoja aparte**

☒ las reivindicaciones, o dichas reivindicaciones Nos. 1-9(parte); 12-19(parte) están tan inadecuadamente soportadas por la descripción que se podría formar ninguna opinión significativa
**ver hoja aparte**

☒ no se ha establecido ningún reporte de búsqueda internacional para la solicitud completa o dichas reivindicaciones Nos. . 1-9(parte); 12-19(parte)

☐ el listado de la secuencia de nucleótido o aminoácido no cumple con el estándar provisto por el Anexo C de las Instrucciones Administrativas en que:

| | | |
|---|---|---|
| la forma escrita | ☐ | no ha sido provista |
| | ☐ | no cumple con el estándar |
| la forma legible por computadora | ☐ | no ha sido provista |
| | ☐ | no cumple con el estándar |

☐ los cuadros relacionados con el listado de la secuencia de nucleótido o aminoácido, si están solamente en una forma legible por computadora, no cumplen con los requerimientos técnicos provistos en el Anexo C-*bis* de las Instrucciones Administrativas

☐ Ver página aparte para detalles adicionales.

**Cuadro No. V Declaración concluida bajo la Regla 43*bis*.1(a)(i) con respecto a la novedad, paso de la invención o aplicabilidad industrial; citas y explicaciones que soportan dicha declaración**

1. Declaración

| | | |
|---|---|---|
| Novedad (N) | Si: Reivindicaciones<br>No: Reivindicaciones | 1-20 |
| Paso de la invención (PI) | Si: Reivindicaciones<br>No: Reivindicaciones | 1-20 |
| Aplicabilidad industrial (AI) | Si: Reivindicaciones<br>No: Reivindicaciones | 1-14, 20 |

2. Citas y explicaciones

**ver hoja aparte**

**Re Punto III**

**No establecimiento de la opinión con respecto a la novedad, paso inventivo y aplicabilidad industrial**

Las reivindicaciones 15-19 se refieren al tema considerado por esta Autoridad a ser cubierto por las provisiones de la Regla 67.1 (iv) PCT. En consecuencia, no se formulará ninguna opinión con respecto a la aplicabilidad industrial del tema de estas reivindicaciones (Artículo 34(4)(a)(I) PCT).

Las presentes reivindicaciones 1-9 y 12-19 se refieren a un número extremadamente grande de compuestos y composiciones posibles. El soporte y la descripción en el sentido del Artículo 6 y 5 PCT es sin embargo encontrar solamente una pequeña proporción de los compuestos y composiciones reivindicados, ya que los ejemplos comprendidos en la Descripción representan un número muy limitado de posibles variantes estructurales dentro del alcance de de los compuestos como se definen en la reivindicación 1.
Además, debido a la exclusión de un gran número de compuestos, imposible evaluar el alcance de la reivindicación 1 y aquellas reivindicaciones dependientes de ésta.
El incumplimiento de las provisiones sustantivas es a tal grado, que la búsqueda de las reivindicaciones 1-9 y 12-19 se restringió a aquellos productos reivindicados que parece que están soportados y una generalización de razonable de los compuestos actualmente ejemplificados (Instrucciones PCT 9.19 y 9.23), es decir

los compuestos de la fórmula Ia o Ib de acuerdo con la reivindicación 1,
en donde A, B, y $R^1$ son como se definieron en la reivindicación 10,

los compuestos de la fórmula Ia de acuerdo con la reivindicación 2,
en donde A, B, y $R^1$ son como se definieron en la reivindicación 11,

las composiciones y sus usos.

Además el tema de las reivindicaciones 21-23 no puede ser investigado, ya que el significado de varias expresiones utilizadas ahí tales como "WW", "YY", "ZZ", y "AAA" no se pueden entender.

Las reivindicaciones o partes de las mismas relacionadas con las invenciones con respecto a las cuales no se ha establecido un Reporte de búsqueda no necesitan someterse al a Opinión Escrita de la Autoridad de Búsqueda Internacional (Regla 43bis.1(b) PCT en combinación con la Regla 66.1(e) PCT).

**Re Punto V**

**Declaración razonada según la Regla 66.2(a)(iii) con respecto a la novedad, paso inventivo o aplicabilidad industrial; citas y explicaciones que soportan dicha declaración**

D1: WO 2005/037796 A (LILLY CO ELI [US]; CAO GUOQUING [US]; ESCRIBANO ANA MARIA [ES]; FERNAND) Abril 28, 2005 (2005-04-28)

D2: US 2002/177708 A1 (SIKORSKI JAMES A [US] Y OTROS) Noviembre 28, 2002 (2002-11-28)

La presente solicitud se refiere a compuestos enantioméricos de las fórmulas generales Ia, Ib y representantes de los mismos (reivindicaciones 1-11, 20), composiciones farmacéuticas de los mismos (reivindicaciones 12-13), métodos de tratamiento mediante la administración de estos compuestos (reivindicaciones 15-19) y procedimientos para la producción de compuestos, la estructura de los cuales no es conocida (cons. punto III de esta comunicación).

Para la evaluación de las presentes reivindicaciones 15-19 en la cuestión de si son industrialmente aplicables, no existe un criterio unificado en los Estados Contrayentes PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO por ejemplo, no reconoce como industrialmente aplicable el tema de las reivindicaciones para el uso de un compuesto en el tratamiento médico, pero puede permitir, sin embargo, reivindicaciones para un compuesto conocido para primer uso en un tratamiento médico y el uso de dicho compuesto para la fabricación de un medicamento para un nuevo tratamiento médico.

Los siguientes comentarios con respecto a la novedad y paso inventivo de las reivindicaciones 1-9 y 12-19 solamente se refieren al tema de las mismas que fue actualmente investigado (Art. 17(2) PCT), ver anterior).

La técnica anterior más cercana es D1 o D2.

El problema subyacente de la presente solicitud fue proporcionar compuestos heterocíclicos adicionales que son adecuados como inhibidores de la proteína de transferencia de éster de colesterilo (CETP) y como tal para el tratamiento de arterioesclerosis y enfermedades cardiovasculares.

Este problema ha sido resuelto, como se puede ver en la descripción.

Los compuestos Ia y Ib como se investigaron así como aquellos compuestos ejemplificados que no son representantes de los mismos no se pueden considerar obvios para el experto en la técnica

ya que están estructuralmente remotos de los compuestos de acuerdo con D1 y D2 y son una clase de compuestos que nunca han sido sugeridos como inhibidores CETP.

Un paso inventivo en el sentido del Artículo 33(3) PCT puede reconocer por consiguiente para el tema de las reivindicaciones 1-20 como se investigaron.

Objeciones adicionales:

En contra de los requerimientos de la Regla 5.1(a)(ii) PCT, la técnica antecedente relevante descrita en los documentos D1-D2 no se menciona en la descripción, ni tampoco estos documentos se identifican ahí.

El término "profármaco" utilizado en la reivindicación 1 es una definición funcional y no proporciona al experto en la técnica la enseñanza necesaria para evaluar que tema está realmente comprendido en la misma.
Al utilizar el término "profármacos" también se pretende definir la invención mediante un resultado a ser logrado que no es permisible (cons. también Instrucciones del Examen Preliminar Internacional PCT III-4.7).
El tema de la reivindicación 1 por consiguiente no cumple con los requerimientos del Artículo 6 PCT.

La reivindicación 20 contiene una referencia a la descripción. De acuerdo con la Regla 6.2(a) PCT, las reivindicaciones no deberán contener dichas referencias excepto cuando es absolutamente necesario, que no es el caso aquí.

EXTRACTOS

2072

Industria y Comercio
SUPERINTENDENCIA

# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
## DIVISION DE NUEVAS CREACIONES
### EXTRACTO PARA PUBLICACIÓN
### SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

| (31) *No.* | 32) *Fecha* | (33) *País* |
|---|---|---|
| 60/739,374 | 23/11/05 | US |
| 11/558,979 | 13/11/06 | US |

(51) Int Cl: C07C 211/29, C07C 215/08, C07C 217/58, C07C 229/36, C07C 229/38, C07C 233/09, C07C 233/13, C07C 233/18, C07C 233/56, C07C 233/60, C07C 233/66, C07C 233/73, C07C 233/78, C07C 235/20, C07C 235/34

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) **SALVATI, MARK E**
**FINLAY, HEATHER**
**Y OTROS**

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

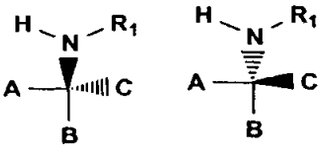
(85) Fecha límite inicio fase nacional: **23/06/08**

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: ***16/11/06***
No. de solicitud **PCT/US2006/060958**

(87) Publicación internacional
Fecha: ***31/05/07***
N° publicación: **WO/2007/062308**

(54) Titulo: **COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO**

Los compuestos de la fórmula Ia y IB




Ia y Ib

en donde A, B, C y R1 son como se describen en la presente.

Industria y Comercio
SUPERINTENDENCIA

# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
## DIVISION DE NUEVAS CREACIONES
### TARJETA ARCHIVO PROPIETARIOS

2073

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud:

(22) Fecha de solicitud:

(51) Clasificación Internacional : C07C 211/29, C07C 215/08, C07C 217/58, C07C 229/36, C07C 229/38, C07C 233/09, C07C 233/13, C07C 233/18, C07C 233/56, C07C 233/60, C07C 233/66, C07C 233/73, C07C 233/78, C07C 235/20, C07C 235/34

(71) Solicitante(s)

**BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) SALVATI, Mark E.; FINLAY, Heather; CHEN, Bang-chi; HARIKRISHNAN, Lalgudi S.; JIANG, Ji; JOHNSON, James A.; KAMAU, Muthoni G.; LAWRENCE, Michael R.; LI, Jianqing; LLOYD, John; MILLER, Michael Matthew; PI, Zulan; QIAO, Jennifer X; RAMPULLA, Richard; WANG, Tammy C.; WANG, Yufeng; YANG, Wu y ROBERGE, Jacques Y.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad

| (31) *No. Prioridad* | 32) *Fecha* | (33) *País* |
|---|---|---|
| 60/739,374 | 23/11/05 | US |
| 11/558,979 | 13/11/06 | US |

(85) Fecha inicio fase nacional: 23/06/08

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **16/11/06**
No. de solicitud **PCT/US2006/060958**

(87) Publicación internacional
Fecha: ***31/05/07***
N° publicación: **WO/2007/062308**

(54) Título:

**COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO**

Industria y Comercio
SUPERINTENDENCIA

# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
## DIVISION DE NUEVAS CREACIONES
### TARJETA ARCHIVO TEMATICO

2074

SUPERINTENDENCIA PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07C 211/29, C07C 215/08, C07C 217/58, C07C 229/36, C07C 229/38, C07C 233/09, C07C 233/13, C07C 233/18, C07C 233/56, C07C 233/60, C07C 233/66, C07C 233/73, C07C 233/78, C07C 235/20, C07C 235/34

(71)Solicitante(s)

**BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) SALVATI, Mark E.; FINLAY, Heather; CHEN, Bang-chi; HARIKRISHNAN, Lalgudi S.; JIANG, Ji; JOHNSON, James A.; KAMAU, Muthoni G.; LAWRENCE, Michael R.; LI, Jianqing; LLOYD, John; MILLER, Michael Matthew; PI, Zulan; QIAO, Jennifer X; RAMPULLA, Richard; WANG, Tammy C.; WANG, Yufeng; YANG, Wu y ROBERGE, Jacques Y.

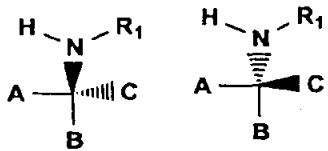
(74) Apoderado: ALVARO CORREA ORDOÑEZ

| (30) Prioridad | (31) *No. Prioridad* | 32) *Fecha* | (33) *País* |
|---|---|---|---|
| | **60/739,374** | **23/11/05** | **US** |
| | **11/558,979** | **13/11/06** | **US** |

(85) Fecha límite inicio fase nacional: **23/06/08**

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: **16/11/06**
No. de solicitud **PCT/US2006/060958**

(87) Publicación internacional:
Fecha: ***31/05/07***
No. Publicación : **WO/2007/062308**




Ia y Ib

(54) Titulo: **COMPUESTOS HOMO- Y HETEROCICLICOS ADECUADOS COMO INHIBIDORES DE LA PROTEINA DE TRANSFERENCIA DE ESTER DE COLESTERILO**

(57) Resumen: Los compuestos de la fórmula Ia y IB en donde A, B, C y R1 son como se describen en la presente

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-052929- -00000-0000

Fecha: 2008-05-23 15:34:21 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 2074

# Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

## REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

| | USUARIO | RADICADOR |
|---|---|---|
| PATENTE DE INVENCIÓN (X) MODELO DE UTILIDAD ( ) | ( ) | ( ) |
| -Indicación de que se solicita la concesión de una patente. | (X) | ( ) |
| -Datos de identificación del solicitante o de la persona que se presenta la solicitud. | (X) | ( ) |
| -Descripción de la invención. | (X) | ( ) |
| -Dibujos de ser estos pertinentes. | ( ) | ( ) |
| -Comprobante de Pago de las tasas establecidas. | (X) | ( ) |
| COMPLETA (X INCOMPLETA | ( ) | ( ) |
| DISEÑO INDUSTRIAL ( ) | | |
| -Indicación de que se solicita el registro de Diseño Industrial. | ( ) | ( ) |
| -Datos de identificación del solicitante o de la persona que se presenta la solicitud. | ( ) | ( ) |
| -Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño. | ( ) | ( ) |
| -Comprobante de Pago de las tasas establecidas. | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| ESQUEMA DE TRAZADO ( ) | | |
| -Indicación de que se solicita el registro de Diseño Industrial. | ( ) | ( ) |
| -Datos de identificación del solicitante o de la persona que se presenta la solicitud. | ( ) | ( ) |
| -Representación gráfica del Esquema Trazado. | ( ) | ( ) |
| -Comprobante de Pago de las tasas establecidas. | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |

Firma Responsable: Mabel Bos

Fecha: Mayo 23, 2008

2076

# REPUBLICA DE COLOMBIA
# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL MYERS SQUIBB COMPANY

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 8 52929 |
| | Solicitud internacional | PCT/US2006/060958 |
| | Fecha inicio fase nacional | 23/06/2008 |
| | Trámite | 11 |
| | Evento | 378 |
| | Actuación | 430 |
| | Oficio No. | 8324 |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1.- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 JUN. 2008
adpa11