SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

09-149364

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: INHIBIDORES DE TETRAHIDROPIRANOCROMENO DE GAMMA SECRETASA

SOLICITANTE: SCHERING CORPORATION

DIRECCIÓN: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 30 de Diciembre de 2009

991

P2009/000211

Fue / No Exitosa
05-01-2010

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-149364- -00000-0000

Fecha: 2009-12-30 17:40:03 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 674

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000211**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** SCHERING CORPORATION **Dirección:** 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A. **Nacionalidad o Domicilio:** Estadounidense **Lugar de Constitución:** Estados Unidos **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10. **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [x] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79.782.747 Btá **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/008192 Fecha Julio 01, 2008

Publicación Internacional No. WO 2009/008980 Fecha Enero 15, 2009

(6) **Título (54)** **INHIBIDORES TETRAHIDROPIRANOCROMENO DE GAMMA SECRETASA**

Clasificación Internacional (51) C07D 311/78; C07D 407/12; C07D 493/04; A61K 31/35; A61K 31/352; A61P 25/28

Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	Junio 5, 2007	60/948,033

(9) **Comprobante de pago No.** 09- **Fecha** Diciembre 30 de 2009

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-132393.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

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3

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 93,676
FECHA : DICIEMBRE 30 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-149364- -00000-0000

Fecha 2009-12-30 17:40:03 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTILIYII Lve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 674

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
PLASTI PAISDEK	CONSIGNACION	BANCO DE BOGOTA	062784387	13452280	30/12/2009	3,803,000.00

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

CANT.	DENTIFICO	CONCEPTO	TOTA CONCEPTO
1	50005 01 01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

1. País: Estados Unidos de América
   - Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguertie La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey 8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el Poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE

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

4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

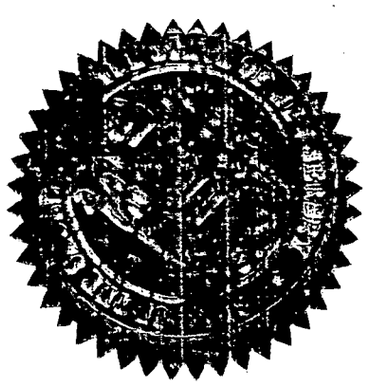
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

John E McCormac

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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9

Power of Attorney

The undersigned,
SCHERING CORPORATION
domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

Poder

El suscrito,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____
Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

City,Country/Ciudad,Pais: Kenilworth, New Jersey, U.S.A.

OLARTERAISBECK

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Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 119 Greenwood Drive, Millburn, New Jersey 07041, U.S.A.
signed the foregoing document.

2. That the grantor has executed the foregoing document as Senior Legal Director of SCHERING CORPORATION

3. That SCHERING CORPORATION having its principal place of business located in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.SA.. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de

de

4. Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

Marguerite La Corte
Notary Public of New Jersey
My Commission Expires October 7, 2003

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2009 (15.01.2009)

PCT

(10) International Publication Number
WO 2009/008980 A2

(51) International Patent Classification:
C07D 311/78 (2006.01) *A61K 31/35* (2006.01)
C07D 407/12 (2006.01) *A61K 31/352* (2006.01)
C07D 493/04 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/US2008/008192

(22) International Filing Date: 1 July 2008 (01.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/948,033 5 July 2007 (05.07.2007) US

(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WU, Wen-lian** [US/US]; 5 Roney Road, Edison, New Jesrey 08820 (US). **BARA, Thomas, A.** [US/US]; 15 West Henry Street, Linden, New Jersey 07036 (US). **BURNETT, Duane, A.** [US/US]; 9 Chestnut Avenue, Bernardsville, New Jersey 07924 (US). **CLADER, John, W.** [US/US]; 428 North Union Avenue, Cranford, New Jersey 07016 (US). **DOMALSKI, Martin S.** [US/US]; 23 East Lincoln Street, Verona, New Jersey 07044 (US). **JIN, Yan** [CN/US]; 402 Berkshire Drive, Princeton, New Jersey 08540 (US). **JOSIEN, Hubert, B.** [US/US]; 293 Pavonia Avenue, Jersey City, New Jersey 07302 (US). **LI, Hongmei** [CN/US]; 16 Hemlock Circle, Warren, New Jersey 07059 (US). **LIANG, Xian** [US/US]; 31 Lexington Road, Monmouth Junction, New Jersey 08852 (US). **PISSARNITSKI, Dmitri, A.** [RU/US]; 22 Blue Ridge Circle, Scotch Plains, New Jersey 07076 (US). **SASIKUMAR, Thavalakulamgara, K.** [IN/US]; 21 Canterbury Lane, Edison, New Jersey 08820 (US). **WONG, Jesse, K.** [US/US]; 2 Hampshire Place, Monroe Township, New Jersey 08831 (US). **XU, Ruo** [US/US]; 66 Dogwood Lane, Watchung, New Jersey 07060 (US). **ZHAO, Zhiqiang** [CN/US]; 413 Henry Street, Scotch Plains, New Jersey 07076 (US). **MCNAMARA, Paul** [US/US]; 1261 Christine Circle, Scotch Plains, New Jersey 07076 (US).

(74) Agent: **JEANETTE, Henry, C.**; SCHERING CORPORATION, 2000 Galloping Hill Road, Patent Dept. K-6-1 1990, Kenilworth, NJ 07033 (US).

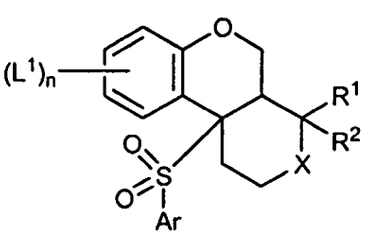
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: TETRAHYDROPYRANOCHROMENE GAMMA SECRETASE INHIBITORS



(I)

(57) **Abstract:** Disclosed are novel gamma secretase inhibitors of the formula. Also disclosed are methods of inhibiting gamma-secretase, methods of treating neurodegenerative diseases, and methods of treating Alzheimer's Disease. Also disclosed are processes for preparing alkenes in one reaction step using a mixture of an aldehyde (or ketone) and an alkyl substituted with two electron withdrawing groups, and reacting the mixture with: (a) a sulfonyl halide (e.g., a sulfonyl chloride) and a basic tertiary amine, or, (b) a sulfonyl anhydride and a basic amine, or (c) an aryl-C(O)-halide and a basic tertiary amine, or (d) an aryl-C(O)-O-C(O)-aryl and a basic tertiary amine, or (e) an heteroaryl-C(O)-halide and a basic tertiary amine, or (f) a heteroaryl-C(O)-O-C(O)-heteroaryl and a basic tertiary amine.

WO 2009/008980 A2

Tetrahydropyranochromene Gamma Secretase Inhibitors

REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/948033 filed July 5, 2007.

BACKGROUND

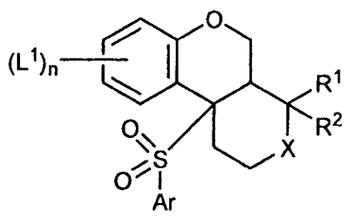
WO 00/50391, published August 13, 2000, discloses compounds having a sulfonamide moiety that are useful for the treatment and prevention of Alzheimer's Disease and other diseases relating to the deposition of amyloid protein.

McCombie et al., Tetrahedron Letters, Vol. 34, No. 50, pp. 8033-8036 (1993) describe methods of preparing chromans and thiochromans. However, the chromans and thiochromans described therein are quite different from the compounds of the present invention.

In view of the present interest in the treatment or prevention of neurodegenerative diseases, such as Alzheimer's Disease, a welcome contribution to the art would be compounds for use in such treatment or prevention. This invention provides such a contribution.

SUMMARY OF THE INVENTION

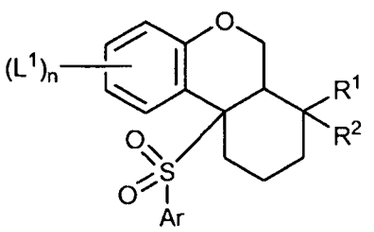
This invention provides compounds that are inhibitors (e.g., antagonists) of gamma-secretase (also termed "γ-secretase") and have the Formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein X, L^1, R^1, R^2 and Ar are independently selected and are as defined below.

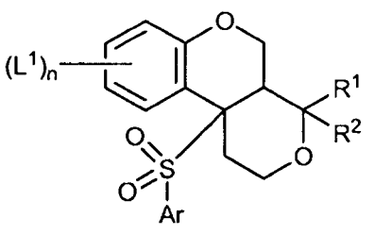
This invention also provides compounds of formula (I) that have the formula (I.A1):



(I.A1)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein L^1, R^1, R^2 and Ar are as defined below.

This invention also provides compounds of formula (I) that have the formula (I.A2):



(I.A2)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein L^1, R^1, R^2 and Ar are as defined below.

This invention also provides the compounds of formula (I) in pure and isolated form.

This invention also provides the compounds of formula (I) in pure form.

This invention also provides the compounds of formula (I) in isolated form.

This invention also provides the compounds of formula (I.A1) in pure and isolated form.

This invention also provides the compounds of formula (I.A1) in pure form.

This invention also provides the compounds of formula (I.A1) in isolated form.

This invention also provides the compounds of formula (I.A2) in pure and isolated form.

This invention also provides the compounds of formula (I.A2) in pure form.

This invention also provides the compounds of formula (I.A2) in isolated form.

This invention also provides compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), which compounds are identified below.

This invention also provides compounds of 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-) in pure form.

This invention also provides compounds of 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-) in isolated form.

This invention also provides a pharmaceutically acceptable salt of a compound of formula (I).

This invention also provides a solvate of a compound of formula (I).

This invention also provides a pharmaceutically acceptable salt of a compound of formula (I.A1).

This invention also provides a solvate of a compound of formula (I.A1).

This invention also provides a pharmaceutically acceptable salt of a compound of formula (I.A2).

This invention also provides a solvate of a compound of formula (I.A2).

This invention also provides a solvate of a compound selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

This invention also provides a pharmaceutically acceptable ester of a compound of formula (I).

This invention also provides a pharmaceutically acceptable ester of a compound of formula (I.A1).

This invention also provides a pharmaceutically acceptable ester of a compound of formula (I.A2).

This invention also provides a pharmaceutical composition comprising an effective amount of one or more compounds of Formula (I) and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more compounds of Formula (I.A1) and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more compounds of Formula (I.A2) and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a compound of Formula (I) and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a compound of Formula (I.A1) and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a compound of Formula (I.A2) and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more pharmaceutically acceptable salts of the compounds of Formula (I), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more pharmaceutically acceptable salts of the compounds of Formula (I.A1), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more pharmaceutically acceptable salts of the compounds of Formula (I.A2), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable salt of a compound of Formula (I), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable salt of a compound of Formula (I.A1), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable salt of a compound of Formula (I.A2), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more solvates of the compounds of Formula (I), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more solvates of the compounds of Formula (I.A1), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more solvates of the compounds of Formula (I.A2), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a solvate of a compound of Formula (I), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a solvate of a compound of Formula (I.A1), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a solvate of a compound of Formula (I.A2), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more pharmaceutically acceptable esters of the compounds of Formula (I), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more pharmaceutically acceptable esters of the compounds of Formula (I.A1), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more pharmaceutically acceptable esters of the compounds of Formula (I.A2), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable ester of a compound of Formula (I), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable ester of a compound of Formula (I.A1), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable ester of a compound of Formula (I.A2), and at least one pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

This invention also provides a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)), and an effective amount of one or more (e.g., one) other pharmaceutically active ingredients (e.g.,) drugs, and a pharmaceutically acceptable carrier. Examples of the other pharmaceutically active ingredients include, but are not limited to drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more (e.g., one) other therapeutically effective pharmaceutical active ingredients (e.g., drugs), and a pharmaceutically acceptable carrier. Examples

of the other drugs include, but are not limited to drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)), and effective amount of one or more BACE inhibitors, and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more BACE inhibitors, and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors), and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formulas (I.A1), or compounds of formula (I.A2)), and effective amount of one or more muscarinic antagonists (e.g., m_1 or m_2 antagonists), and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-),

78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more muscarinic antagonists (e.g., m_1 or m_2 antagonists), and a pharmaceutically acceptable carrier.

This invention also provides a method for inhibiting gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I) to a patient in need of treatment.

This invention also provides a method for inhibiting gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A1) to a patient in need of treatment.

This invention also provides a method for inhibiting gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A2) to a patient in need of treatment.

This invention also provides a method for inhibiting gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment.

This invention also provides a method for inhibiting gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A1) to a patient in need of treatment.

This invention also provides a method for inhibiting gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A2) to a patient in need of treatment.

This invention also provides a method for inhibiting gamma-secretase comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

This invention also provides a method of treating one or more neurodegenerative diseases comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I) to a patient in need of treatment.

This invention also provides a method of treating one or more neurodegenerative diseases comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A1) to a patient in need of treatment.

This invention also provides a method of treating one or more neurodegenerative diseases comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A2) to a patient in need of treatment.

This invention also provides a method of treating one or more neurodegenerative diseases comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment.

This invention also provides a method of treating one or more neurodegenerative diseases comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A1) to a patient in need of treatment.

This invention also provides a method of treating one or more neurodegenerative diseases comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A2) to a patient in need of treatment.

This invention also provides a method for treating one or more neurodegenerative diseases comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+),106(-), 107(-), 108(-), and 111(-).

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I) to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A1) to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A2) to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A1) to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A2) to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I) to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A1) to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A2) to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A1) to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A2) to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

This invention also provides combination therapies for (1) inhibiting gamma-secretase, or (2) treating one or more neurodegenerative diseases, or (3)inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (4) treating Alzheimer's disease. The combination therapies are directed to methods comprising the administration of one or more (e.g. one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)) and the administration of one or more (e.g., one) other pharmaceutical active ingredients (e.g., drugs). The compounds of formula (I) and the other drugs can be administered separately (i.e., each is in its own separate dosage form), or the compounds of formula (I) can be combined with the other drugs in the same dosage form.

Thus, this invention also provides any one of the methods of treatment, or methods of inhibiting, described herein, wherein the compound of formula (I) (e.g., the compound of formula (I.A1), or the compound of formula (I.A2)) is used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., m_1 or m_2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors (e.g., ezetimibe).

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I), in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A1), in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula (I.A2), in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for

example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I), in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A1), in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I.A2), in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

The phrase "any one of the above methods" as used below means that the description below applies to each method described above just as if each method above was separatedly described with the scope described below.

This invention also provides any one of the above methods wherein a pharmaceutically acceptable salt of a compound of formula (I) is used instead of the compound of formula (I).

This invention also provides any one of the above methods wherein a pharmaceutically acceptable salt of a compound of formula (I.A1) is used instead of the compound of formula (I.A1).

This invention also provides any one of the above methods wherein a pharmaceutically acceptable salt of a compound of formula (I.A2) is used instead of the compound of formula (I.A2).

This invention also provides any one of the above methods wherein a pharmaceutically acceptable ester of a compound of formula (I) is used instead of the compound of formula (I).

This invention also provides any one of the above methods wherein a pharmaceutically acceptable ester of a compound of formula (I.A1) is used instead of the compound of formula (I.A1).

This invention also provides any one of the above methods wherein a pharmaceutically acceptable ester of a compound of formula (I.A2) is used instead of the compound of formula (I.A2).

This invention also provides any one of the above methods wherein a solvate of a compound of formula (I) is used instead of the compound of formula (I).

This invention also provides any one of the above methods wherein a solvate of a compound of formula (I.A1) is used instead of the compound of formula (I.A1).

This invention also provides any one of the above methods wherein a solvate of a compound of formula (I.A2) is used instead of the compound of formula (I.A2).

This invention also provides a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound of formula (I) (e.g., a compound of formula (I.A1), or a compound of formula (I.A2)) in a pharmaceutically acceptable carrier, and another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient (as described above), the combined quantities of the compound of formula (I) and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) inhibit gamma-secretase.

This invention also provides a process for preparing alkenes (i.e., diester alkenes), said processing comprising reacting:

(1) a mixture of

(a) an aldehyde or a ketone and

(b) an alkyl substituted with two electron withdrawing groups (i.e., a (EWG)-CH_2-(EWG) moiety), such as, for example, a diester of a dicarboxylic acid, (EWG represents an electron withdrawing group), and

(2) either:

(a) a sulfonyl halide (e.g., a sulfonyl chloride) and a basic amine (e.g., a basic tertiary amine), or,

(b) a sulfonyl anhydride and a basic amine (e.g., a basic tertiary amine), or

(c) an aryl-C(O)-halide and a basic amine (e.g., a basic tertiary amine), or

(d) an aryl-C(O)-O-C(O)-aryl and a basic amine (e.g., a basic tertiary amine), or

(e) an heteroaryl-C(O)-halide and a basic amine (e.g., a basic tertiary amine), or

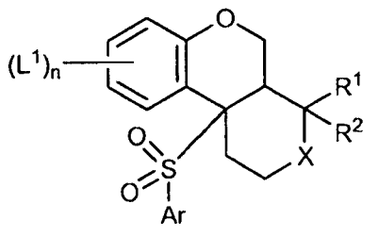
(f) a heteroaryl-C(O)-O-C(O)-heteroaryl and a basic amine (e.g., a basic tertiary amine).

The process (reaction) is conducted in a suitable organic solvent (i.e., an organic solvent wherein moieties in (1) and (2) are in solution in a suitable concentration, i.e., an organic solvent wherein the moieties in (1) and (2) are in admixture). The organic solvent is preferably anhydrous. The process (reaction) is conducted at a suitable temperature (i.e., a temperature that allows the reaction to proceed at a reasonable rate to produce the desired end product without producing undesirable reaction by-products). The reaction can be, and is preferably, carried out under an inert atmosphere (e.g., N_2). The desired product can be separated and isolated by techniques well known in the art (e.g., extraction with an organic solvent and concentration of the organic solvent).

This process produces the desired end product in one reaction.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides novel compounds, useful as gamma secretase inhibitors, of the formula:



(I)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

X is selected from the group consisting of N and CH_2;

R^1 is selected from the group consisting of: (1) -alkylene-$S(O)_2$-(C_1-C_6)alkyl, (2) -alkylene-$S(O)_2$-(C_1-C_6)haloalkyl; (3) -alkylene-$S(O)_2$-R^6, (4) -alkylene-$S(O)_2$-R^8, (5) -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl, (6) –alkylene-(tetrahydrothiophene 1,1-dioxide), (7) -alkenyl-$S(O)_2$-(C_1-C_6)alkyl, and (8) –cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl;

wherein said -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl R^1 group is substituted with one or more substituents independently selected from the group consisting of: -OH, halo, -CN, $–CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), and -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$), and preferably –OH, and more preferably one –OH, and wherein an example of said -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl R^1 group is -alkylene-$S(O)_2$- (C_1-C_6)hydroxyalkyl;

R^2 is selected from the group consisting of: H and alkyl (e.g., C_1-C_6alkyl or (C_1-C_2)alkyl), and in one example R^2 is H, and in another example R^2 is methyl;

R^6 is selected from the group consisting of: (1) unsubstituted (C_6-C_{14})aryl, (2) (C_6-C_{14})aryl substituted with one or more L^{1A} groups, (3) unsubstituted (C_5-C_{14})heteroaryl, (4) (C_5-C_{14})heteroaryl substituted with one or more L^{1A} groups, (5) unsubstituted (C_5-C_{14})heteroarylalkyl-, and (5) (C_5-C_{14})heteroarylalkyl- substituted with one or more L^{1A} groups;

R^8 is selected from the group consisting of unsubstituted cycloalkyl and cycloalkyl substituted with one or more L^3 groups (wherein examples of said cycloalkyl groups (unsubstituted or substituted) include C_3 –C_{10} cycloalkyl rings);

each L^3 is independently selected from the group consisting of: (1) -CN, (2) =O, (3) $-CH_2OH$, (4) amino (i.e., $-NH_2$), (5) halo (e.g., Cl, F, and Br), (6) $-CH_2NH_2$, (7) $-CH_2$NHalkyl (such as, for example, $-CH_2NH$(C_1-C_6)alkyl), (8) -C(O)OH, (9) -alkylene-C(O)NH(C_1 to C_6)alkyl, (10) -alkylene-C(O)N((C_1 to C_6)alkyl)$_2$ wherein each alkyl is independently selected, (11) -alkylene-C(O)NH(C_1 to C_6)haloalkyl, and (12) -alkylene-C(O)N((C_1 to C_6)haloalkyl)$_2$ wherein each alkyl is independently selected);

Ar is selected from the group consisting of: (1) unsubstituted aryl (e.g., unsubstituted phenyl), (2) aryl (e.g., phenyl) substituted with one or more L^{1A} groups, (3) unsubstituted heteroaryl (e.g., pyridyl), and (4) substituted heteroaryl (e.g., substituted pyridyl) substituted with one or more L^{1A} groups;

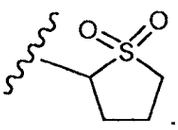
each L^1 is independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$ and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-), and $-S(O)_2$(C_1-C_6)alkyl (e.g., $-S(O)_2CH_2CH_3$);

each L^{1A} is independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$ and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-), and $-S(O)_2$(C_1-C_6)alkyl (e.g., $-S(O)_2CH_2CH_3$); and

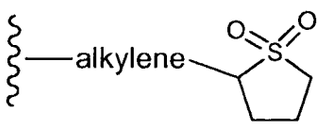
n is 0, 1, 2 or 3.

In the compounds of this invention, the $-S(O)_2$- moiety of the R^1 substituents can be bound to any carbon of the alkylene chain. In general the $-S(O)_2$- moiety of the R^1 substituents is bound to the terminal carbon of the alkylene chain.

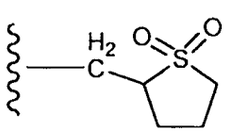
An example of a tetrahydrothiophene 1,1-dioxide moiety is:



Thus, and example of the –alkylene-(tetrahydrothiophene 1,1-dioxide) R^1 moiety is:



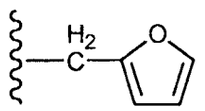
such as, for example,



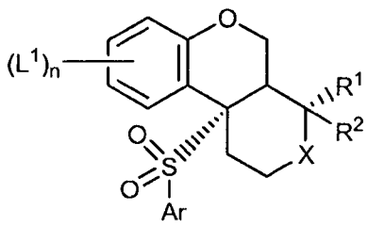
An example of the -alkenyl-$S(O)_2$-(C_1-C_6)alkyl R^1 moiety is–(C_2 to C_6)alkenyl-$S(O)_2$-(C_1-C_6)alkyl, such as, for example, –(C_2 to C_3)alkenyl-$S(O)_2$-(C_1-C_6)alkyl, such as, for example, -CH=CH-$S(O)_2$-(C_1-C_6)alkyl.

An example of the –cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl R^1 moiety is -(C_3 to C_6)cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl, such as for example, -(C_3 to C_5)cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl, such as, for example, -cyclopropyl- $S(O)_2$-(C_1-C_6)alkyl.

An example of the heteroarylalkyl moiety of the R^6 unsubstituted (C_5-C_{14})heteroarylalkyl or the substituted (C_5-C_{14})heteroarylalkyl substituent is furanyl-alkyl-, such as, for example, furanyl-CH_2-, such as, for example,

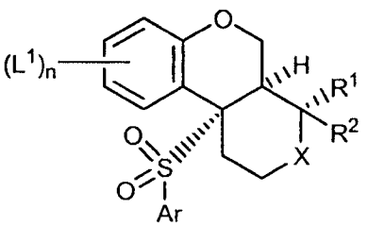


Compounds of formula (I) include compounds of formula (Ii):



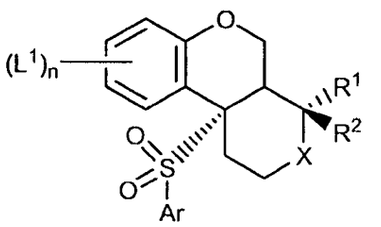
(Ii)

Compounds of formula (I) include compounds of formula (Iii):



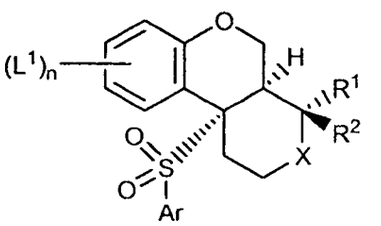
(Iii)

Compounds of formula (I) include compounds of formula (Iiii):



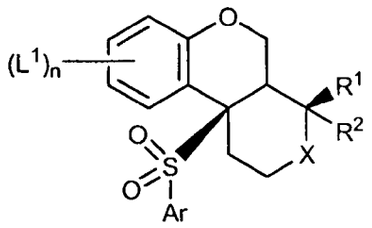
(Iiii)

Compounds of formula (I) include compounds of formula (Iiv):



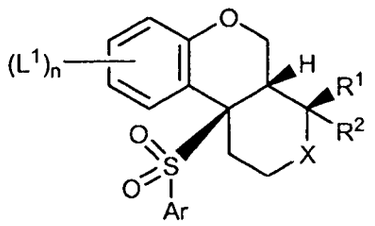
(Iiv)

Compounds of formula (I) include compounds of formula (Iv):



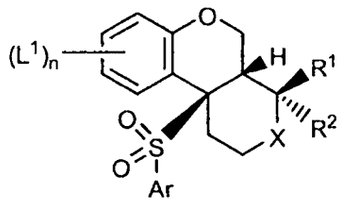
(Iv)

Compounds of formula (I) include compounds of formula (Ivi):



(Ivi)

Compounds of formula (I) include compounds of formula (Ivii):

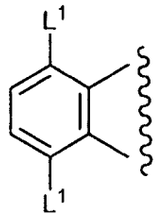


(Ivii)

The phrase "any one of the compounds" used below for the compounds of formulas (Ii) to (Ivii), (I.A1a) to (I.A1h), and (I.A2a) to (I.A2h), unless stated otherwise, means that such description applies to each compound mentioned in the description just as if each compound mentioned was separately described. Thus, for example, the description below that the "compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) wherein n is 2" is intended to describe an embodiment directed to a compound of formula (Ii) wherein n is 2. It is also intended to describe an embodiment directed to a compound of formula (Iii) wherein n is 2. It is also intended to describe an embodiment directed to a compound of formula (Iiii) wherein n is 2. It is also intended to describe an embodiment directed to a compound of formula (Iiv) wherein n is 2. It is also intended to describe an embodiment directed to a compound of formula (Iv) wherein n is 2. It is also intended to describe an embodiment directed to a compound of formula (Ivi) wherein n is 2. It is also intended to describe an embodiment directed to a compound of formula (Ivii) wherein n is 2.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2.

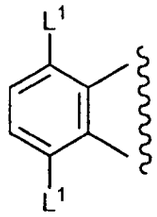
Compounds of formula (I) also include any one of the compounds of formulas (I.A1) or (I.A2) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as as shown in (IIA):



(IIA)

(wherein the squiggly line ~~~ represents the rest of the formula).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as as shown in (IIA):



(IIA)

(wherein the squiggly line ~~~ represents the rest of the formula).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and each L^1 is the same or different halo.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and each L^1 is F.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivi) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, –CF_3, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and –OCH_2CF_3), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (-CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

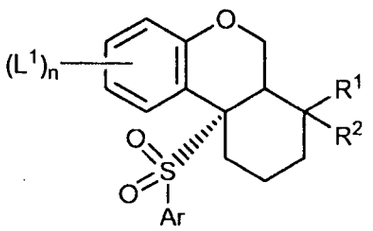
Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, –CF_3, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with substituent selected from the group consisting of:–Cl, -CF_3 and -CN.

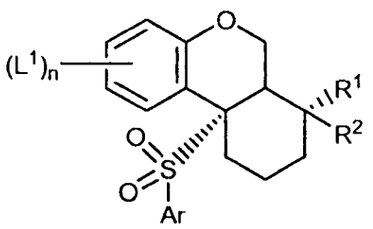
Compounds of formula (I) include compounds of formula (I.A1a):



(I.A1a)

wherein all substituents are as defined for formula (I).

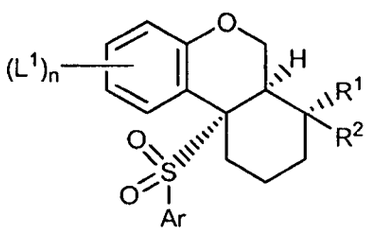
Compounds of formula (I) include compounds of formula (I.A1b):



(I.A1b)

wherein all substituents are as defined for formula (I).

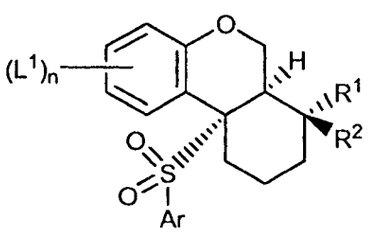
Compounds of formula (I) include compounds of formula (I.A1c):



(I.A1c)

wherein all substituents are as defined for formula (I).

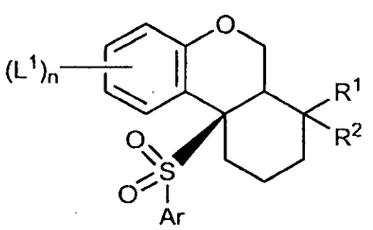
Compounds of formula (I) incluse compounds of formula (I.A1d):



(I.A1d)

wherein all substituents are as defined for formula (I).

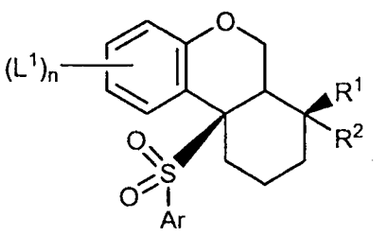
Compounds of formula (I) include compounds of formula (I.A1e):



(I.A1e)

wherein all substituents are as defined for formula (I).

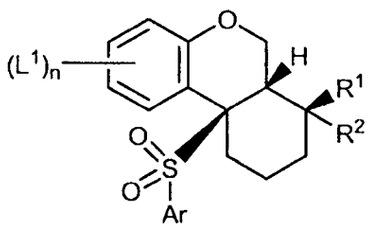
Compounds of formula (I) include compounds of formula (I.A1f):



(I.A1f)

wherein all substituents are as defined for formula (I).

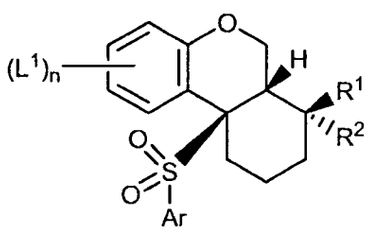
Compounds of formula (I) include compounds of formula (I.A1g):



(I.A1g)

wherein all substituents are as defined for formula (I).

Compounds of formula (I) include compounds of formula (I.A1h):



(I.A1h)

wherein all substituents are as defined for formula (I).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and each L^1 is the same or different halo.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and each L^1 is F.

Compounds of formula (I) also include any one of the compounds of formulas I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH

(e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, –CF_3, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, –CF_3, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and

$-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, -CF_3 and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting

of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$ and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O-$), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O-$).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O-$), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O-$).

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-Cl-phenyl-.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CN-phenyl-.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-$CH_3CH_2SO_2$phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-Br-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is m,p-di-F-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is m,p-di-CN-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CH_3O-phenyl.

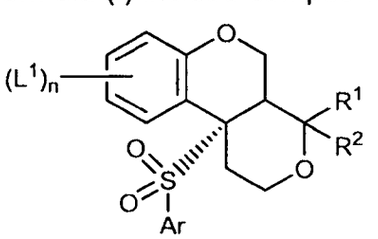
Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CF_3CH_2Ophenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) described above wherein R^2 is H.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) described above wherein R^2 is alkyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A1a) to (I.A1h) described above wherein R^2 is methyl.

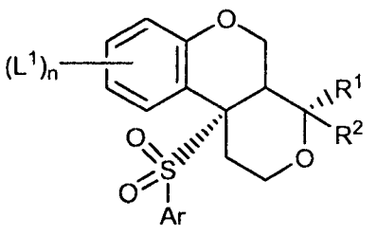
Compounds of formula (I) include compounds of formula (I.A2a):



(I.A2a)

wherein all substituents are as defined for formula (I).

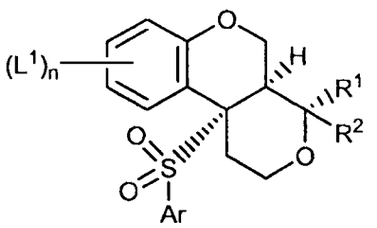
Compounds of formula (I) include compounds of formula (I.A2b):



(I.A2b)

wherein all substituents are as defined for formula (I).

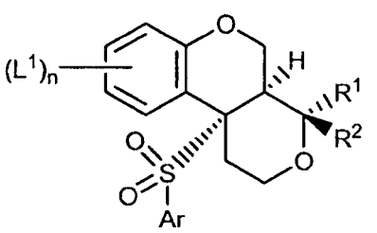
Compounds of formula (I) include compounds of formula (I.A2c):



(I.A2c)

wherein all substituents are as defined for formula (I).

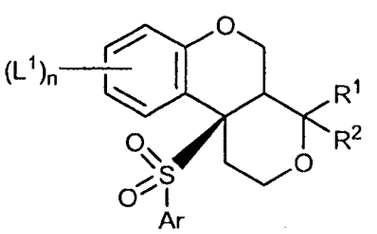
Compounds of formula (I) incluse compounds of formula (I.A2d):



(I.A2d)

wherein all substituents are as defined for formula (I).

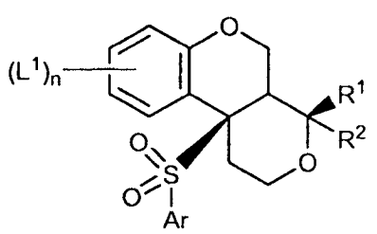
Compounds of formula (I) include compounds of formula (I.A2e):



(I.A2e)

wherein all substituents are as defined for formula (I).

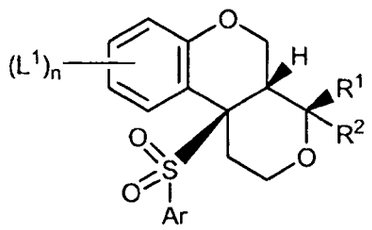
Compounds of formula (I) include compounds of formula (I.A2f):



(I.A2f)

wherein all substituents are as defined for formula (I).

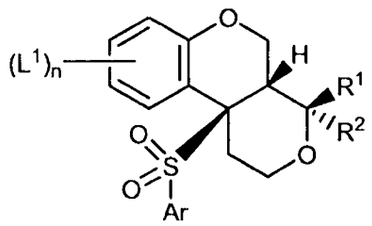
Compounds of formula (I) include compounds of formula (I.A2g):



(I.A2g)

wherein all substituents are as defined for formula (I).

Compounds of formula (I) include compounds of formula (I.A2h):



(I.A2h)

wherein all substituents are as defined for formula (I).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and each L^1 is the same or different halo.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and each L^1 is F.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., -OCH_3), -O-(halo(C_1-C_6)alkyl) (e.g., -OCF_3 and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., -C(O)OCH_3), -alkylene-OH (e.g., -CH_2OH), halo(C_1-C_6)alkyl (e.g., -CF_3), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl),

-CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA) and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$ and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl

substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is the same or different halo, and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$ and $-OCH_2CF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of

p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl (e.g., $-OCH_3$), -O-(halo(C_1-C_6)alkyl) (e.g., $-OCF_3$), -C(O)-O-(C_1-C_6)alkyl (e.g., $-C(O)OCH_3$), -alkylene-OH (e.g., $-CH_2OH$), halo(C_1-C_6)alkyl (e.g., $-CF_3$), hydroxyalkoxy- (e.g., $HOCH_2CH_2O$-), and alkoxyalkoxy- (e.g., $CH_3OCH_2CH_2O$-).

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of: –Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, and p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is selected from the group consisting of: pyridyl, and pyridyl substituted with 1 substituent selected from the group consisting of:–Cl, $-CF_3$ and -CN.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-Cl-phenyl-.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CN-phenyl-.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CF_3-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-$CH_3CH_2SO_2$phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-Br-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is m,p-di-F-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is m,p-di-CN-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CH_3O-phenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) above wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA), each L^1 is F, and Ar is p-CF_3CH_2Ophenyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) described above wherein R^2 is H.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) described above wherein R^2 is alkyl.

Compounds of formula (I) also include any one of the compounds of formulas (I.A2a) to (I.A2h) described above wherein R^2 is methyl.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above wherein R^1 is –alkylene-(tetrahydrothiophene 1,1-dioxide).

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above R^1 is -alkenyl-$S(O)_2$-(C_1-C_6)alkyl.

Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above wherein R^1 is –cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl.

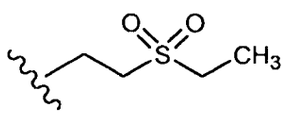
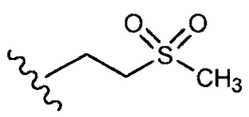
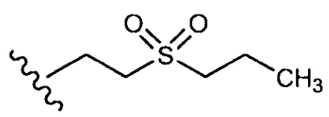
Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above wherein R^1 is an - alkylene-$S(O)_2$-(C_1-C_6)alkyl group.

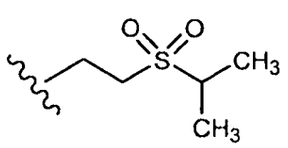
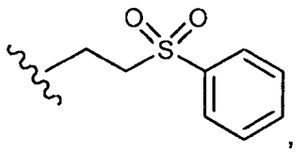
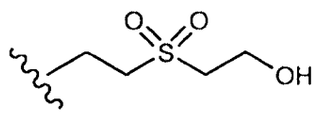
Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_6)alkyl group.

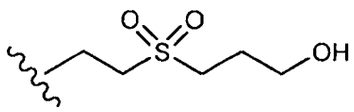
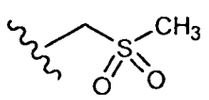
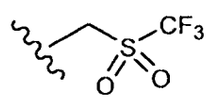
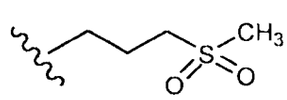
Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_3)alkyl group.

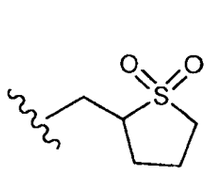
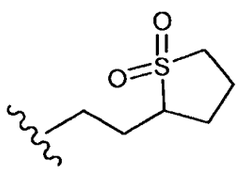
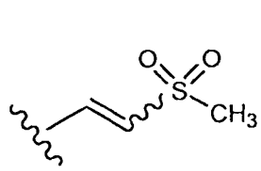
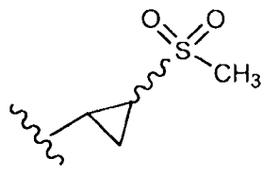
Compounds of formula (I) also include any one of the compounds of formulas (Ii) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) described above wherein R^1 is a -(C_2) alkylene-$S(O)_2$-(C_1-C_6)alkyl group.

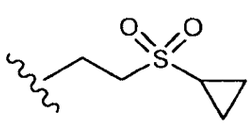
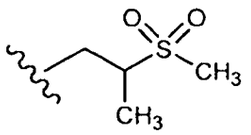
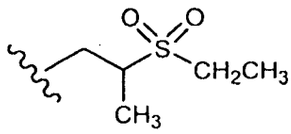
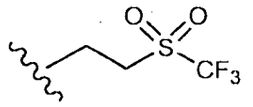
Compounds of formula (I) also include any one of the compounds of formulas (I.A1), (I.A2), (I.A1a), (I.A1e), (I.A2a) or (I.A2e) wherein R^1 is selected from the group consisting of:

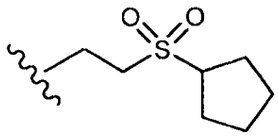
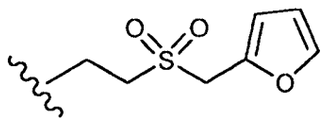
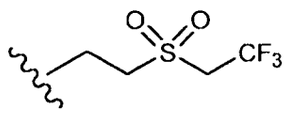

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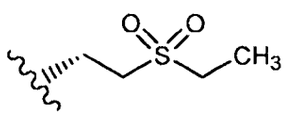
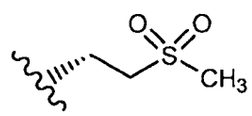
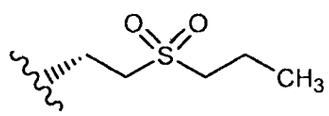

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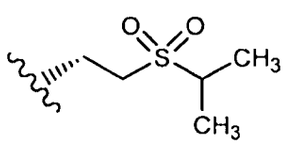
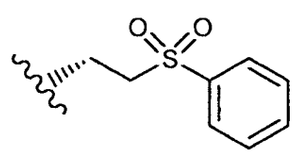
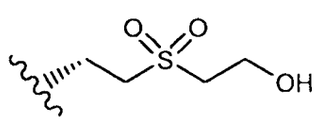

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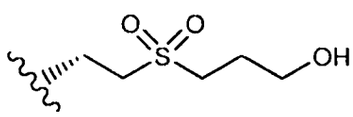
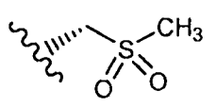
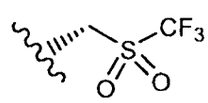
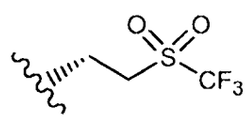

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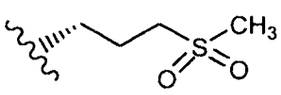
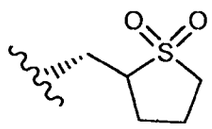
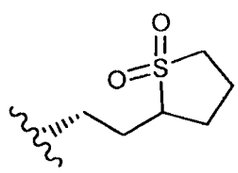

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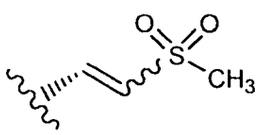
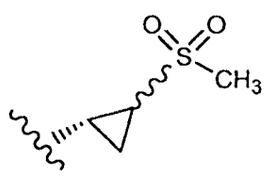
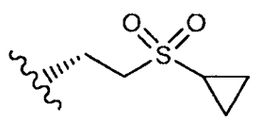
Compounds of formula (I) also include any one of the compounds of formulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d) wherein R^1 is selected from the group consisting of:

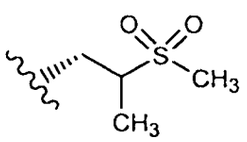
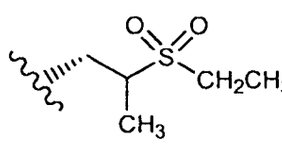
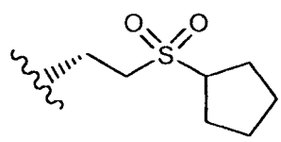

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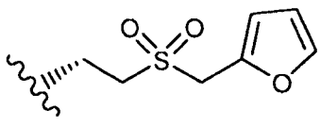
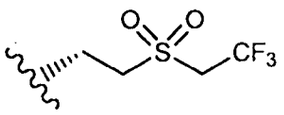

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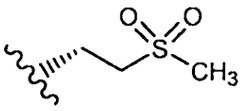

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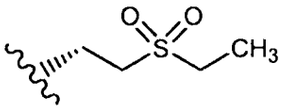

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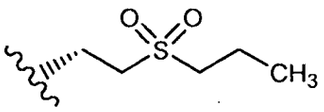
Compounds of formula (I) also include any one of the compounds of formulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is


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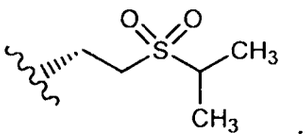
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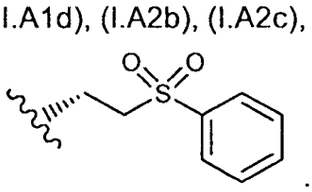
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Compounds of formula (I) also include any one of the compounds of formulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is


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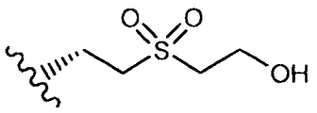
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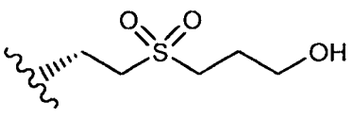
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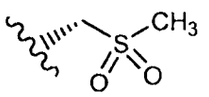
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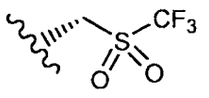
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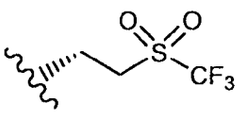
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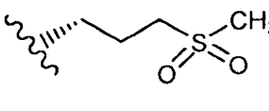
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Compounds of formula (I) also include any one of the compounds of formulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is

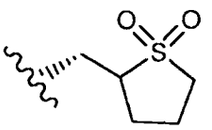


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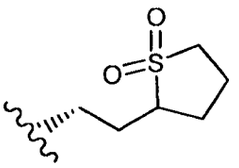


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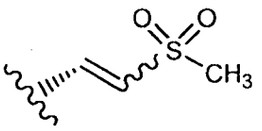
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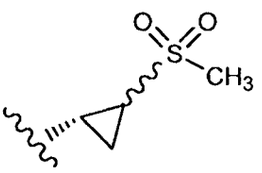
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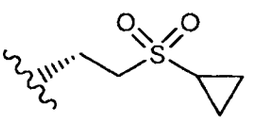
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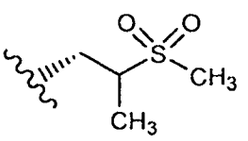
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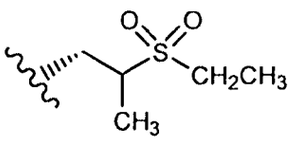
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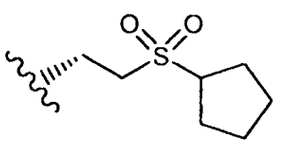
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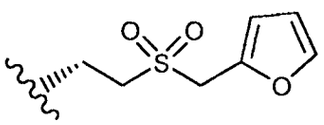
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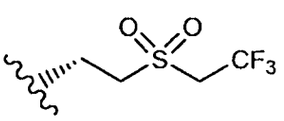
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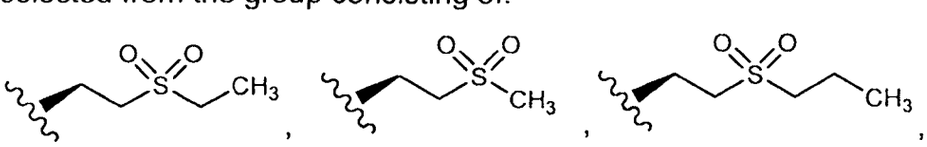
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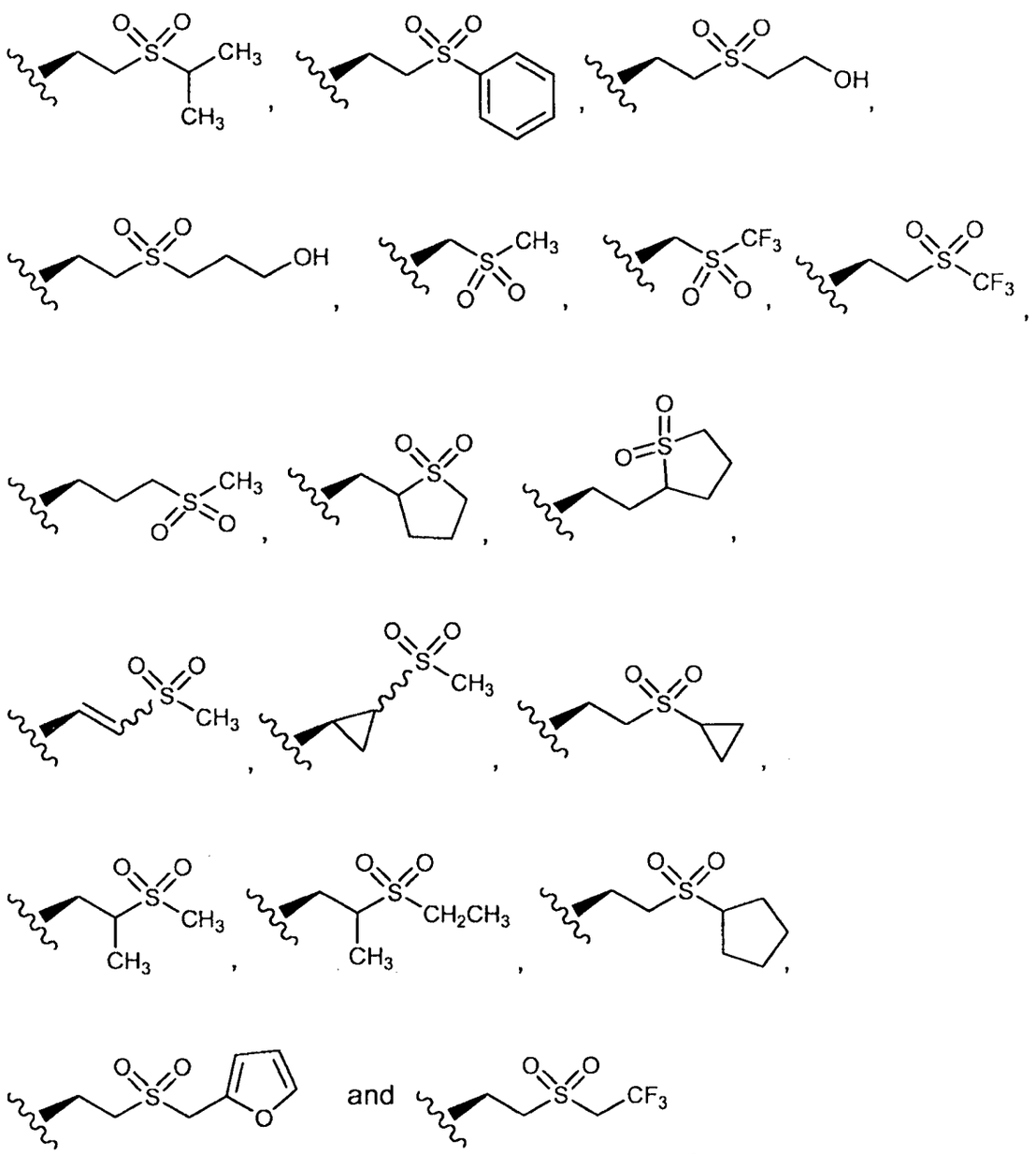


Compounds of formula (I) also include any one of the compounds of formulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is

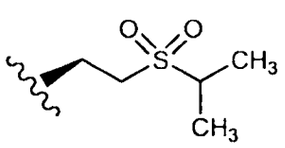


Compounds of formula (I) also include any one of the compounds of formulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 is selected from the group consisting of:

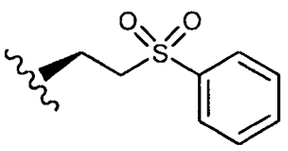




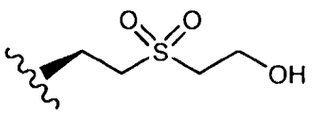
Compounds of formula (I) also include any one of the compounds of formulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 is



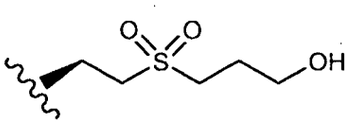
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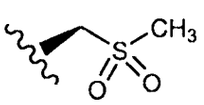
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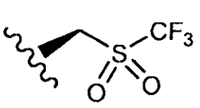
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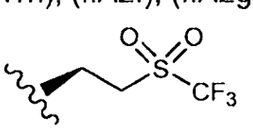
Compounds of formula (I) also include any one of the compounds of formulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 is



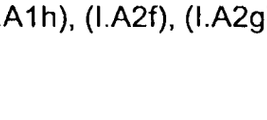
Compounds of formula (I) also include any one of the compounds of formulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 is



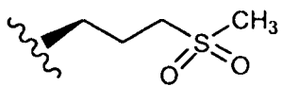
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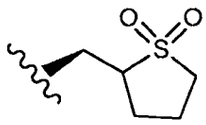
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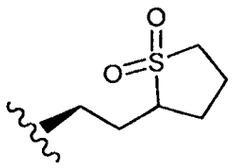
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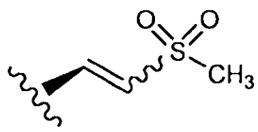
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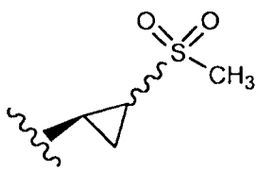
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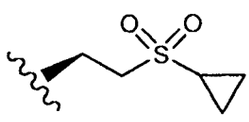
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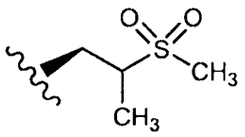


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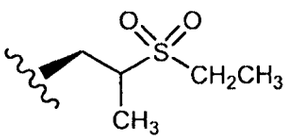


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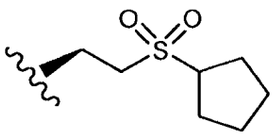
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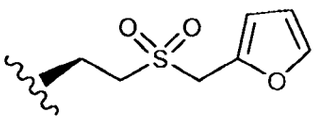
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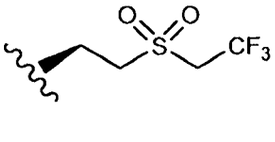
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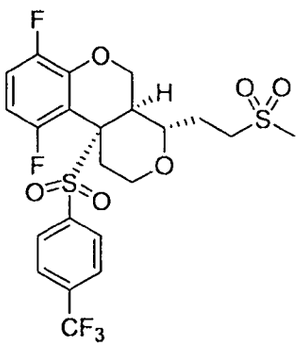
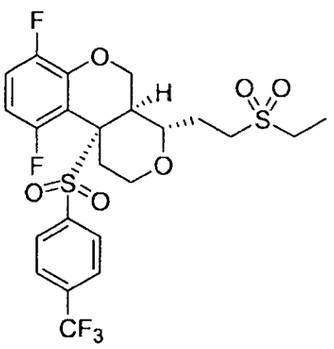
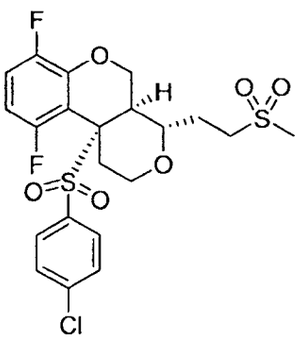
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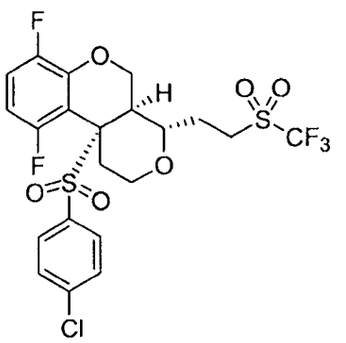
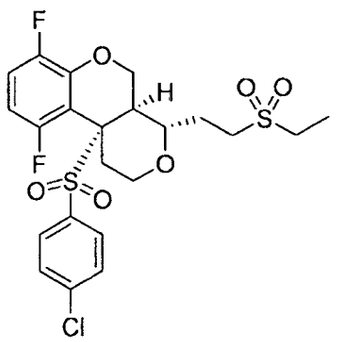
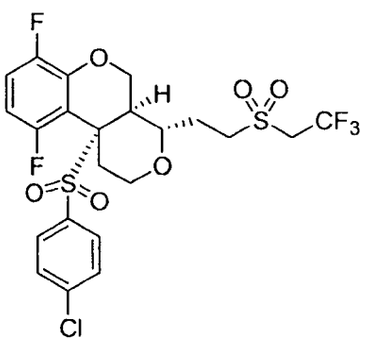
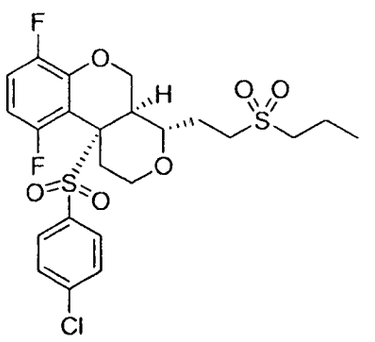


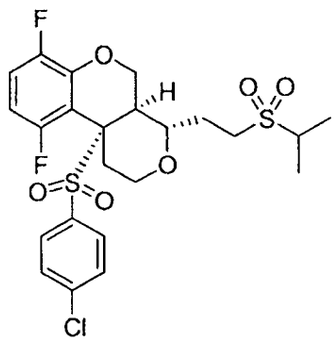
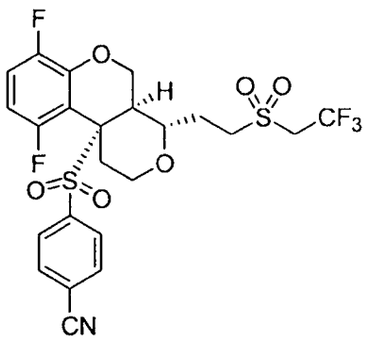
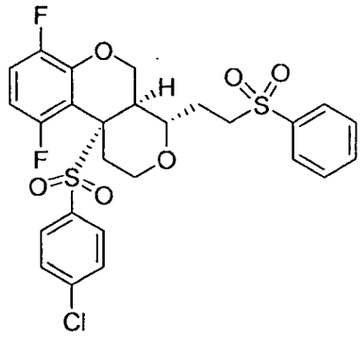
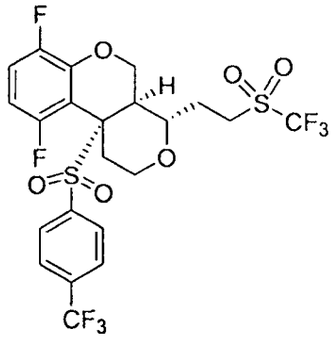
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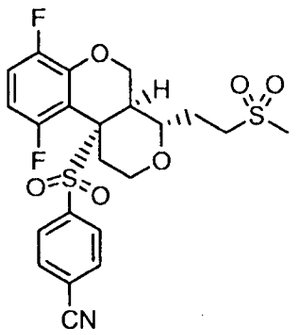
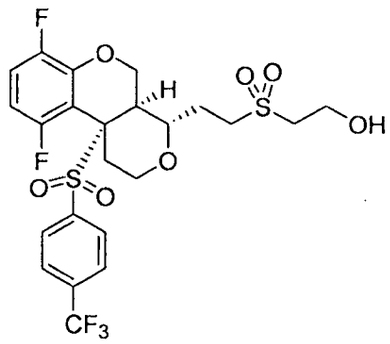
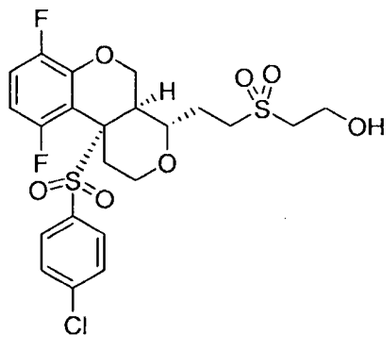
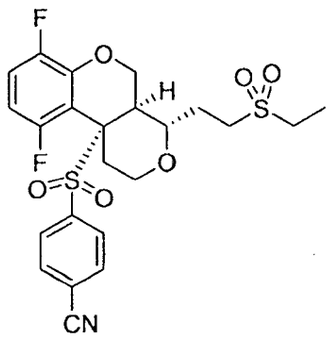


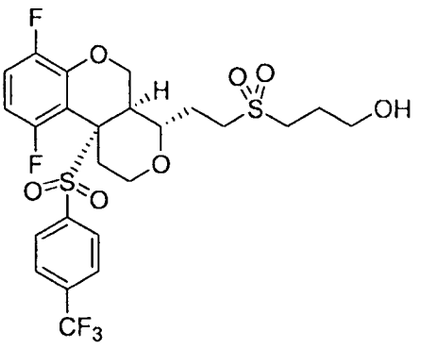
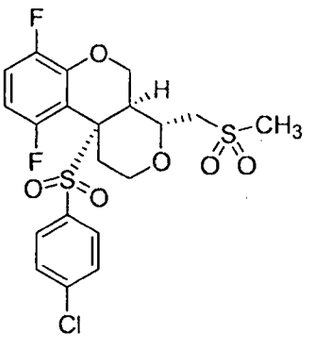
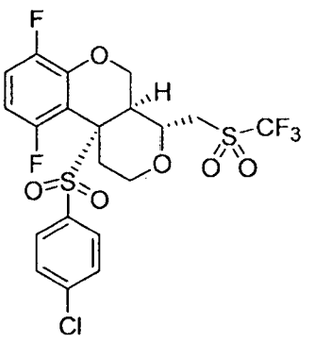
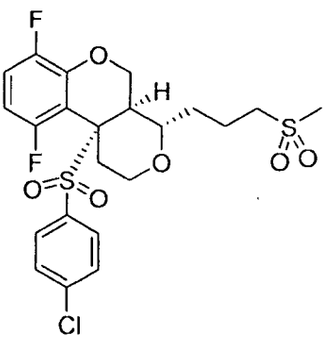
Representative compounds of formula (I) include, but are not limited to:

Compd No.	STRUCTURE
12	
13	
22A	

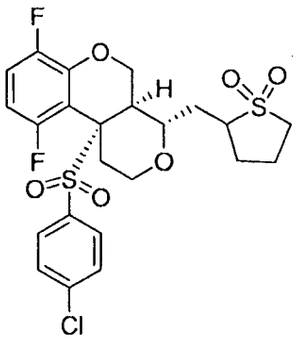
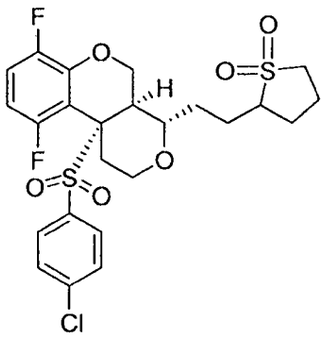
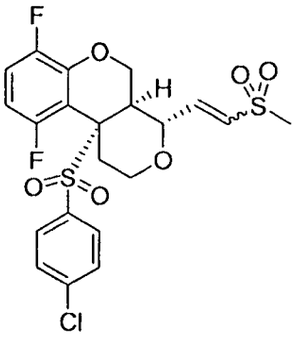
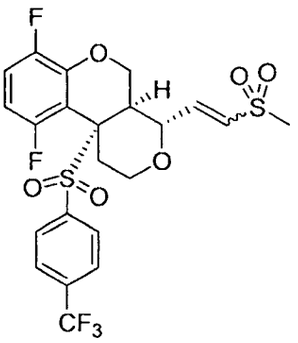
Compd No.	STRUCTURE
22B	
22C	
22D	
22E	

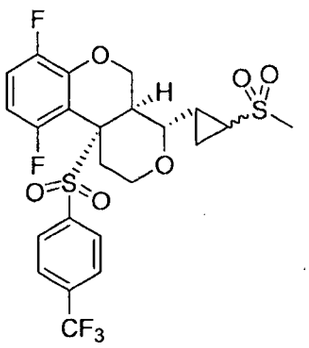
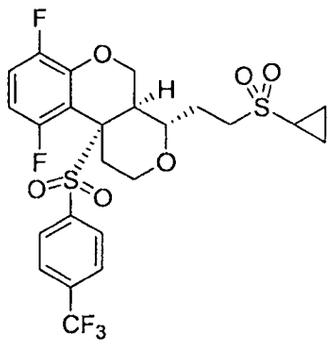
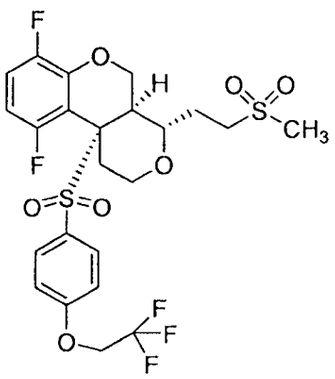
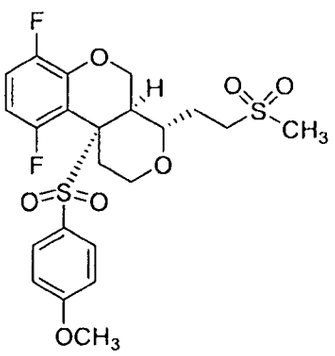
Compd No.	STRUCTURE
22F	
22G	
22H	
22I	

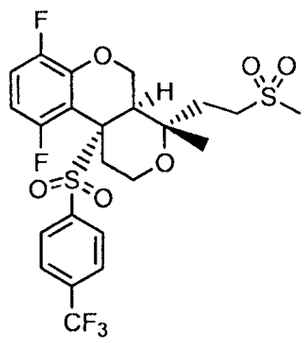
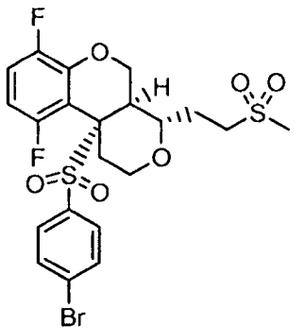
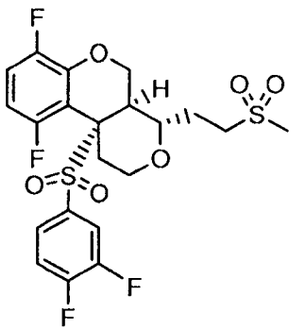
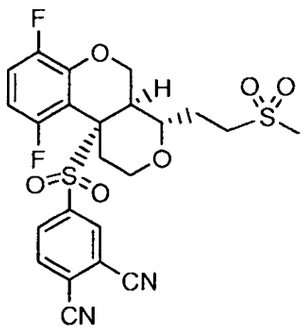
Compd No.	STRUCTURE
22J	
22K	
22L	
22M	

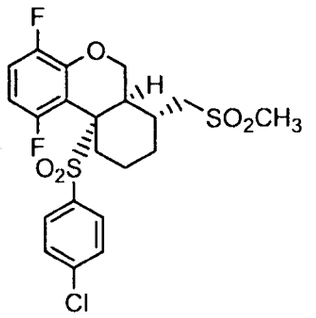
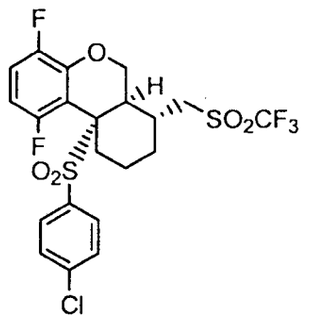
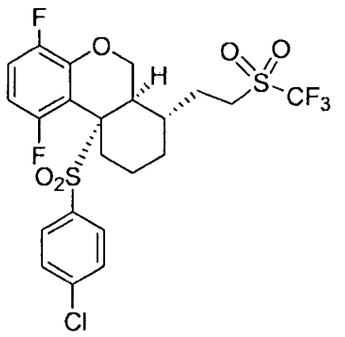
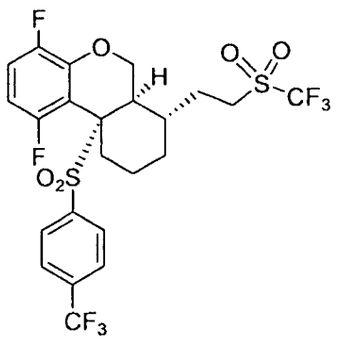
Compd No.	STRUCTURE
22N	
26A	
26B	
27	

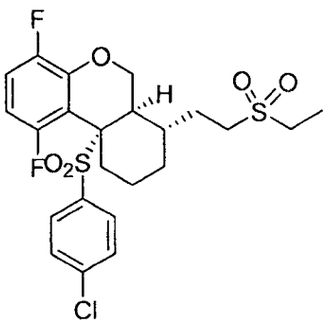
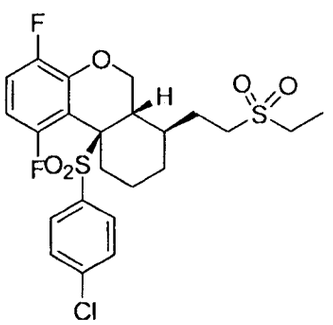
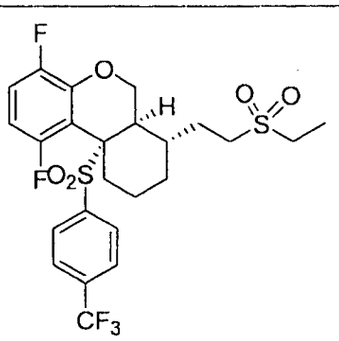
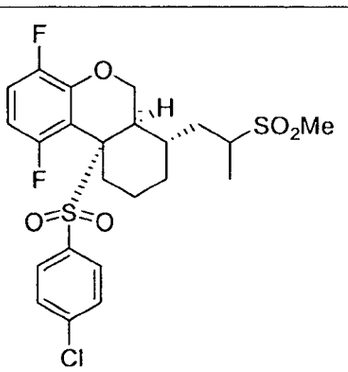
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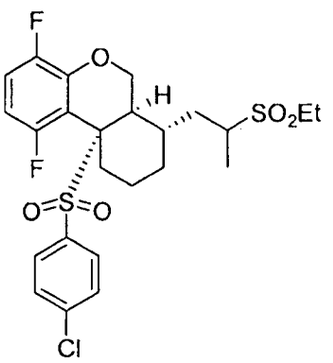
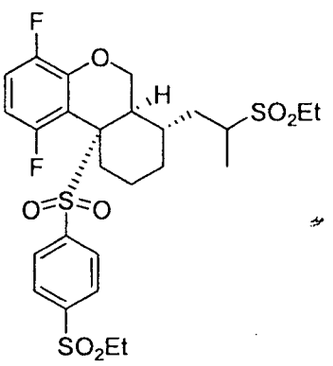
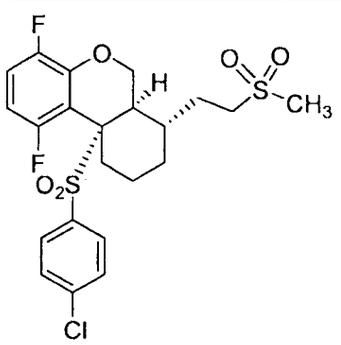
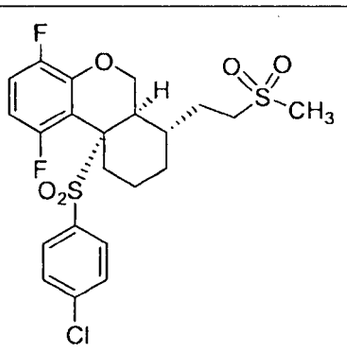
Compd No.	STRUCTURE
28	
31	
33 (-)	
36	

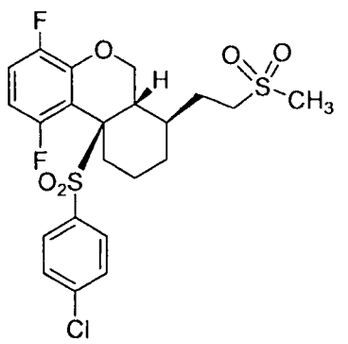
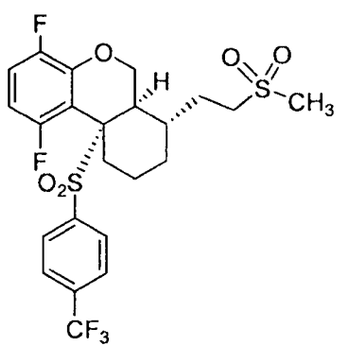
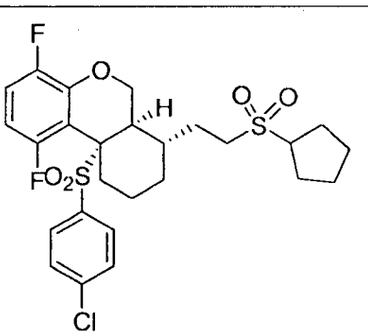
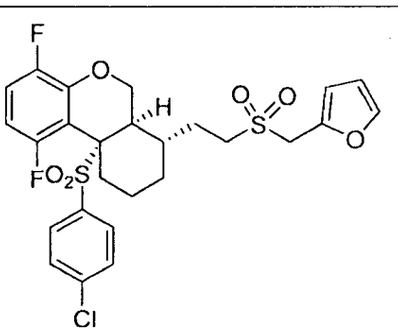
Compd No.	STRUCTURE
37	
39	
44A	
44B	

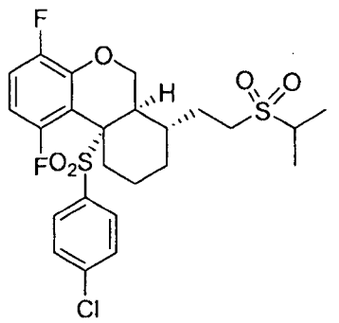
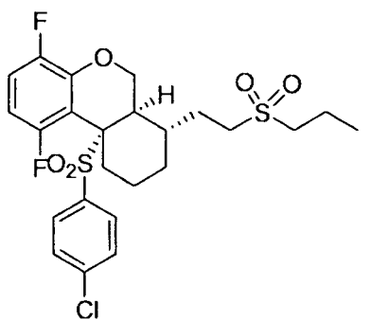
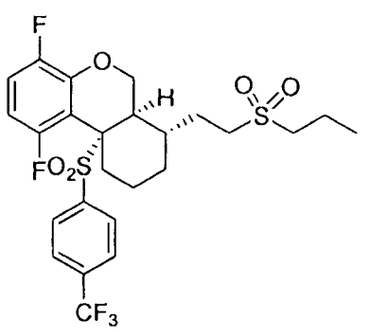
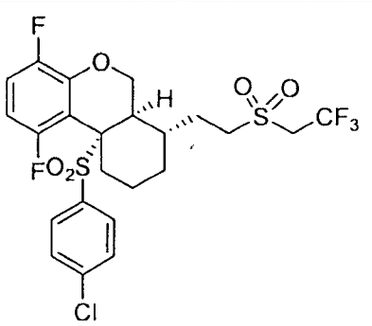
Compd No.	STRUCTURE
55	
56	
57	
60	

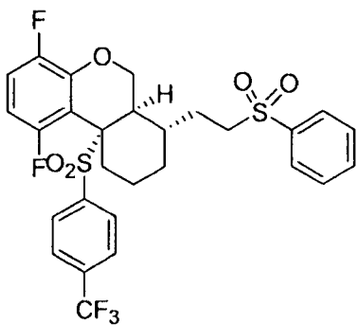
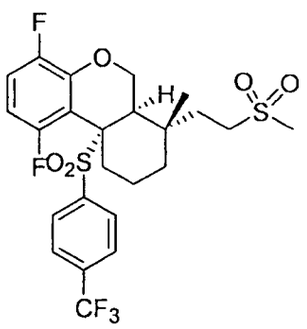
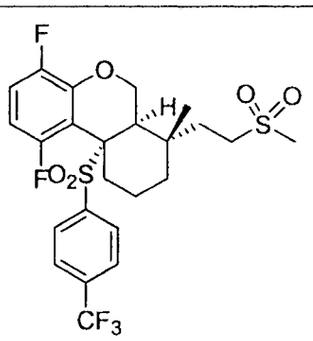
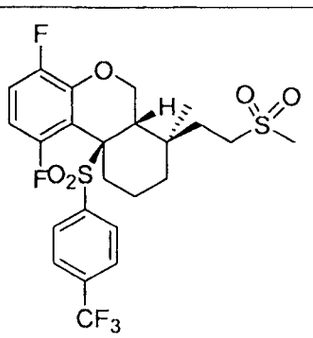
Compd No.	STRUCTURE
70A	
71A (-)	
75A-rac	
75B (-)	

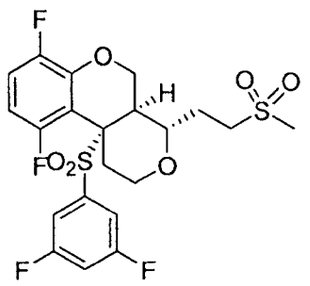
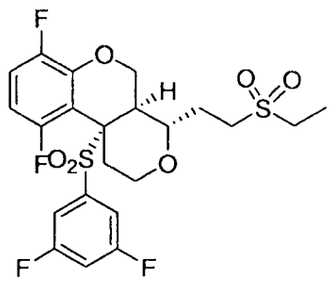
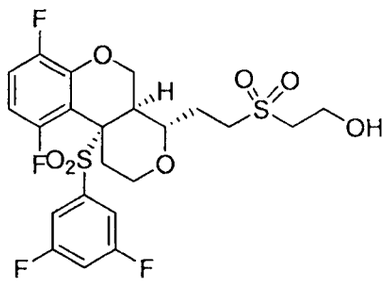
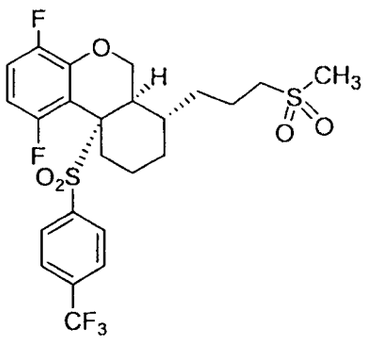
Compd No.	STRUCTURE
76A (-)	
76A (+)	
76B (-)	
78A (-)	

Compd No.	STRUCTURE
79A (-)	
80A (-)	
81A-rac	
81A (-)	

Compd No.	STRUCTURE
81A (+)	
81B (-)	
82A	
83A	

Compd No.	STRUCTURE
84A	
85A	
85B (-)	
86A	

Compd No.	STRUCTURE
87B	
95B-rac	
95B (-)	
95B (+)	

Compd No.	STRUCTURE
106 (-)	
107 (-)	
108 (-)	
111 (-)	

One embodiment of the present invention is directed to compounds of Formula (I), or pharmaceutically acceptable salts, solvates or esters thereof.

Another embodiment of this invention is directed to compounds of formula (I).

Another embodiment of this invention is directed to pharmaceutically acceptable salts of the compounds of formula (I).

Another embodiment of this invention is directed to solvates of the compounds of formula (I).

Another embodiment of this invention is directed to pharmaceutically acceptable esters of the compounds of formula (I).

Another embodiment of the present invention is directed to any one of the compounds of formulas (Ii) to (Ivii), or pharmaceutically acceptable salts, solvates or esters thereof.

Another embodiment of this invention is directed to any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of this invention is directed to pharmaceutically acceptable salts of any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of this invention is directed to solvates of any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of this invention is directed to pharmaceutically acceptable esters of any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of the present invention is directed to any one of the compounds of formulas (I.A1a) to (I.A1h), or pharmaceutically acceptable salts, solvates or esters thereof.

Another embodiment of this invention is directed to any one of the compounds of formulas (I.A1a) to (I.A1h).

Another embodiment of this invention is directed to pharmaceutically acceptable salts of any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of this invention is directed to solvates of any one of the compounds of formulas (I.A1a) to (I.A1h).

Another embodiment of this invention is directed to pharmaceutically acceptable esters of any one of the compounds of formulas (I.A1a) to (I.A1h).

Another embodiment of the present invention is directed to any one of the compounds of formulas (I.A2a) to (I.A2h), or pharmaceutically acceptable salts, solvates or esters thereof.

Another embodiment of this invention is directed to any one of the compounds of formulas (I.A2a) to (I.A2h).

Another embodiment of this invention is directed to pharmaceutically acceptable salts of any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of this invention is directed to solvates of any one of the compounds of formulas (I.A2a) to (I.A2h).

Another embodiment of this invention is directed to pharmaceutically acceptable esters of any one of the compounds of formulas (I.A2a) to (I.A2h).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is any one of the compounds of formulas (Ii) to (Ivii).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a pharmaceutically acceptable salt of any one of the compounds of (Ii) to (Ivii) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of any one of the compounds of formulas (Ii) to (Ivii) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a pharmaceutically acceptable ester of any one of the compounds of formulas (Ii) to (Ivii) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein any one of the compounds of formulas (I.A1a) to (I.A1h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a pharmaceutically acceptable salt of any one of the compounds of formulas (I.A1a) to (I.A1h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of any one of the compounds of formulas (I.A1a) to (I.A1h).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a pharmaceutically acceptable ester of any one of the compounds of formulas (I.A1a) to (I.A1h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein any one of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention a pharmaceutically acceptable salt of any one of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of any one of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a pharmaceutically acceptable ester of any one of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound used is selected from the group consisting of compounds: 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound used is selected from the group consisting of: the solvates of compounds 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 12.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 12.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 13.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 13.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22B-RAC.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22B-RAC.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22C.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22C.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22D.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22D.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22E.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22E.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22F.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22F.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22G.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22G.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22H.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22H.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22I.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22I.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22J.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22J.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22K.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22K.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22L.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22L.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22M.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22M.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 22N.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 22N.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 26A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 26A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 26B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 26B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 27.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 27.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 28.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 28.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 31.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 31.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 33(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 33(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 36.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 36.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 37.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 37.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 39.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 39.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 44A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 44A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 44B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 44B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 55.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 55.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 56.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 56.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 57.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 57.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 60.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 60.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 70A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 70A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 71A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 71A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 75A-rac.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 75A-rac.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 75B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 75B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 76A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 76A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 76A(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 76A(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 76B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 76B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 78A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 78A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 79A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 79A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 80A(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 80A(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 81A-rac.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 81A-rac.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 81A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 81A(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 81A(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 81A(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 81B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 81B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 82A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 82A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 83A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 83A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 84A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 84A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 85A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 85A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 85B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 85B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 86A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 86A.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 87B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 87B.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 95B-rac.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 95B-rac.

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 95B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 95B(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 95B(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 95B(+).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 106(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 106(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 107(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 107(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 108(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 108(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein the compound of formula (I) is compound 111(-).

Another embodiment of this invention is directed to any one of the methods of treatment described in the Summary of the invention wherein a solvate of a compound of formula (I) is used, and the solvate is a solvate of compound 111(-).

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a compound of any one of formulas (Ii) to (Ivii) is used. .

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a pharmaceutically acceptable salt of any one of the compounds of formulas (Ii) to (Ivii) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a solvate of any one of the compounds of formulas (Ii) to (Ivii) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a pharmaceutically acceptable ester of the compounds of formulas (Ii) to (Ivii) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a compound of any one of formulas (I.A1a) to (I.A1h) is used. .

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a pharmaceutically acceptable salt of any one of the compounds of formulas (I.A1a) to (I.A1h) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a solvate of any one of the compounds of formulas (I.A1a) to (I.A1h) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a pharmaceutically acceptable ester of the compounds of formulas (I.A1a) to (I.A1h) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a compound of any one of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a pharmaceutically acceptable salt of any one of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a solvate of any one of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to any one of the pharmaceutical compositions described above wherein a pharmaceutically acceptable ester of the compounds of formulas (I.A2a) to (I.A2h) is used.

Another embodiment of this invention is directed to compound 12.

Another embodiment of this invention is directed to compound 12 in pure form.

Another embodiment of this invention is directed to compound 12 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 12.

Another embodiment of this invention is directed to compound 13.

Another embodiment of this invention is directed to compound 13 in pure form.

Another embodiment of this invention is directed to compound 13 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 13.

Another embodiment of this invention is directed to compound 22A.

Another embodiment of this invention is directed to compound 22A in pure form.

Another embodiment of this invention is directed to compound 22A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22A.

Another embodiment of this invention is directed to compound 22B.

Another embodiment of this invention is directed to compound 22B in pure form.

Another embodiment of this invention is directed to compound 22B in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22B.

Another embodiment of this invention is directed to compound 22B-RAC.

Another embodiment of this invention is directed to compound 22B-RAC in pure form.

Another embodiment of this invention is directed to compound 22B-RAC in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22B-RAC.

Another embodiment of this invention is directed to compound 22C.

Another embodiment of this invention is directed to compound 22C in pure form.

Another embodiment of this invention is directed to compound 22C in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22C.

Another embodiment of this invention is directed to compound 22D.

Another embodiment of this invention is directed to compound 22D in pure form.

Another embodiment of this invention is directed to compound 22D in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22D.

Another embodiment of this invention is directed to compound 22E.

Another embodiment of this invention is directed to compound 22E in pure form.

Another embodiment of this invention is directed to compound 22E in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22E.

Another embodiment of this invention is directed to compound 22F.

Another embodiment of this invention is directed to compound 22F in pure form.

Another embodiment of this invention is directed to compound 22F in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22F.

Another embodiment of this invention is directed to compound 22G.

Another embodiment of this invention is directed to compound 22G in pure form.

Another embodiment of this invention is directed to compound 22G in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22G.

Another embodiment of this invention is directed to compound 22H.

Another embodiment of this invention is directed to compound 22H in pure form.

Another embodiment of this invention is directed to compound 22H in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22H.

Another embodiment of this invention is directed to compound 22I.

Another embodiment of this invention is directed to compound 22I in pure form.

Another embodiment of this invention is directed to compound 22I in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22I.

Another embodiment of this invention is directed to compound 22J.

Another embodiment of this invention is directed to compound 22J in pure form.

Another embodiment of this invention is directed to compound 22J in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22J.

Another embodiment of this invention is directed to compound 22K.

Another embodiment of this invention is directed to compound 22K in pure form.

Another embodiment of this invention is directed to compound 22K in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22K.

Another embodiment of this invention is directed to compound 22L.

Another embodiment of this invention is directed to compound 22L in pure form.

Another embodiment of this invention is directed to compound 22L in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22L.

Another embodiment of this invention is directed to compound 22M.

Another embodiment of this invention is directed to compound 22M in pure form.

Another embodiment of this invention is directed to compound 22M in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22M.

Another embodiment of this invention is directed to compound 22N.

Another embodiment of this invention is directed to compound 22N in pure form.

Another embodiment of this invention is directed to compound 22N in isolated form.

Another embodiment of this invention is directed to a solvate of compound 22N.

Another embodiment of this invention is directed to compound 26A.

Another embodiment of this invention is directed to compound 26A in pure form.

Another embodiment of this invention is directed to compound 26A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 26A.

Another embodiment of this invention is directed to compound 26B.

Another embodiment of this invention is directed to compound 26B in pure form.

Another embodiment of this invention is directed to compound 26B in isolated form.

Another embodiment of this invention is directed to a solvate of compound 26B.

Another embodiment of this invention is directed to compound 27.

Another embodiment of this invention is directed to compound 27in pure form.

Another embodiment of this invention is directed to compound 27in isolated form.

Another embodiment of this invention is directed to a solvate of compound 27.

Another embodiment of this invention is directed to compound 28.

Another embodiment of this invention is directed to compound 28 in pure form.

Another embodiment of this invention is directed to compound 28 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 28.

Another embodiment of this invention is directed to compound 31.

Another embodiment of this invention is directed to compound 31 in pure form.

Another embodiment of this invention is directed to compound 31 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 31.

Another embodiment of this invention is directed to compound 33(-).

Another embodiment of this invention is directed to compound 33(-) in pure form.

Another embodiment of this invention is directed to compound 33(-) in isolated form.

Another embodiment of this invention is directed to a solvate of compound 33(-).

Another embodiment of this invention is directed to compound 36.

Another embodiment of this invention is directed to compound 36 in pure form.

Another embodiment of this invention is directed to compound 36 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 36.

Another embodiment of this invention is directed to compound 37.

Another embodiment of this invention is directed to compound 37 in pure form.

Another embodiment of this invention is directed to compound 37 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 37.

Another embodiment of this invention is directed to compound 39.

Another embodiment of this invention is directed to compound 39 in pure form.

Another embodiment of this invention is directed to compound 39 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 39.

Another embodiment of this invention is directed to compound 44A.

Another embodiment of this invention is directed to compound 44A in pure form.

Another embodiment of this invention is directed to compound 44A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 44A.

Another embodiment of this invention is directed to compound 44B.

Another embodiment of this invention is directed to compound 44B in pure form.

Another embodiment of this invention is directed to compound 44B in isolated form.

Another embodiment of this invention is directed to a solvate of compound 44B.

Another embodiment of this invention is directed to compound 55.

Another embodiment of this invention is directed to compound 55 in pure form.

Another embodiment of this invention is directed to compound 55 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 55.

Another embodiment of this invention is directed to compound 56.

Another embodiment of this invention is directed to compound 56 in pure form.

Another embodiment of this invention is directed to compound 56 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 56.

Another embodiment of this invention is directed to compound 57.

Another embodiment of this invention is directed to compound 57 in pure form.

Another embodiment of this invention is directed to compound 57 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 57.

Another embodiment of this invention is directed to compound 60.

Another embodiment of this invention is directed to compound 60 in pure form.

Another embodiment of this invention is directed to compound 60 in isolated form.

Another embodiment of this invention is directed to a solvate of compound 60.

Another embodiment of this invention is directed to compound 70A.

Another embodiment of this invention is directed to compound 70A in pure form.

Another embodiment of this invention is directed to compound 70A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 70A.

Another embodiment of this invention is directed to compound 71A(-).

Another embodiment of this invention is directed to compound 71A(-)in pure form.

Another embodiment of this invention is directed to compound 71A(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 71A(-).

Another embodiment of this invention is directed to compound 75A-rac.

Another embodiment of this invention is directed to compound 75A-rac in pure form.

Another embodiment of this invention is directed to compound 75A-rac in isolated form.

Another embodiment of this invention is directed to a solvate of compound 75A-rac.

Another embodiment of this invention is directed to compound 75B(-).

Another embodiment of this invention is directed to compound 75B(-)in pure form.

Another embodiment of this invention is directed to compound 75B(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 75B(-).

Another embodiment of this invention is directed to compound 76A(-).

Another embodiment of this invention is directed to compound 76A(-)in pure form.

Another embodiment of this invention is directed to compound 76A(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 76A(-).

Another embodiment of this invention is directed to compound 76A(+).

Another embodiment of this invention is directed to compound 76A(+)in pure form.

Another embodiment of this invention is directed to compound 76A(+)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 76A(+).

Another embodiment of this invention is directed to compound 76B(-).

Another embodiment of this invention is directed to compound 76B(-)in pure form.

Another embodiment of this invention is directed to compound 76B(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 76B(-).

Another embodiment of this invention is directed to compound 78A(-).

Another embodiment of this invention is directed to compound 78A(-)in pure form.

Another embodiment of this invention is directed to compound 78A(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 78A(-).

Another embodiment of this invention is directed to compound 79A(-).

Another embodiment of this invention is directed to compound 79A(-)in pure form.

Another embodiment of this invention is directed to compound 79A(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 79A(-).

Another embodiment of this invention is directed to compound 80A(+).

Another embodiment of this invention is directed to compound 80A(+)in pure form.

Another embodiment of this invention is directed to compound 80A(+)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 80A(+).

Another embodiment of this invention is directed to compound 81A-rac.

Another embodiment of this invention is directed to compound 81A-rac in pure form.

Another embodiment of this invention is directed to compound 81A-rac in isolated form.

Another embodiment of this invention is directed to a solvate of compound 81A-rac.

Another embodiment of this invention is directed to compound 81A(-).

Another embodiment of this invention is directed to compound 81A(-)in pure form.

Another embodiment of this invention is directed to compound 81A(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 81A(-).

Another embodiment of this invention is directed to compound 81A(+).

Another embodiment of this invention is directed to compound 81A(+)in pure form.

Another embodiment of this invention is directed to compound 81A(+)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 81A(+).

Another embodiment of this invention is directed to compound 81B(-).

Another embodiment of this invention is directed to compound 81B(-)in pure form.

Another embodiment of this invention is directed to compound 81B(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 81B(-).

Another embodiment of this invention is directed to compound 82A.

Another embodiment of this invention is directed to compound 82A in pure form.

Another embodiment of this invention is directed to compound 82A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 82A.

Another embodiment of this invention is directed to compound 83A.

Another embodiment of this invention is directed to compound 83A in pure form.

Another embodiment of this invention is directed to compound 83A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 83A.

Another embodiment of this invention is directed to compound 84A.

Another embodiment of this invention is directed to compound 84A in pure form.

Another embodiment of this invention is directed to compound 84A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 84A.

Another embodiment of this invention is directed to compound 85A.

Another embodiment of this invention is directed to compound 85A in pure form.

Another embodiment of this invention is directed to compound 85A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 85A.

Another embodiment of this invention is directed to compound 85B(-).

Another embodiment of this invention is directed to compound 85B(-)in pure form.

Another embodiment of this invention is directed to compound 85B(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 85B(-).

Another embodiment of this invention is directed to compound 86A.

Another embodiment of this invention is directed to compound 86A in pure form.

Another embodiment of this invention is directed to compound 86A in isolated form.

Another embodiment of this invention is directed to a solvate of compound 86A.

Another embodiment of this invention is directed to compound 87B.

Another embodiment of this invention is directed to compound 87B in pure form.

Another embodiment of this invention is directed to compound 87B in isolated form.

Another embodiment of this invention is directed to a solvate of compound 87B.

Another embodiment of this invention is directed to compound 95B-rac.

Another embodiment of this invention is directed to compound 95B-rac in pure form.

Another embodiment of this invention is directed to compound 95B-rac in isolated form.

Another embodiment of this invention is directed to a solvate of compound 95B-rac.

Another embodiment of this invention is directed to compound 95B(-).

Another embodiment of this invention is directed to compound 95B(-)in pure form.

Another embodiment of this invention is directed to compound 95B(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 95B(-).

Another embodiment of this invention is directed to compound 95B(+).

Another embodiment of this invention is directed to compound 95B(+)in pure form.

Another embodiment of this invention is directed to compound 95B(+)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 95B(+).

Another embodiment of this invention is directed to compound 106(-).

Another embodiment of this invention is directed to compound 106(-)in pure form.

Another embodiment of this invention is directed to compound 106(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 106(-).

Another embodiment of this invention is directed to compound 107(-).

Another embodiment of this invention is directed to compound 107(-)in pure form.

Another embodiment of this invention is directed to compound 107(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 107(-).

Another embodiment of this invention is directed to compound 108(-).

Another embodiment of this invention is directed to compound 108(-)in pure form.

Another embodiment of this invention is directed to compound 108(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 108(-).

Another embodiment of this invention is directed to compound 111(-).

Another embodiment of this invention is directed to compound 111(-)in pure form.

Another embodiment of this invention is directed to compound 111(-)in isolated form.

Another embodiment of this invention is directed to a solvate of compound 111(-).

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more compounds selected from the group consisting of: 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: 12, 13, 22A to 22N, 22B-rac, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 12, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 13, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22B-RAC, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22C, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22D, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22E, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22F, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22G, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22H, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22I, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22J, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22K, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22L, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22M, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 22N, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 26A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 26B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 27, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 28, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 31, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 33(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 36, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 37, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 39, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 44A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 44B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 55, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 56, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 57, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 60, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 70A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 71A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 75A-rac, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 75B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 76A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 76A(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 76B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 78A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 79A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 80A(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 81A-rac, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 81A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 81A(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 81B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 82A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 83A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 84A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 85A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 85B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 86A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 87B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 95B-rac, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 95B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 95B(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 106(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 107(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 108(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound 111(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more solvates selected from the group consisting of: the solvates of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate selected from the group

consisting of: the solvates of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 12, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 13, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22B-RAC, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22C, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22D, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22E, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22F, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22G, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22H, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22I, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22J, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22K, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22L, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22M, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 22N, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 26A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 26B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 27, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 28, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 31, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 33(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 36, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 37, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 39, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 44A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 44B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 55, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 56, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 57, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 60, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 70A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 71A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 75A-rac, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 75B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 76A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 76A(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 76B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 78A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 79A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 80A(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 81A-rac, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 81A(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 81A(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 81B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 82A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 83A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 84A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 85A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 85B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 86A, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 87B, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 95B-rac, and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 95B(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 95B(+), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 106(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 107(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 108(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of compound 111(-), and at least one pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)), and an effective amount of one or more (e.g., one) other pharmaceutically active ingredients (e.g.,) drugs, and a pharmaceutically acceptable carrier. Examples of the other pharmaceutically active ingredients include, but are not limited to drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

Another embodiment of this invention also provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more (e.g., one) other therapeutically effective pharmaceutical active ingredients (e.g., drugs), and a pharmaceutically acceptable carrier. Examples of the other drugs include, but are not limited to drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

The other pharmaceutically active ingredients (e.g., drugs), used in the pharmaceutical compositions with the compounds of formula (I), as well as being used in the methods of treatment with the compounds of formula (I) (i.e., the combination therapies described herein) include, but are not limited to: BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., m_1 or m_2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators, HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase, PDE-10 inhibitors, and cholesterol absorption inhibitors (e.g., ezetimibe).

Thus, another embodiment of this invention is directed to pharmaceutical compositions comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)), and an effective amount of one or more (e.g., one) other pharmaceutically active ingredients (e.g., drugs), and a pharmaceutically acceptable carrier, wherein said

other pharmaceutically active ingredients are selected from the group consisting of: : BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., m_1 or m_2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators, HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity, PDE-10 inhibitors and cholesterol absorption inhibitors (e.g., ezetimibe).

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)), and effective amount of one or more BACE inhibitors, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more BACE inhibitors, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds of formulas (I.A1), or compounds of formula (I.A2)), and effective amount of one or more muscarinic antagonists (e.g., m_1 or m_2 antagonists), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-), and effective amount of one or more muscarinic antagonists (e.g., m_1 or m_2 antagonists), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a method for inhibiting gamma-secretase comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

Another embodiment of this invention is directed to a method for treating one or more neurodegenerative diseases comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+),106(-), 107(-), 108(-), and 111(-).

Another embodiment of this invention is directed to a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain) comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds

selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease comprising administering to a patient in need of treatment an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

Other embodiments of this invention are directed to combination therapies for (1) inhibiting gamma-secretase, or (2) treating one or more neurodegenerative diseases, or (3)inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (4) treating Alzheimer's disease. The combination therapies are directed to methods comprising the administration of one or more (e.g. one) compounds of formula (I) (e.g., compounds of formula (I.A1), or compounds of formula (I.A2)) and the administration of one or more (e.g., one) other pharmaceutical active ingredients (e.g., drugs). The compounds of formula (I) and the other drugs can be administered separately (i.e., each is in its own separate dosage form), or the compounds of formula (I) can be combined with the other drugs in the same dosage form.

Thus, other embodiments of this invention are directed to any one of the methods of treatment, or methods of inhibiting, described herein, wherein the compound of formula (I) (e.g., the compound of formula (I.A1), or the compound of formula (I.A2)) is used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., m_1 or m_2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate

receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors (e.g., ezetimibe).

Examples of cholinesterase inhibitors are tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine, with tacrine, donepezil, rivastigmine and galantamine being preferred.

Examples of m_1 antagonists are known in the art. Examples of m_2 antagonists are also known in the art; in particular, m_2 antagonists are disclosed in US patents 5,883,096; 6,037,352; 5,889,006; 6,043,255; 5,952,349; 5,935,958; 6,066,636; 5,977,138; 6,294,554; 6,043,255; and 6,458,812; and in WO 03/031412, all of which are incorporated herein by reference.

Examples of BACE inhibitors include those described in: US2005/0119227 published 06/02/2005 (see also WO2005/016876 published 02/24/2005), US2005/0043290 published 02/24/2005 (see also WO2005/014540 published 02/17/2005), WO2005/058311 published 06/30/2005 (see also US2007/0072852 published 03/29/2007), US2006/0111370 published 05/25/2006 (see also WO2006/065277 published 06/22/2006), US Application Serial No. 11/710582 filed 02/23/2007, US2006/0040994 published 02/23/2006 (see also WO2006/014762 published 02/09/2006), WO2006/014944 published 02/09/2006 (see also US2006/0040948 published 02/23/2006), WO2006/138266 published 12/28/2006 (see also US2007/0010667 published 01/11/2007), WO2006/138265 published 12/28/2006, WO2006/138230 published 12/28/2006, WO2006/138195 published 12/28/2006 (see also US2006/0281729 published 12/14/2006), WO2006/138264 published 12/28/2006 (see also US2007/0060575 published 03/15/2007), WO2006/138192 published 12/28/2006 (see also US2006/0281730 published 12/14/2006), WO2006/138217 published 12/28/2006 (see also US2006/0287294 published 12/21/2006), US2007/0099898 published 05/03/200 (see also WO2007/050721 published 05/03/2007), WO2007/053506 published 05/10/2007 (see also US2007/099875 published 05/03/2007), U.S. Application Serial No. 11/759336 filed 06/07/2007, U.S. Application Serial No. 60/874362 filed 12/12/2006, and U.S.

Application Serial No. 60/874419 filed 12/12/2006, the disclosures of each being incorporated incorporated herein by reference thereto.

Other embodiments of this invention are described below. The embodiments have been numbered for ease of reference. When an Embodiment refers to "any one of" that Embodiment describes a separate embodiment to each group or embodiment listed. For example, Embodiment No. 1 is meant to describe: (1) an embodiment directed to compounds of formula (I) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl), (2) an embodiment directed to any one of compounds (iI) to (Ivii) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl), (3) an embodiment directed to compounds of formula (I.A1) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl), (4) an embodiment directed to any one of compounds (I.A1a) to (I.A1h) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl), (5) an embodiment directed to compounds of formula (I.A2) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl), and (6) an embodiment directed to any one of compounds (I.A2a) to (I.A2h) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl).

Embodiment No. 1 is directed to any one of the compounds of formulas (I), (iI) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein Ar is unsubstituted aryl (e.g., unsubstituted phenyl).

Embodiment No. 2 is directed to any one of the compounds of formulas (I), (iI) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein Ar is substituted aryl (e.g., substituted phenyl). Examples of substituted phenyls include, for example, (1) halo substituted phenyl (such as, for example chloro substituted phenyl, such as, for example, p-Cl-phenyl-), (2) haloalkyl substituted phenyl (such as, for example, $-CF_3$ substituted phenyl, such as, for example, p-CF_3-phenyl-), and (3) cyano substituted phenyl (such as, for example, p-CN-phenyl-).

Embodiment No. 3 is directed to any one of the compounds of formulas (I), (iI) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein Ar is unsubstituted heteroaryl (e.g., unsubstituted pyridyl).

Embodiment No. 4 is directed to any one of the compounds of formulas (I), (iI) to (Ivii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein Ar is substituted heteroaryl (e.g., substituted pyridyl). Examples of substituted pyridyls include, for example, (1) halo substituted pyridyl (such as, for example chloro substituted pyridyl),

(2) haloalkyl substituted pyridyl (such as, for example, -CF_3 substituted pyridyl), and (3) cyano substituted pyridyl.

Embodiment No. 5 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein each L^1 is the same or different halo.

Embodiment No. 6 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein n is 2 and each L^1 is the same or different halo.

Embodiment No. 7 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein n is 2 and each L^1 is the same halo.

Embodiment No. 8 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h) wherein n is 2 and each L^1 is F.

Embodiment No. 9 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein each L^1 is the same or different halo, and Ar is unsubstituted aryl (e.g., unsubstituted phenyl).

Embodiment No. 10 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same or different halo, and Ar is unsubstituted aryl (e.g., unsubstituted phenyl).

Embodiment No. 11 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same halo, and Ar is unsubstituted aryl (e.g., unsubstituted phenyl).

Embodiment No. 12 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is F, and Ar is unsubstituted aryl (e.g., unsubstituted phenyl).

Embodiment No. 13 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein each L^1 is the same or different halo, and Ar is substituted aryl (e.g., substituted phenyl). Examples of substituted phenyls include, for example, (1) halo substituted phenyl (such as, for example chloro substituted phenyl, such as, for example, p-Cl-phenyl-), (2) haloalkyl substituted phenyl (such as, for example, -CF_3 substituted phenyl, such as, for

example, p-CF_3-phenyl-), and (3) cyano substituted phenyl (such as, for example, p-CN-phenyl-).

Embodiment No. 14 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same or different halo, and Ar is substituted aryl (e.g., substituted phenyl). Examples of substituted phenyls include, for example, (1) halo substituted phenyl (such as, for example chloro substituted phenyl, such as, for example, p-Cl-phenyl-), (2) haloalkyl substituted phenyl (such as, for example, -CF_3 substituted phenyl, such as, for example, p-CF_3-phenyl-), and (3) cyano substituted phenyl (such as, for example, p-CN-phenyl-).

Embodiment No. 15 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same halo, and Ar is substituted aryl (e.g., substituted phenyl). Examples of substituted phenyls include, for example, (1) halo substituted phenyl (such as, for example chloro substituted phenyl, such as, for example, p-Cl-phenyl-), (2) haloalkyl substituted phenyl (such as, for example, -CF_3 substituted phenyl, such as, for example, p-CF_3-phenyl-), and (3) cyano substituted phenyl (such as, for example, p-CN-phenyl-).

Embodiment No. 16 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is F, and Ar is substituted aryl (e.g., substituted phenyl). Examples of substituted phenyls include, for example, (1) halo substituted phenyl (such as, for example chloro substituted phenyl, such as, for example, p-Cl-phenyl-), (2) haloalkyl substituted phenyl (such as, for example, -CF_3 substituted phenyl, such as, for example, p-CF_3-phenyl-), and (3) cyano substituted phenyl (such as, for example, p-CN-phenyl-).

Embodiment No. 17 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein each L^1 is the same or different halo, and Ar is unsubstituted heteroaryl (e.g., unsubstituted pyridyl).

Embodiment No. 18 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same or different halo, and Ar is unsubstituted heteroaryl (e.g., unsubstituted pyridyl).

Embodiment No. 19 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same halo, and Ar is unsubstituted heteroaryl (e.g., unsubstituted pyridyl).

Embodiment No. 20 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is F, and Ar is unsubstituted heteroaryl (e.g., unsubstituted pyridyl).

Embodiment No. 21 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein each L^1 is the same or different halo, and Ar is substituted heteroaryl (e.g., substituted pyridyl). Examples of substituted pyridyls include, for example, (1) halo substituted pyridyl (such as, for example chloro substituted pyridyl), (2) haloalkyl substituted pyridyl (such as, for example, -CF_3 substituted pyridyl), and (3) cyano substituted pyridyl.

Embodiment No. 22 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same or different halo, and Ar is substituted heteroaryl (e.g., substituted pyridyl). Examples of substituted pyridyls include, for example, (1) halo substituted pyridyl (such as, for example chloro substituted pyridyl), (2) haloalkyl substituted pyridyl (such as, for example, -CF_3 substituted pyridyl), and (3) cyano substituted pyridyl.

Embodiment No. 23 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is the same halo, and Ar is substituted heteroaryl (e.g., substituted pyridyl). Examples of substituted pyridyls include, for example, (1) halo substituted pyridyl (such as, for example chloro substituted pyridyl), (2) haloalkyl substituted pyridyl (such as, for example, -CF_3 substituted pyridyl), and (3) cyano substituted pyridyl.

Embodiment No. 24 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is F, and Ar is substituted heteroaryl (e.g., substituted pyridyl). Examples of substituted pyridyls include, for example, (1) halo substituted pyridyl (such as, for example chloro substituted pyridyl), (2) haloalkyl substituted pyridyl (such as, for example, -CF_3 substituted pyridyl), and (3) cyano substituted pyridyl.

Embodiment No. 25 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1

is the same halo, and Ar is substitued aryl selected from the group consisting p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, and p-CF_3CH_2Ophenyl.

Embodiment No. 26 is directed to any one of the compounds of formulas (I), (il) to (lvii), (I.A1), (I.A1a) to (I.A1h), (I.A2), and (I.A2a) to (I.A2h), wherein n is 2, each L^1 is F, and Ar is substituted aryl selected from the group consisting p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, and p-CF_3CH_2Ophenyl.

Embodiment No. 27 is directed to any one of Embodiment Nos. 1 to 26 wherein R^2 is H.

Embodiment No. 28 is directed to any one of Embodiment Nos. 1 to 26 wherein R^2 is alkyl.

Embodiment No. 29 is directed to any one of Embodiment Nos. 1 to 26 wherein R^2 is methyl.

Embodiment No. 30 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is –alkylene-(tetrahydrothiophene 1,1-dioxide).

Embodiment No. 31 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is -alkenyl-$S(O)_2$-(C_1-C_6)alkyl.

Embodiment No. 32 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is –cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl.

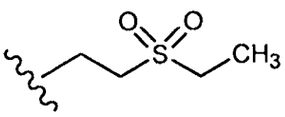
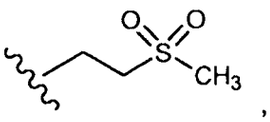
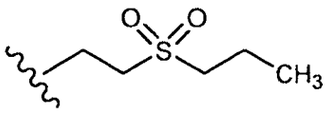
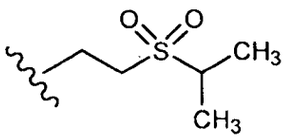
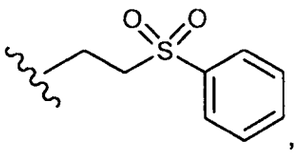
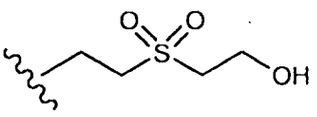
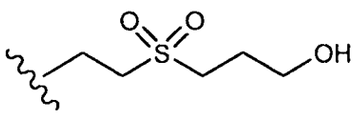
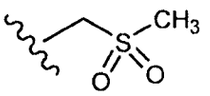
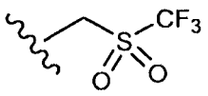
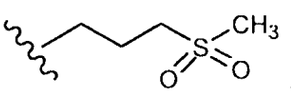
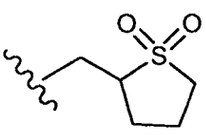
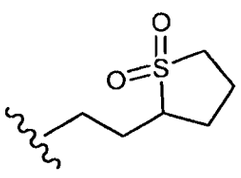
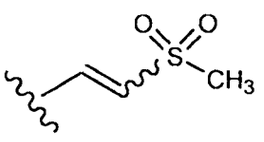
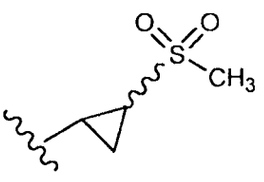
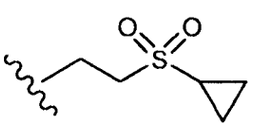
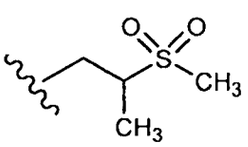
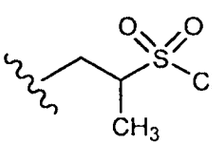
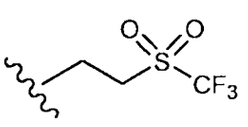
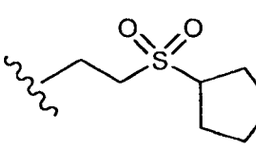
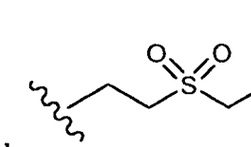
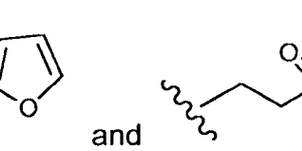
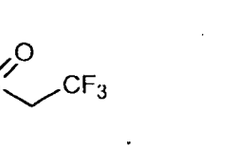
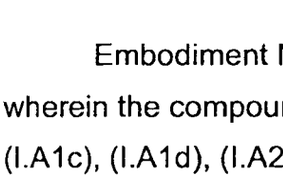
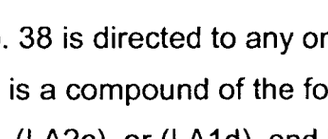
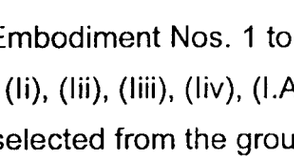
Embodiment No. 33 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is an - alkylene-$S(O)_2$-(C_1-C_6)alkyl group.

Embodiment No. 34 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_6)alkyl group.

Embodiment No. 35 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_3)alkyl group.

Embodiment No. 36 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_2) alkylene-$S(O)_2$-(C_1-C_6)alkyl group.

Embodiment No. 37 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (I), (I.A1), (I.A2), (I.A1a), (I.A1e), (I.A2a) or (I.A2e) wherein R^1 is selected from the group consisting of:

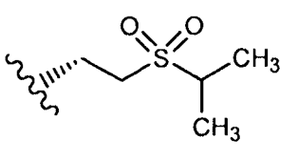
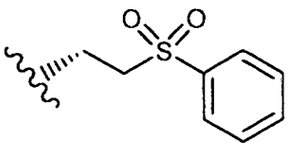
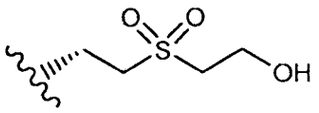
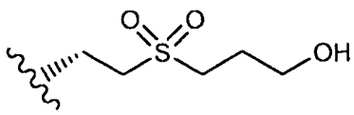
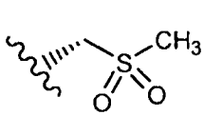
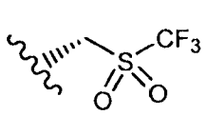
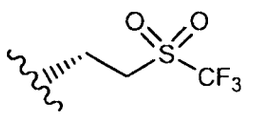
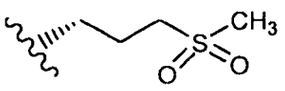
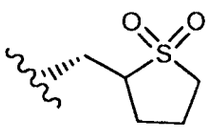
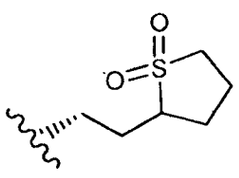
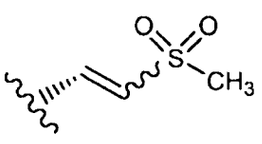
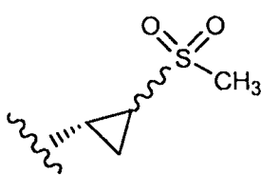
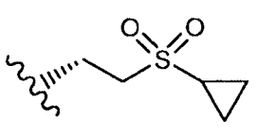
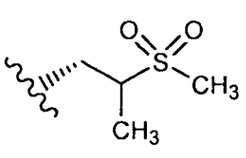
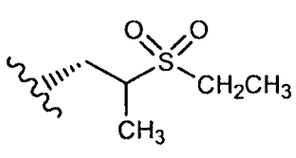
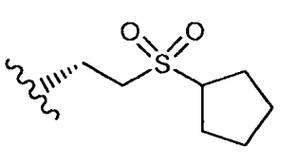
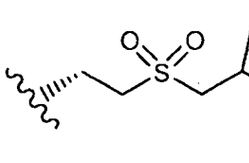
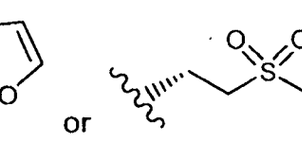
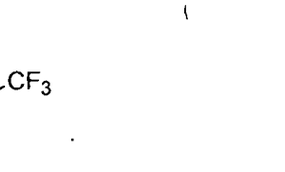
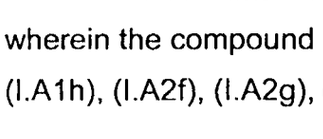
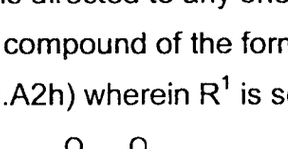

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Embodiment No. 38 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is selected from the group consisting of:

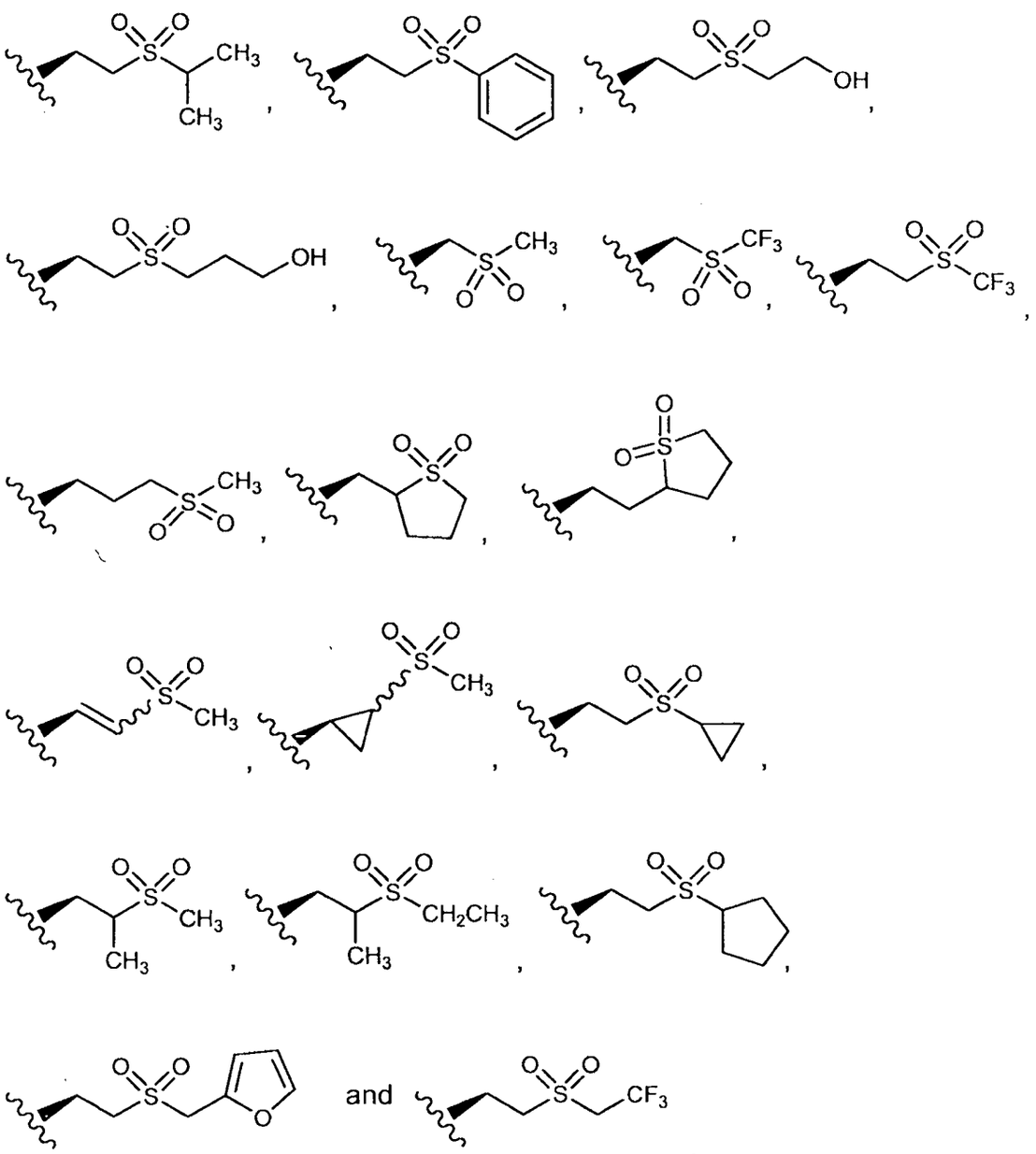
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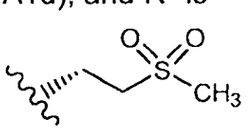
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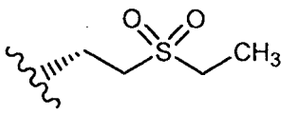
Embodiment No. 39 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 is selected from the group consisting of:



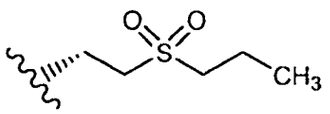
Embodiment No. 40 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



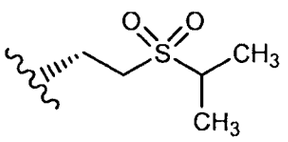
Embodiment No. 41 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



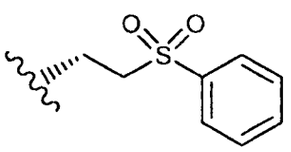
Embodiment No. 42 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



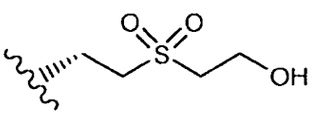
Embodiment No. 43 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



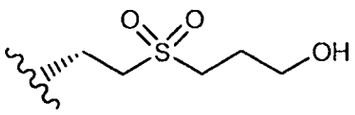
Embodiment No. 44 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



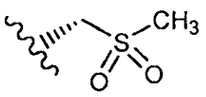
Embodiment No. 45 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



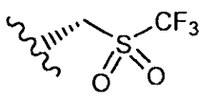
Embodiment No. 46 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



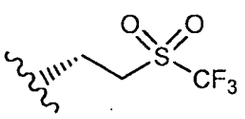
Embodiment No. 47 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



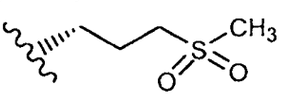
Embodiment No. 48 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



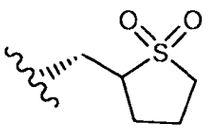
Embodiment No. 49 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



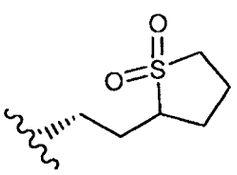
Embodiment No. 50 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



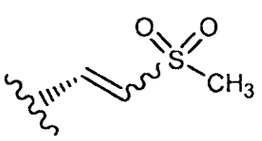
Embodiment No. 51 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



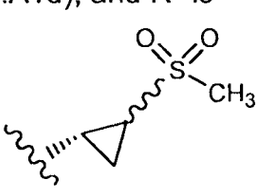
Embodiment No. 52 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



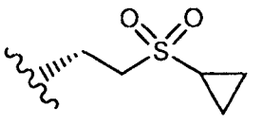
Embodiment No. 53 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



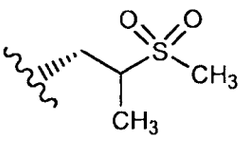
Embodiment No. 54 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



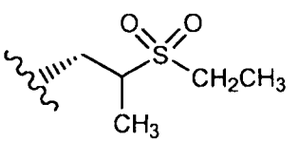
Embodiment No. 55 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



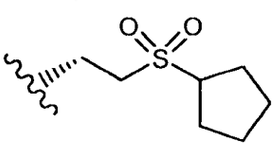
Embodiment No. 56 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



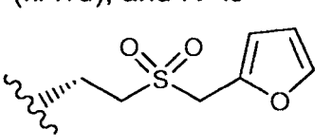
Embodiment No. 57 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



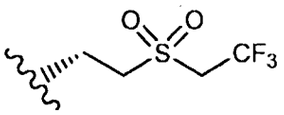
Embodiment No. 58 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



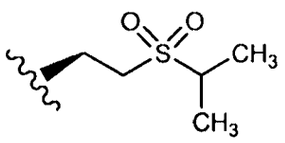
Embodiment No. 59 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



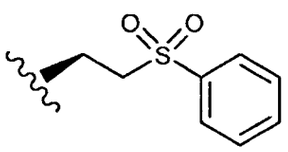
Embodiment No. 60 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is



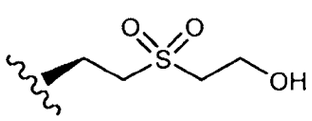
Embodiment No. 61 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 is



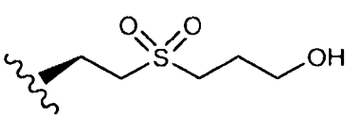
Embodiment No. 62 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



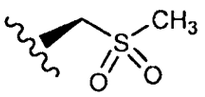
Embodiment No. 63 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



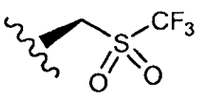
Embodiment No. 64 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



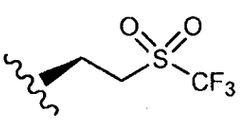
Embodiment No. 65 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



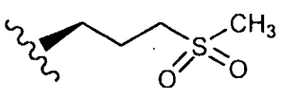
Embodiment No. 66 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



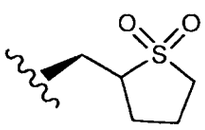
Embodiment No. 67 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



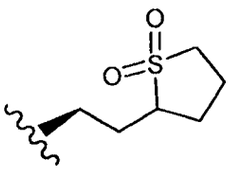
Embodiment No. 68 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



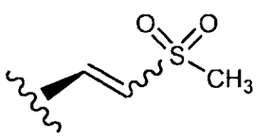
Embodiment No. 69 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



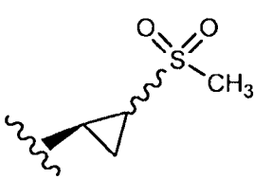
Embodiment No. 70 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



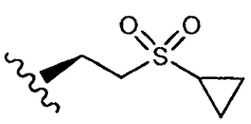
Embodiment No. 71 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



Embodiment No. 72 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i

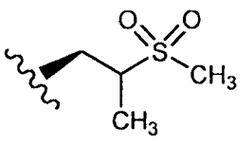


Embodiment No. 73 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i

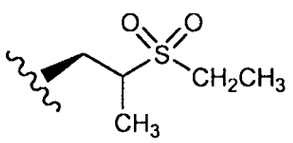


Embodiment No. 74 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i

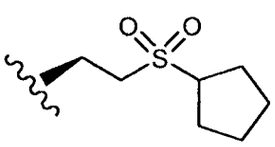
Embodiment No. 75 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



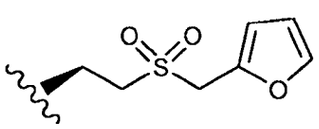
Embodiment No. 76 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



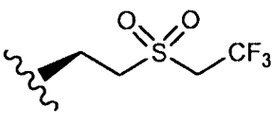
Embodiment No. 77 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



Embodiment No. 78 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



Embodiment No. 79 is directed to any one of Embodiment Nos. 1 to 26, wherein the compound is a compound of the formula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), or (I.A2h) wherein R^1 i



Embodiment No. 80 is directed to any one of Embodiment Nos. 37 to 79 wherein R^2 is H.

Embodiment No. 81 is directed to any one of Embodiment Nos. 37 to 79 wherein R^2 is alkyl.

Embodiment No. 82 is directed to any one of Embodiment Nos. 37 to 79 wherein R^2 is methyl.

Embodiment No. 83 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -alkylene-$S(O)_2$-(C_1-C_6)haloalkyl group.

Embodiment No. 84 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_3)haloalkyl group.

Embodiment No. 85 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_2)haloalkyl group.

Embodiment No. 86 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_2) alkylene-$S(O)_2$-(C_1-C_2)haloalkyl group.

Embodiment No. 87 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a –alkylene-(tetrahydrothiophene 1,1-dioxide) group.

Embodiment No. 88 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -alkenyl-$S(O)_2$-(C_1-C_6)alkyl group.

Embodiment No. 89 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a –cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl group.

Embodiment No. 90 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -alkylene-$S(O)_2$-(C_1-C_6)haloalkyl group, wherein the terminal carbon of said haloalkyl group is substituted with 1 to 3 of the same or different halo atoms. Examples of said haloalkyl groups include groups wherein the terminal carbon is substituted with 1 to 3 F atoms, or 2 to 3 F atoms, or 3 F atoms (with 3 F atoms being preferred).

Embodiment No. 91 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_3)haloalkyl group, wherein the terminal carbon of said haloalkyl group is substituted with 1 to 3 of the same or different halo atoms. Examples of said haloalkyl groups include groups wherein the terminal carbon

is substituted with 1 to 3 F atoms, or 2 to 3 F atoms, or 3 F atoms (with 3 F atoms being preferred)..

Embodiment No. 92 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_2)haloalkyl group, wherein the terminal carbon of said haloalkyl group is substituted with 1 to 3 of the same or different halo atoms. Examples of said haloalkyl groups include groups wherein the terminal carbon is substituted with 1 to 3 F atoms, or 2 to 3 F atoms, or 3 F atoms (with 3 F atoms being preferred).

Embodiment No. 93 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_2) alkylene-$S(O)_2$-(C_1-C_2)haloalkyl group, wherein the terminal carbon of said haloalkyl group is substituted with 1 to 3 of the same or different halo atoms. Examples of said haloalkyl groups include groups wherein the terminal carbon is substituted with 1 to 3 F atoms, or 2 to 3 F atoms, or 3 F atoms (with 3 F atoms being preferred).

Embodiment No. 94 is directed to any one of Embodiment Nos. 83 to 93 wherein the compound is a compound of formula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d), and R^1 is any one of the R^1 groups described in any one of Embodiment Nos. 40 to 60.

Embodiment No. 95 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is an -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl group, such as, for example, an -alkylene-$S(O)_2$-(C_1-C_6)hydroxyalkyl group.

Embodiment No. 96 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-substituted(C_1-C_3)alkyl group, such as, for example, a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_3)hydroxyalkyl group.

Embodiment No. 97 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-substituted(C_1-C_2) alkyl group, such as, for example, a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_2)hydroxyalkyl group..

Embodiment No. 98 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_2) alkylene-$S(O)_2$-substituted(C_1-C_2)alkyl group, such as, for example, a -(C_2) alkylene-$S(O)_2$-substituted(C_1-C_2)hydroxyalkyl group.

Embodiment No. 99 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is an -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl group, such as, for example,

an -alkylene-$S(O)_2$-(C_1-C_6)hydroxyalkykl group, wherein the terminal carbon of said substituted alkyl group is substituted.

Embodiment No. 100 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-substituted(C_1-C_3) alkyl group, such as, for example, a -(C_1 to C_2) alkylene-$S(O)_2$- (C_1-C_3)hydroxyalkyl group, wherein the terminal carbon of said alkyl group is substituted.

Embodiment No. 101 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_1 to C_2) alkylene-$S(O)_2$-substituted(C_1-C_2)alkyl group, such as, for example, a -(C_1 to C_2) alkylene-$S(O)_2$- (C_1-C_2)hydroxyalkyl group, wherein the terminal carbon of said alkyl group is substituted.

Embodiment No. 102 is directed to any one of Embodiment Nos. 1 to 26 wherein R^1 is a -(C_2) alkylene-$S(O)_2$-substituted(C_1-C_2)alkyl group, such as, for example, a -(C_1 to C_2) alkylene-$S(O)_2$-(C_1-C_2)hydroxyalkyl group, wherein the terminal carbon of said alkyl group is substituted.

Embodiment No. 103 is directed to any one of Embodiment Nos. 83 to 102 wherein R^2 is H.

Embodiment No. 104 is directed to any one of Embodiment Nos. 83 to 102 wherein R^2 is alkyl.

Embodiment No. 105 is directed to any one of Embodiment Nos. 83 to 102 wherein R^2 is methyl.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"RAC" (or "rac") means racemate.

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"One or more" means at least one, for example, 1, 2 or 3, or 1 or 2, or 1, thus, for example, "one or more L^3 groups" means at least one L^3 group, and examples include 1-3 L^3 groups, 1 or 2 L^3 groups, and one L^3 group.

"At least one" means there is at least one, and examples include 1, 2 or 3, or 1 or 2, or 1.

"Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred

alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain, which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl (unless expressly defined otherwise). Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain, which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Alkylene" means a divalent aliphatic hydrocarbon radical derived from an alkyl group, as defined above. Both "open" valences may be on the same carbon atom, or on different carbon atoms. Examples of alkylene groups include C_1-C_6 alkylene groups, for example, C_1 to C_4 alkylene groups, and in another example, C_1-C_3 alkylene groups, and in another example C_1 to C_2 alkylene groups. Non-limiting examples of alkylene groups include –CH_2-, -CH_2-CH_2-, -$CH(CH_3)$-, etc.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon

atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain, which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

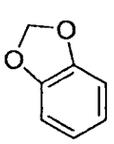
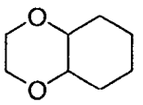
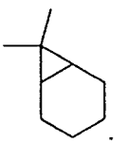
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable saturated monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, and non-limiting examples of non-aromatic, unsaturated monocyclic cycloalkyls include cyclopentenyl, cyclohexenyl, etc. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" or "halo" means fluorine, chlorine, bromine, or iodine. Fluorine, chlorine and bromine are preferred.

"Heteroalkyl" means an alkyl group (as defined herein) wherein one or more carbon atoms have been replaced with heteroatoms, such as, for example, heteroatoms each independently selected from the group consisting of: N, -(NR^{13A})-, O, S(O), and $S(O)_2$.

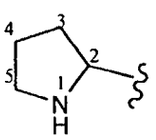
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system, which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl (substituted or unsubstituted, heteroaryl (substituted or unsubstituted, alkylene-aryl, heteroarylalkenyl, heteroarylalkynyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aryl substituted alkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, arylalkylthio, heteroarylalkylthio, cycloalkyl, heterocycloalkyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and -alkylene-aryl (unless expressly defined otherwise). The term "ring system substituent" may also mean a single moiety in which two available hydrogens on two adjacent carbon atoms are simultaneously replaced (e.g., one H on

each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



and

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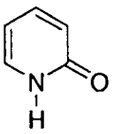
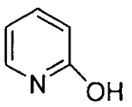
"Heterocycloalkyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocycloalkyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocycloalkyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocycloalkyl ring may exist in protected form, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protected forms are also considered part of this invention. The heterocycloalkyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocycloalkyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. Non-limiting examples of non-aromatic, unsaturated monocyclic heterocycloalkyl rings include thiazolinyl, 2,3-dihydrofuranyl, 2,3-dihydrothiophenyl, etc.

It should be noted that in the hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon atoms adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:

are considered equivalent in this invention.

"Hydroxyalkyl" means an alkyl group substituted with a hydroxyl (-OH) group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Haloalkyl" means an alkyl group substituted with one or more independently selected halo atoms (e.g., F, Cl and Br, and in one example, one or more F atoms), and wherein one example is $-CF_3$.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an -O-alkyl; group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkoxyalkyl" means an –alkyl-O-alkyl group wherein alkyl is as previously described.

"Aryloxy" means an -O-aryl group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an -S-alkyl group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an -S-aryl group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Arylalkylthio" means an -S-alkylene-aryl group in which the alkylene and aryl groups are as previously described. A non-limiting example of a suitable arylalkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Arylalkoxycarbonyl" means an -C(O)-O-alkylene-aryl group. A non-limiting example of a suitable arylalkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is a lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

"Alkanoyl" means an alkyl-C(O)- group.

"Carbamoyl" means an NH_2-C(O)- group.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

When a group is substituted with "one or more" substituents, the indicated group may be substituted with one substituent, two substituents, etc., provided that the resulting substituted group forms a stable structure, as described above.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties. For example, an aryl optionally substituted with an

indicated group of substituents includes unsubstituted aryl as well as aryl substituted with any of the indicated substituents.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon atom as well as any heteroatom with unsatisfied valences in the text, schemes, examples, Tables, etc. herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is present in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene et al, Protective Groups in Organic Synthesis (1991), Wiley, New York, herein incorporated by reference in its entirety.

When any variable (e.g., aryl, heterocycloalkyl, L^1, etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence (unless otherwise expressly indicated).

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

An "electron withdrawing group" (abbreviated as EWG), as used herein is a group that will draw electrons to itself more than a hydrogen atom would if it occupied the same position in the molecule (see, for example, Jerry March, "Advanced Organic Chemistry", 4th Edition, page 18, John Wiley & Sons, 1992)

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound

that is a drug precursor that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula (I) or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. A "hydrate" is a solvate wherein the solvent molecule(s) is/are H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in preventing the formation and/or deposition of amyloid protein, and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula (I) can form salts, which are also within the scope of this invention. Reference to a compound of Formula (I) herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, 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. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound of Formula (I) 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.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

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 dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula (I), and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those

which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). 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. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula (I), and of the salts, solvates and prodrugs of the compounds of Formula (I), are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula (I) can inhibit gamma-secretase, and are therefore useful in the treatment or prevention of neurodegenerative diseases, e.g., Alzheimer's Disease.

Representative compounds of the invention include but are not limited to the compounds and Examples described herein.

Pharmaceutical compositions can comprise one or more of the compounds of Formula (I). For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active compound. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania, herein incorporated by reference in its entirety.

Liquid form preparations include solutions, suspensions and emulsions. Water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions are examples. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active compound, e.g., an effective amount to achieve the desired purpose.

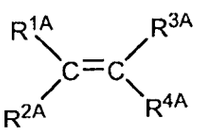
The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most

preferably from about 0.01 mg to about 250 mg, according to the particular application.The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in one to four divided doses.

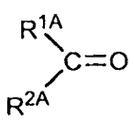
This invention is also directed to a process (Process 1) for preparing a compound of the formula:



said process comprising reacting:

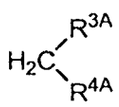
(1) a mixture comprising:

(a) a compound of the formula:



, and

(b) a compound of the formula:

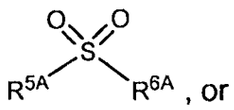


, and

(c) a suitable organic solvent (preferably anhydrous); with

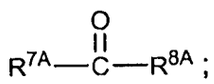
(2) either:

(a) a basic amine, and a compound of the formula



, or

(b) a basic amine, and a compound of the formula



;

wherein:

R^{1A} and R^{2A} are each independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroalkyl, aryl, heteroaryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl; wherein said substituted groups are substituted with one or more (e.g., 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1) substituents each independently selected from the group consisting of: $-NO_2$, -NO, $-SO_2R^{7B}$, $-SO_2$-aryl (e.g., $-SO_2$-phenyl), $-SO_2$-heteroaryl (e.g., $-SO_2$-pyridyl), $-SO_2OR^{7B}$, -CN, -COOH, halo (e.g., F, Cl, Br, and I), $-CF_3$, -Oaryl (e.g., -O-phenyl), -Oheteroaryl (e.g., -O-pyridyl), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, -CHO, $-OR^{7B}$, $-COR^{7B}$, -SH, $-SR^{7B}$, -OH, aryl (e.g., phenyl), and heteroaryl (e.g., pyridyl); and wherein in one example said substituted groups are substituted with one or more (e.g., 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1) substituents each independently selected from the group consisting of: halo (e.g., Cl, F, and Br), $-NO_2$, -CN, $-C(O)OR^{12A}$, $-C(O)R^{12A}$, $-CF_3$, -S(O), and $-S(O)_2$; wherein:

(1) examples of the heterocycloalkyl ring of said R^{1A} or R^{2A} heterocycloalkyl ring, or of said R^{1A} or R^{2A} substituted heterocycloalkyl ring, include, but are not limited to: heterocycloalkyl rings comprising a total of 3 to 7 ring members (e.g., 3 to 6, or 3 to 5, or 3 to 4 total ring members) wherein 1 to 4 (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2) ring members are hetero atoms independently selected from the group consisting of: N, $-(NR^{13A})-$, -O-, -S-, -S(O)-, and $-S(O)_2-$; and examples of said heterocycloalkyl rings also include, but are not limited to: piperidine, piperazine, pyrrolidine, azetidine, homopiperazine, tetrahydropyran, tetrahydropyran and oxetane; and examples of said substituted heterocycloalkyl rings include, but are not limited to: substituted piperidine, substituted piperazine, substituted pyrrolidine, substituted azetidine, substituted homopiperazine, substituted

tetrahydropyran, substituted tetrahydrofuran and substituted oxetane, wherein the substituents are as defined above for said R^{1A} and R^{2A} substituted heterocycloalkyl groups;

(2) examples of the heteroaryl ring of said R^{1A} or R^{2A} heteroaryl ring, or of said R^{1A} or R^{2A} substituted heteroaryl ring, include, but are not limited to: heteroaryl rings comprising a total of 5 to 6 ring members (e.g., 5 total ring members, or 6 total ring members) wherein 1 to 4 (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2) ring members are hetero atoms independently selected from the group consisting of: N, -(NR^{13A})-, -O-, -S-,-S(O)-, and–$S(O)_2$-; and examples of said heteroaryl rings also include, but are not limited to: pyridine, pyrimidine, pyrazine, thiophene, and furan; and examples of said substituted heteroaryl rings include, but are not limited to: substituted pyridine, substituted pyrimidine, substituted pyrazine, substituted thiophene, and substituted furan, wherein the substituents are as defined above for said R^{1A} and R^{2A} substituted heteroaryl groups; and

(3) examples of the heteroalkyl group of said R^{1A} or R^{2A} heteroalkyl group, or of said R^{1A} or R^{2A} substituted heteroalkyl group, include, but are not limited to: hetero(C_3 to C_{20})alkyl groups comprising at least one (e.g., 1 to 3, or 1 to 2, or 1 or 2) heteroatoms each independently selected from the group consisting of: N, -(NR^{13A})-, O, S(O), and $S(O)_2$;

R^{3A} and R^{4A} are each independently selected from the group consisting of: -NO_2, -NO, -SO_2R^{7B}, -SO_2-aryl (e.g., -SO_2-phenyl), -SO_2-heteroaryl (e.g., -SO_2-pyridyl), -SO_2OR^{7B}, -CN, -COOH, halo (e.g., F, Cl, Br, and I), -CF_3, -Oaryl (e.g., -O-phenyl), -Oheteroaryl (e.g., -O-pyridyl), -$COOR^{7B}$, -$CONH_2$, -$CONHR^{7B}$, $CON(R^{7B})_2$, -CHO, -OR^{7B}, -COR^{7B}, -SH, -SR^{7B}, -OH, aryl (e.g., phenyl), and heteroaryl (e.g., pyridyl); and in one example R^{3A} and R^{4A} are each independently selected from the group consisting of: -$C(O)OR^{12A}$, -CN, -NO_2, -CF_3, -$C(O)R^{12A}$, -S(O),and –$S(O)_2$;

R^{5A} is selected from the group consisting of: H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroalkyl, aryl, heteroaryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl; and wherein:

said substituted alkyl groups are substituted with one or more (e.g., 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1) substituents each independently selected from the group consisting of: halo (e.g., Cl, F, and Br), $-NO_2$, -CN, and $-OR^{12A}$; and

said substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl groups are substituted with one or more (e.g., 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1) substituents each independently selected from the group consisting of: halo (e.g., Cl, F, and Br), $-NO_2$, -CN, and $-OR^{12A}$, alkyl and halo substituted alkyl (e.g., F substituted alkyl, such as, for example, $-CF_3$); and wherein:

(1) examples of the heterocycloalkyl ring of said R^{5A} heterocycloalkyl ring, or of said R^{5A} substituted heterocycloalkyl ring, include, but are not limited to: heterocycloalkyl rings comprising a total of 3 to 7 ring members (e.g., 3 to 6, or 3 to 5, or 3 to 4 total ring members) wherein 1 to 4 (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2) ring members are hetero atoms independently selected from the group consisting of: N, $-(NR^{13A})-$, -O-, -S-, -S(O)-, and $-S(O)_2-$; and examples of said heterocycloalkyl rings also include, but are not limited to: piperidine, piperazine, pyrrolidine, azetidine, homopiperazine, tetrahydropyran, tetrahydropyran and oxetane; and examples of said substituted heterocycloalkyl rings also include, but are not limited to: substituted piperidine, substituted piperazine, substituted pyrrolidine, substituted azetidine, substituted homopiperazine, substituted tetrahydropyran, substituted tetrahydrofuran and substituted oxetane, wherein the substituents are as defined above for said R^{5A} substituted heterocycloalkyl groups;

(2) examples of the heteroaryl ring of said R^{5A} heteroaryl ring, or of said R^{5A} substituted heteroaryl ring, include, but are not limited to: heteroaryl rings comprising a total of 5 to 6 ring members (e.g., 5 total ring members, or 6 total ring members) wherein 1 to 4 (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2) ring members are hetero atoms independently selected from the group consisting of: N, $-(NR^{13A})-$, -O-, -S-,-S(O)-, and$-S(O)_2-$; and examples of said heteroaryl rings also include, but are not limited to: pyridine,

pyrimidine, pyrazine, thiophene, and furan; and examples of said substituted heteroaryl rings also include, but are not limited to: substituted pyridine, substituted pyrimidine, substituted pyrazine, substituted thiophene, and substituted furan, wherein the substituents are as defined above for said R^{5A} substituted heteroaryl groups; and

(3) examples of the heteroalkyl group of said R^{5A} heteroalkyl group, or of said R^{5A} substituted heteroalkyl group, include, but are not limited to: hetero(C_3 to C_{20})alkyl groups comprising at least one (e.g., 1 to 3, or 1 to 2, or 1 or 2) heteroatoms each independently selected from the group consisting of: N, -(NR^{13A})-, O, S(O), and $S(O)_2$;

R^{6A} is selected from the group consisting of: halo (e.g., Cl, F, and Br, and preferably Cl), and $-OSO_2R^{5A}$ (and preferably R^{6A} is halo);

R^{7A} is selected from the group consisting of: unsubstituted aryl, aryl substituted with at least one (e.g., 1 to 3, or 1 to 2, or 1) electron withdrawing group, heteroaryl, and heteroaryl substituted with at least one electron withdrawing group (e.g., 1 to 3, or 1 to 2, or 1); and wherein an example of said aryl moiety (of said R^{7A} aryl, or said R^{7A} substituted aryl groups) is phenyl; and wherein an example of said heteroaryl moiety (of said R^{7A} heteroaryl, or said R^{7A} substituted heteroaryl groups) is pyridyl; and wherein:

(1) in one example each electron withdrawing group is independently selected from the group consisting of: $-NO_2$, -NO, $-SO_2R^{7B}$, $-SO_2$-aryl (e.g., $-SO_2$-phenyl), $-SO_2$-heteroaryl (e.g., $-SO_2$-pyridyl), $-SO_2OR^{7B}$, -CN, -COOH, halo (e.g., F, Cl, Br, and I), $-CF_3$, -Oaryl (e.g., -O-phenyl), -Oheteroaryl (e.g., -O-pyridyl), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, -CHO, $-OR^{7B}$, $-COR^{7B}$, -SH, $-SR^{7B}$, -OH, aryl (e.g., phenyl), and heteroaryl (e.g., pyridyl); and

(2) in another example, each electron withdrawing group is independently selected from the group consisting of: $-NO_2$, -CN, $-CF_3$, $-C(O)R^{12A}$, -S(O), $-SO_2$, and halo (e.g., Cl, F, and Br); and

(3) in another example, said heteroaryl moiety of said R^{7A} substituted heteroaryl group comprises 1 to 4 ring hetero atoms (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2 hetero atoms) wherein each heteroatom is independently selected

from the group consisting of: -O-, -S-, -S(O)-, and $-S(O)_2-$, and said heteroaryl ring comprises a total of 5 or 6 ring members;

(4) in another example, said heteroaryl moiety of said R^{7A} substituted heteroaryl group comprises 1 to 4 ring hetero atoms (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2 hetero atoms) wherein each heteroatom is independently selected from the group consisting of: -O-, -S-, -S(O)-, and $-S(O)_2-$, and said heteroaryl ring comprises a total of 5 or 6 ring members, and each electron withdrawing group is independently selected from the group consisting of: $-NO_2$, -NO, $-SO_2R^{7B}$, $-SO_2$-aryl (e.g., $-SO_2$-phenyl), $-SO_2$-heteroaryl (e.g., $-SO_2$-pyridyl), $-SO_2OR^{7B}$, -CN, -COOH, halo (e.g., F, Cl, Br, and I), $-CF_3$, -Oaryl (e.g., -O-phenyl), -Oheteroaryl (e.g., -O-pyridyl), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, -CHO, $-OR^{7B}$, $-COR^{7B}$, -SH, $-SR^{7B}$, -OH, aryl (e.g., phenyl), and heteroaryl (e.g., phenyl); and

(5) in another example, said heteroaryl moiety of said R^{7A} substituted heteroaryl group comprises 1 to 4 ring hetero atoms (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2 hetero atoms) wherein each heteroatom is independently selected from the group consisting of: -O-, -S-, -S(O)-, and $-S(O)_2-$, and said heteroaryl ring comprises a total of 5 or 6 ring members, and each electron withdrawing group is independently selected from the group consisting of: $-NO_2$, -CN, $-CF_3$, $-C(O)R^{12A}$, -S(O), $-SO_2$, and halo (e.g., Cl, F, and Br);

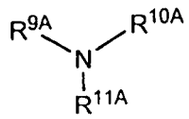
Each R^{7B} is independently selected from the group consisting of: alkyl (e.g., C_1 to C_6, or C_1 to C_4, or C_1 to C_2, or methyl, or ethyl), cycloalkyl and heteroalkyl;

R^{8A} is selected from the group consisting of: halo (e.g., Cl, F, and Br), and $-OC(O)R^{7A}$;

R^{12A} is alkyl (e.g., C_1 to C_6, or C_1 to C_4, or C_1 to C_2, or methyl, or ethyl); and

R^{13A} is selected from the the group consisting of: alkyl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aryl, heteroaryl, aroyl, and carbamoyl, and preferably alkyl.

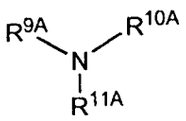
Examples of the basic amine used in the processes of this invention (see, for example, steps (2)(a) and (2)(b)), include, but are not limited to: (1) nitrogen based heteroaryls (i.e., the only hetero atom is N), and (2) amines of the formula:



(wherein R^{9A}, R^{10A} and R^{11A} are definied below).

Examples of the nitrogen based heteroaryl basic amine include, but are not limited to: imidazolyl and pyridyl.

Examples of the basic amine of the formula:



include, but are not limited to trialkylamines (i.e., R^{9A}, R^{10A}, and R^{11A} are each alkyl and are each independently selected), such as, for example, triethylamine (TEA) and diisopropyl ethyl amine (i.e., two of R^{9A}, R^{10A}, and R^{11A} groups are diisopropyl groups, and the remaining group is an ethyl group), with TEA being preferred.

Each R^{9A}, R^{10A}, and R^{11A} is independently selected from the group consisting of: alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroalkyl, aryl, heteroaryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl; wherein said substituted groups are substituted with one or more (e.g., 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1) substituents each independently selected from the group consisting of: halo (e.g., Cl, F, and Br), alkyl and alkoxy; wherein:

(1) examples of the heterocycloalkyl ring of said R^{9A}, R^{10A}, or R^{11A} heterocycloalkyl ring, or of said R^{9A}, R^{10A}, or R^{11A} substituted heterocycloalkyl ring, include, but are not limited to: heterocycloalkyl rings comprising a total of 3 to 7 ring members (e.g., 3 to 6, or 3 to 5, or 3 to 4 total ring members) wherein 1 to 4 (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2) ring members are hetero atoms independently selected from the group consisting of: N, -(NR^{13A})-, -O-, -S-, -S(O)-, and $-S(O)_2-$; examples of said heterocycloalkyl rings also include, but are not limited to: piperidine, piperazine, pyrrolidine, azetidine, homopiperazine, tetrahydropyran, tetrahydropyran and oxetane; examples of said substituted heterocycloalkyl rings include, but are not limited to: substituted piperidine, substituted piperazine, substituted pyrrolidine, substituted azetidine, substituted homopiperazine, substituted tetrahydropyran, substituted tetrahydrofuran and substituted oxetane, wherein the substituents

are as defined above for said R^{9A}, R^{10A}, and R^{11A} substituted heterocycloalkyl groups;

(2) examples of the heteroaryl ring of said R^{9A}, R^{10A}, or R^{11A} heteroaryl ring, or of said R^{9A}, R^{10A}, or R^{11A} substituted heteroaryl ring, include, but are not limited to: heteroaryl rings comprising a total of 5 to 6 ring members (e.g., 5 total ring members, or 6 total ring members) wherein 1 to 4 (e.g., 1 to 4, 1 to 3, 1 to 2, 1, or 2) ring members are hetero atoms independently selected from the group consisting of: N, -(NR^{13A})-, -O-, -S-,-S(O)-, and–$S(O)_2$-; examples of said heteroaryl rings also include, but are not limited to: pyridine, pyrimidine, pyrazine, thiophene, and furan; examples of said substituted heteroaryl rings include, but are not limited to: substituted pyridine, substituted pyrimidine, substituted pyrazine, substituted thiophene, and substituted furan, wherein the substituents are as defined above for said R^{9A}, R^{10A}, and R^{11A} substituted heteroaryl groups; and

(3) examples of the heteroalkyl group of said R^{9A}, R^{10A}, or R^{11A} heteroalkyl group, or of said R^{9A}, R^{10A}, or R^{11A} substituted heteroalkyl group, include, but are not limited to: hetero(C_3 to C_{20})alkyl groups comprising at least one (e.g., 1 to 3, or 1 to 2, or 1 or 2) heteroatoms each independently selected from the group consisting of: N, -(NR^{13A})-, O, S(O), and $S(O)_2$.

Examples of the alkyl groups in the processes of this invention include, but are not limited to: C_1 to C_6 alkyl, C_1 to C_4 alkyl, C_1 to C_2 alkyl, ethyl and methyl);

The processes of this invention are carried out in suitable organic solvents (preferably anhydrous). Examples of such solvents include, but are not limited to: (1) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (2) arylhalides (such as, for example, chlorobenzene), (3) DMSO, (4) DMF, (5) THF, (6) ethers (such as, for example, diethyl ether), and (7) mixtures thereof.

In one embodiment the organic solvent (preferably anhydrous) is selected from the group consisting of: dichloromethane, dichloroethane, chlorobenzene, DMSO, DMF, THF, and diethylether.

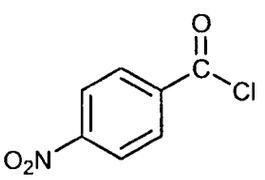
In one embodiment the solvent is a haloalkane.

In another embodiment the solvent is dichloromethane.

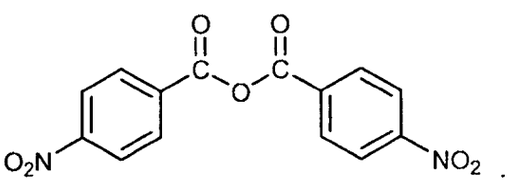
Examples of the (-$NR^9R^{10}R^{11}$) basic tertiary amine used in the processes of this invention include, but are not limited to: triethylamine (i.e., TEA), and diisopropyl ethyl amine (i.e., $C_2H_5N(CH_2CH_3)_2$).

In one embodiment of the processes of this invention the basic tertiary amine (-$NR^9R^{10}R^{11}$) is triethylamine (i.e., TEA).

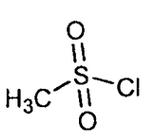
Examples of the $R^{7A}C(O)R^{8A}$ moiety include, but are not limited to:



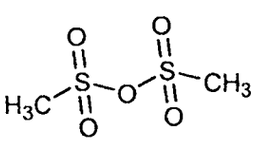
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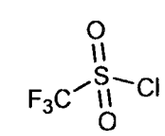
Examples of the $R^{5A}S(O)_2R^{6A}$ moiety include, but are not limited to:



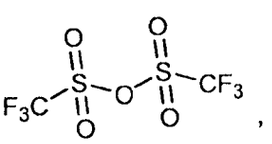
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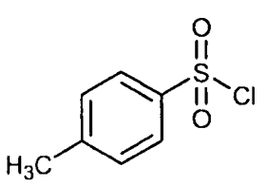
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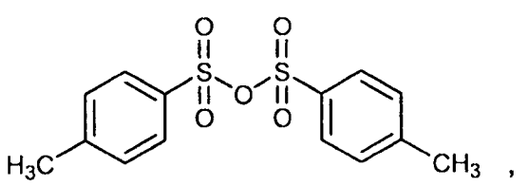
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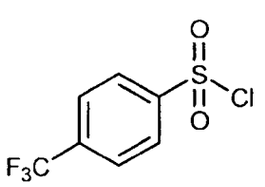
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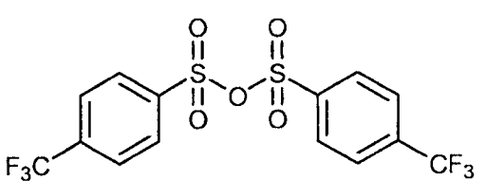
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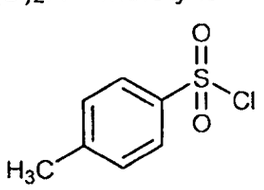


and



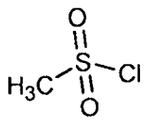
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In one example the $R^{5A}S(O)_2R^{6A}$ moiety is



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Preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:



The processes of this invention are carried at a suitable temperature. A suitable temperature is one wherein the reaction proceeds at a reasonable rate, and one wherein the production of unwanted by-products or degradation products are minimized.

In one embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C.

In another embodiment of Process 1 the basic amine is a trialkylamine.

In another embodiment of Process 1 the basic amine is TEA.

In another embodiment of Process 1 the basic amine is diisopropyl ethyl amine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, and the basic amine is a trialkylamine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, and the basic amine is a trialkylamine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, and the basic amine is a trialkylamine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, and the basic amine is TEA.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, and the basic amine is TEA.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, and the basic amine is TEA.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, and the basic amine is diisopropyl ethyl amine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, and the basic amine is diisopropyl ethyl amine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, and the basic amine is diisopropyl ethyl amine.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i)

haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii)

DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of this invention, Process 1 is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

Another embodiment of the processes of this invention is directed to any one of the above process embodiments wherein the mixture of (1)(a) and (1)(b) is reacted with (2)(a).

Thus, in another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent

is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for

example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

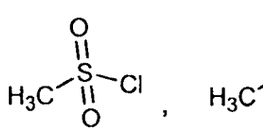
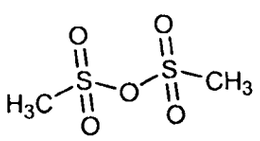
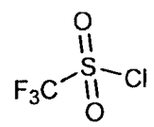
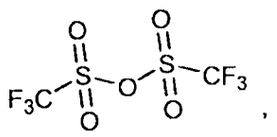
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

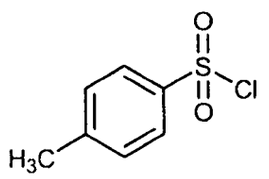
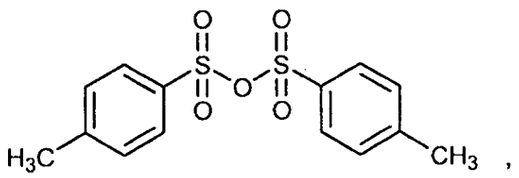
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent

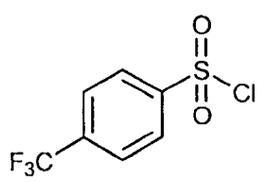
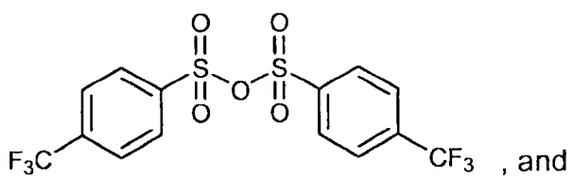
is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane.

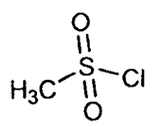
Another embodiment of Process 1 is directed to any of the above process embodiments wherein the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:


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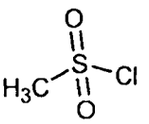

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and

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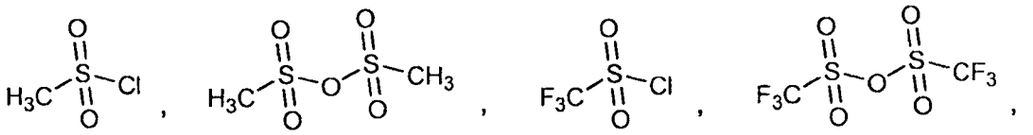
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:

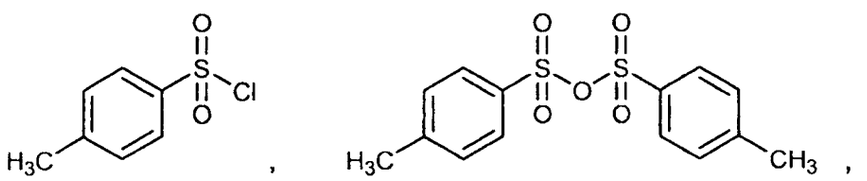

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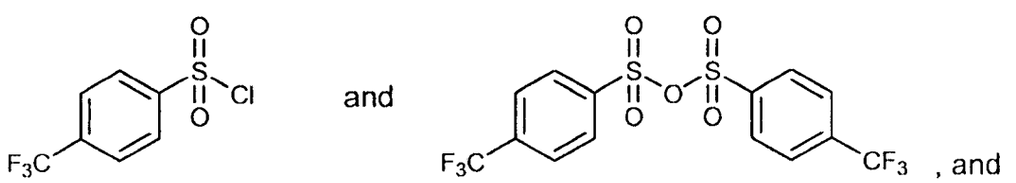
Another embodiment of Process 1 is directed to any of the above process embodiments wherein the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:



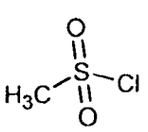
Thus, in another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:



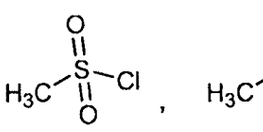
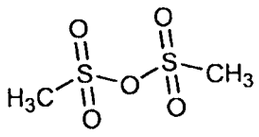
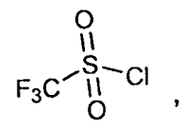
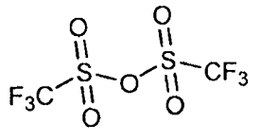


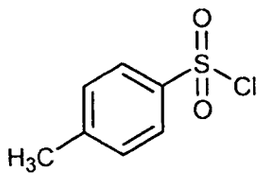
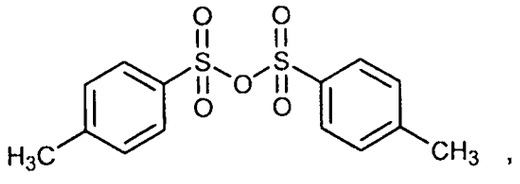


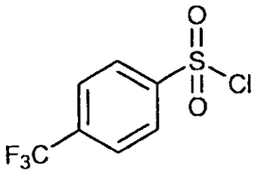
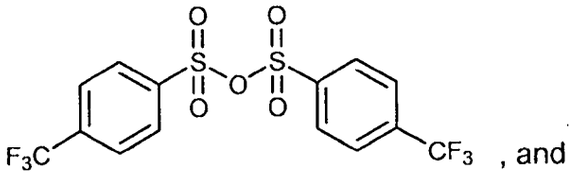
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:



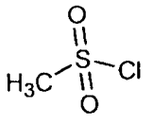
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:


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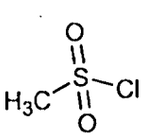
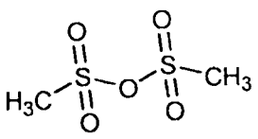
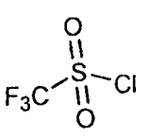
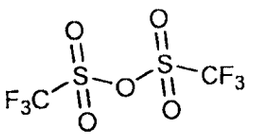

and

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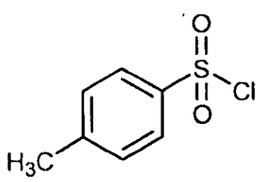
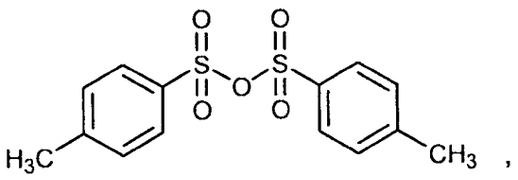
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:

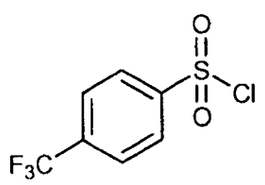
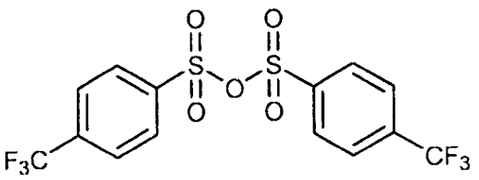


In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example,

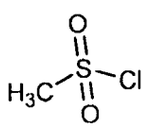
chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:


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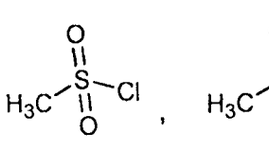
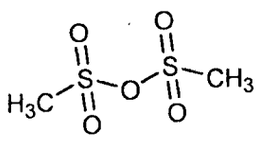
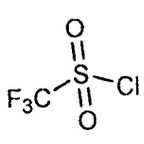
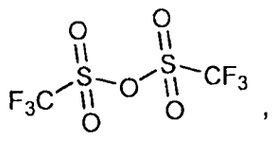
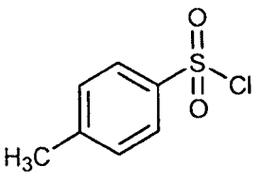
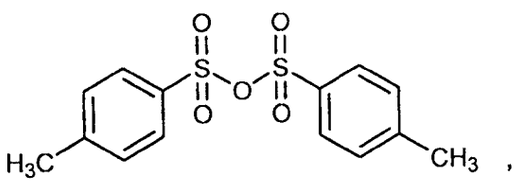
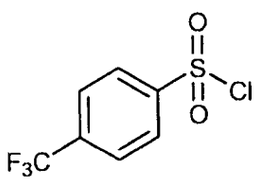
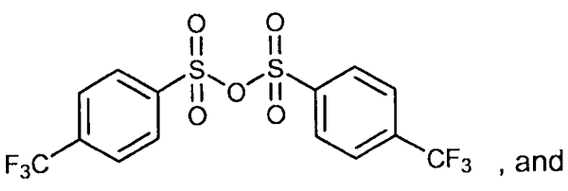

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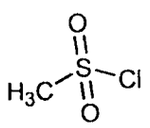
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:


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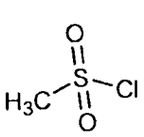
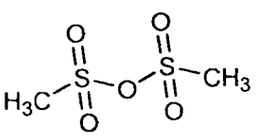
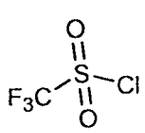
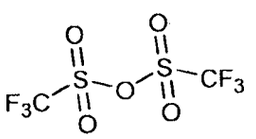
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:

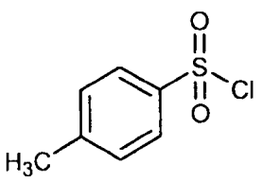
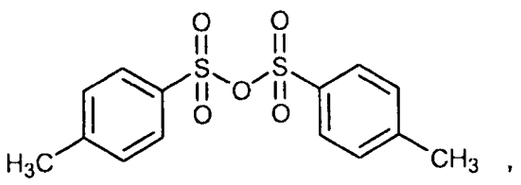







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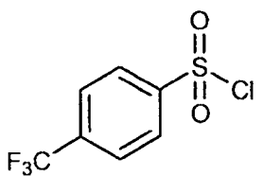
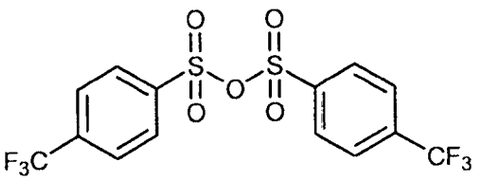
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:


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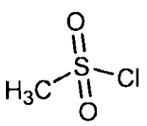
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:

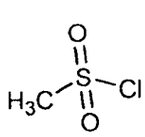
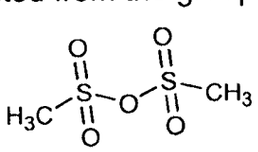
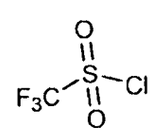
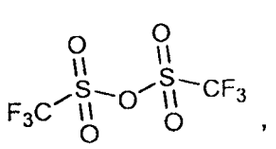

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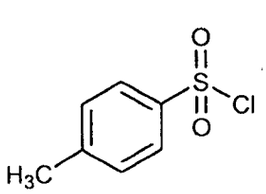
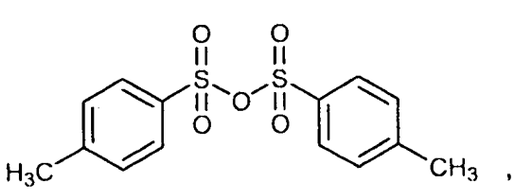

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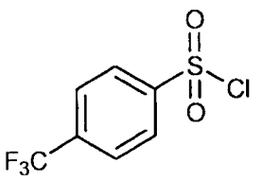
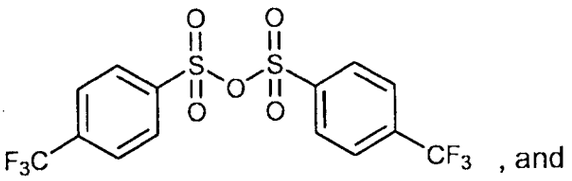
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:


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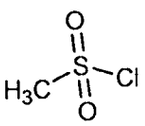
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:


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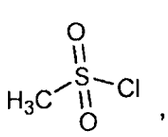
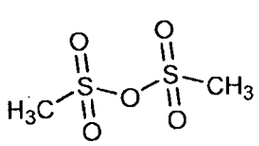
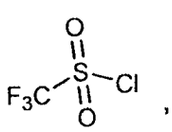
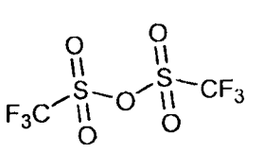

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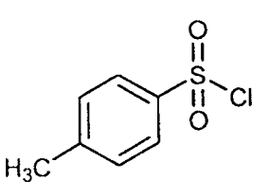
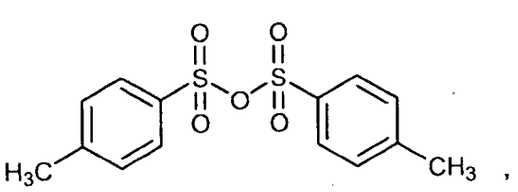
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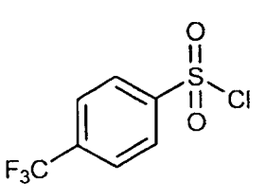
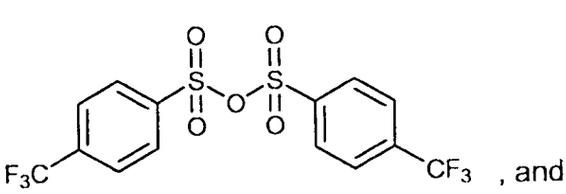
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:

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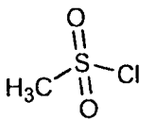
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:

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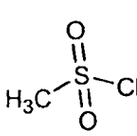
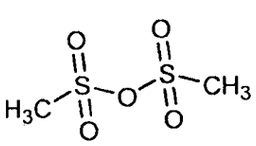
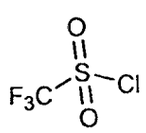
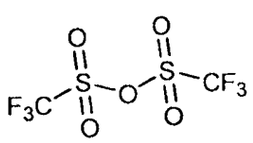
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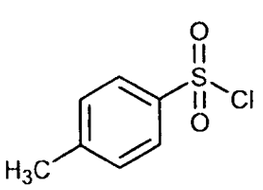
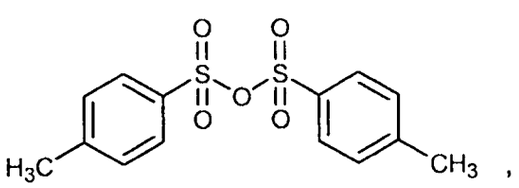
 and  , and

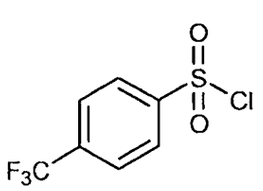
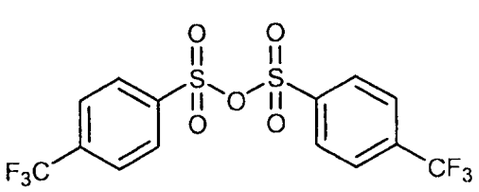
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:



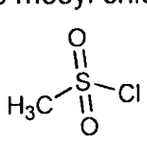
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:

 ,  ,  ,  ,

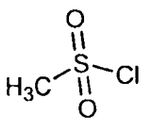
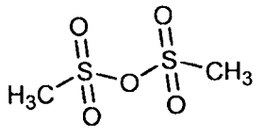
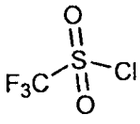
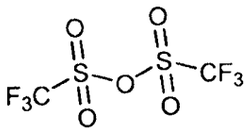
 ,  ,

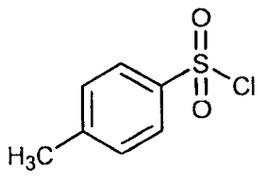
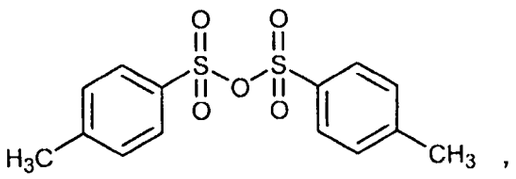
 and  , and

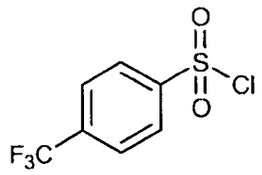
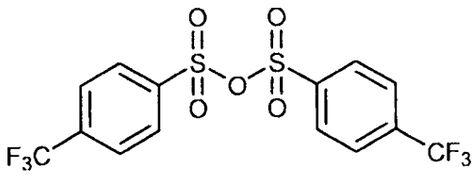
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:



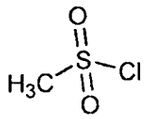
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consisting of:


,

,

,

,

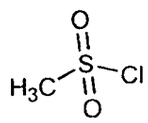

,

,


and

, and

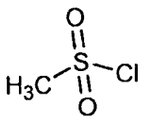
preferably, the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:


.

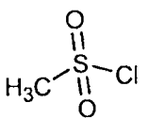
Another embodiment of Process 1 is directed to any of the above process embodiments wherein the $R^{5A}S(O)_2R^{6A}$ moiety is mesyl chloride:


.

Thus, in another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is

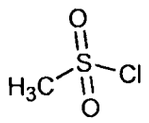


In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is

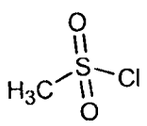


In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example,

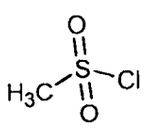
chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



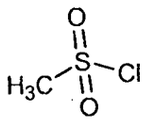
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



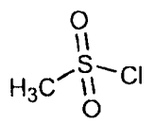
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is:

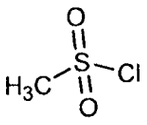


In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is

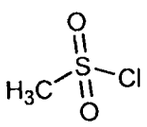


In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-

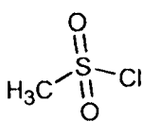
CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



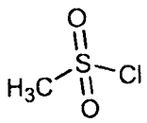
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably the organic solvent is a haloalkane, and more preferably the organic solvent is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



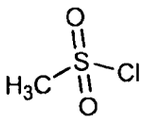
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is

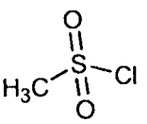


In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



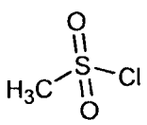
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, and the organic solvent (step (1)(c) (preferably is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



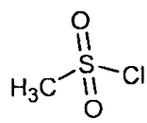
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



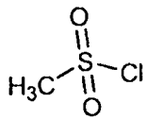
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is:



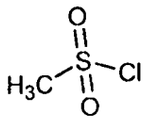
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



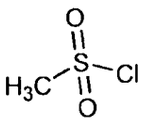
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is



.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, and the organic solvent (step (1)(c) is anhydrous dichloromethane, and the $R^{5A}S(O)_2R^{6A}$ moiety is

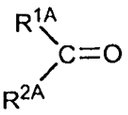


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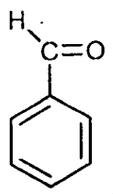
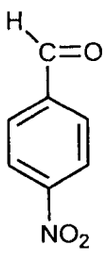
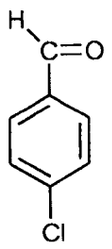
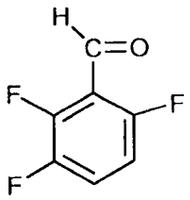
Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H.

Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, wherein said substituted aryl is substituted with one or more (e.g., 1 to 3, 1 to 2 or 1) substitutent independently selected from the group consisting of: $-NO_2$ and halo (e.g., Cl and F).

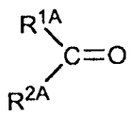
Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein



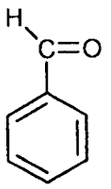
is selected from the group consisting of:


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and

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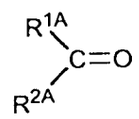
Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein



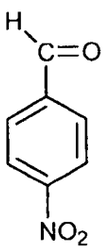
is


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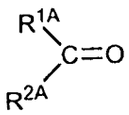
Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein



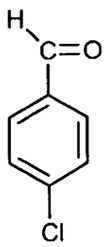
is


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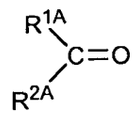
Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein



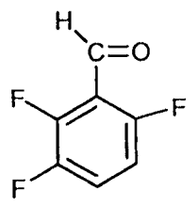
is



Another embodiment of Process 1 is directed to any one of the process embodiments described above wherein



is



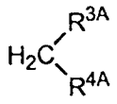
Another embodiment of Process 1 is directed to any one of the above process embodiments wherein R^{3A} and R^{4A} are each independently selected from the group consisting of: $-C(O)OR^{12A}$.

Another embodiment of Process 1 is directed to any one of the above process embodiments wherein R^{3A} and R^{4A} are the same $-C(O)OR^{12A}$ moiety.

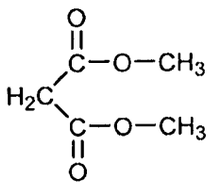
Another embodiment of Process 1 is directed to any one of the above process embodiments wherein R^{3A} and R^{4A} are the same $-C(O)OR^{12A}$ moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

Another embodiment of Process 1 is directed to any one of the above process embodiments wherein R^{3A} and R^{4A} are the same $-C(O)OR^{12A}$ moiety, and wherein R^{12A} is methyl or ethyl.

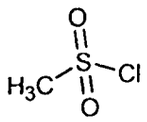
Another embodiment of Process 1 is directed to any one of the above process embodiments wherein



is:

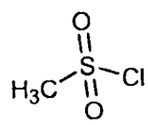


Thus, in another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



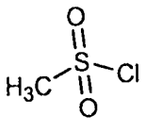
one of R^{1A} and R^{2A} is selected from the group consisting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same $-C(O)OR^{12A}$ moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



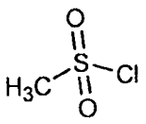
one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same $-C(O)OR^{12A}$ moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



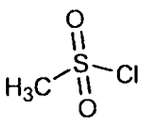
one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



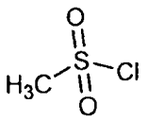
one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



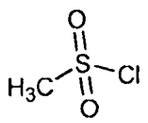
one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is:



one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

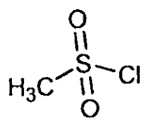
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



,

one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

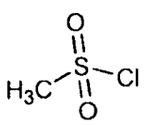
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



,

one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

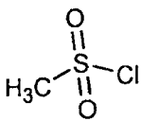
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



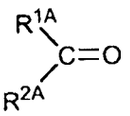
,

one of R^{1A} and R^{2A} is selected from the group consiting of: aryl (e.g., phenyl), and substituted aryl (e.g., substituted phenyl), and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and wherein R^{12A} is a C_1 to C_4 alkyl.

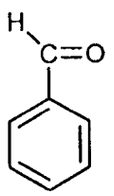
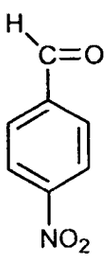
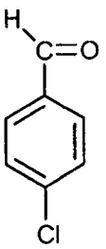
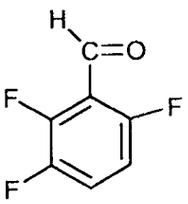
Thus, in another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is a trialkylamine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



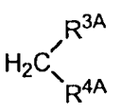
the moiety



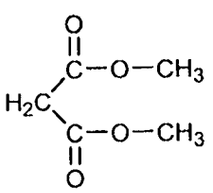
is selected from the group consisting of:


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and

, and

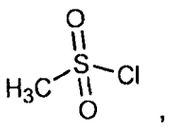
the moiety



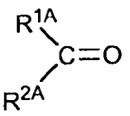
is


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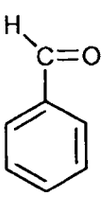
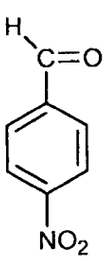
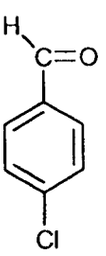
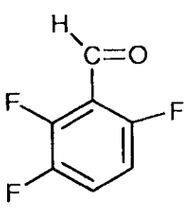
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



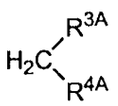
the moiety



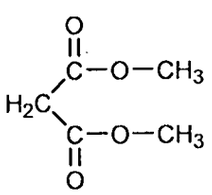
is selected from the group consisting of:




and

, and

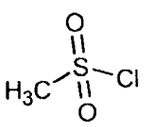
the moiety



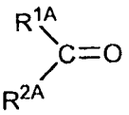
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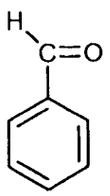
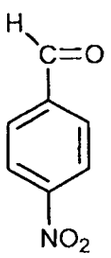
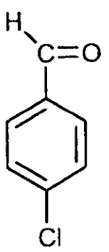
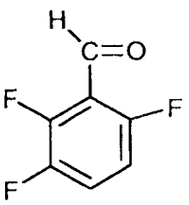
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



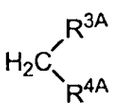
the moiety



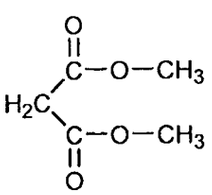
is selected from the group consisting of:


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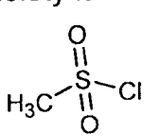
the moiety



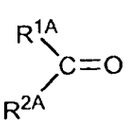
is


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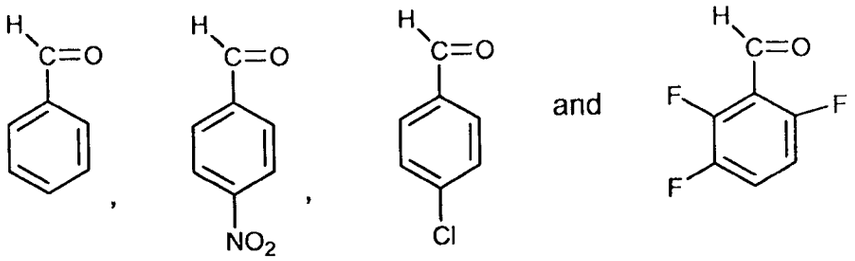
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is TEA, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is


,

the moiety

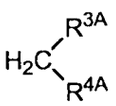


is selected from the group consisting of:

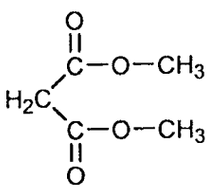


, and

the moiety

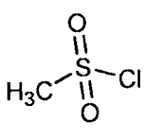


is



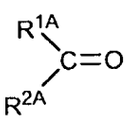
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is TEA, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is

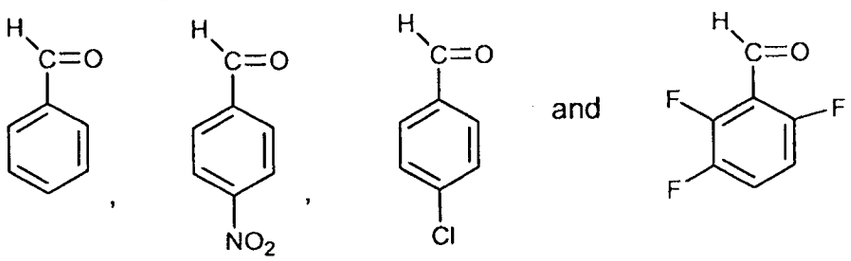


,

the moiety

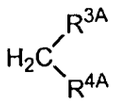


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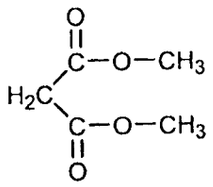


, and

the moiety

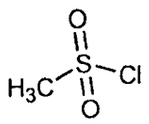


is



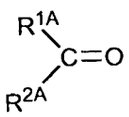
.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is TEA, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is:

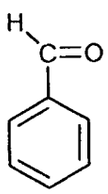


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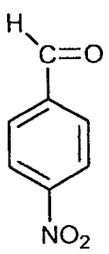
the moiety



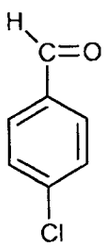
is selected from the group consisting of:



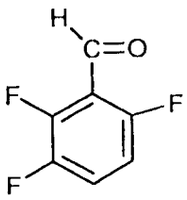
,



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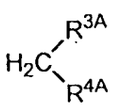


and

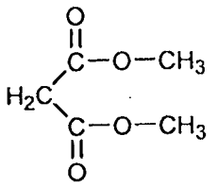


, and

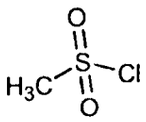
the moiety



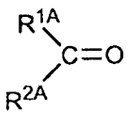
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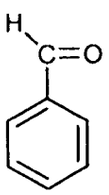
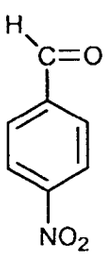
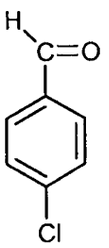
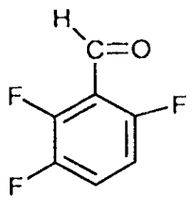
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about -40°C to about 40°C, the basic amine is diisopropyl ethyl amine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



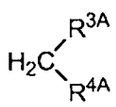
the moiety



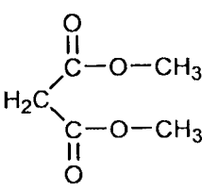
is selected from the group consisting of:


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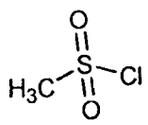
the moiety



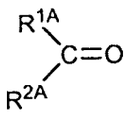
is



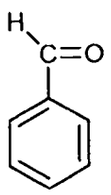
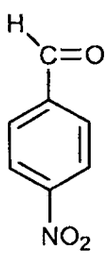
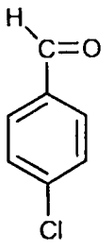
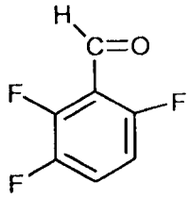
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is diisopropyl ethyl amine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



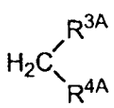
the moiety



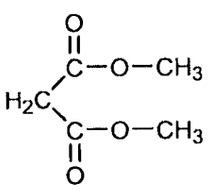
is selected from the group consisting of:


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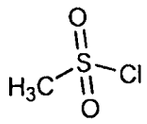
the moiety



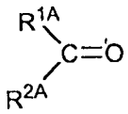
is


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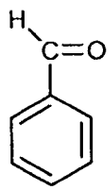
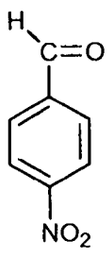
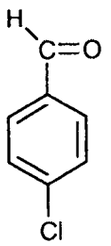
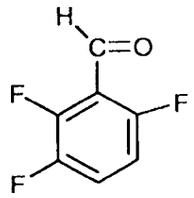
In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is diisopropyl ethyl amine, the organic solvent (step (1)(c) is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is



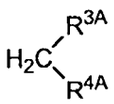
the moiety



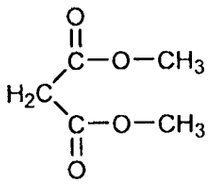
is selected from the group consisting of:


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and

, and

the moiety



is


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In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with a basic amine (e.g., a trialkylamine as defined above) and the compound $R^{7A}C(O)R^{8A}$.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with a basic amine (e.g., a trialkylamine as defined above) and the compound $R^{7A}C(O)R^{8A}$, wherein the reaction is carried out at a temperature within the range of about -40°C to about 40°C, and preferably about 0°C to about 30°C, and more preferably about 0°C to about 10°C.

In another embodiment of Process 1, the mixture of (1)(a) and (1)(b) is reacted with a basic amine (e.g., a trialkylamine as defined above) and the compound $R^{7A}C(O)R^{8A}$, wherein the reaction is carried out at a temperature within the range of about -40°C to about 40°C, and preferably about 0°C to about 30°C, and more preferably about 0°C to about 10°C, and wherein the (1)(c) organic solvent (preferably anhydrous) is selected from the group consisting of (i) haloalkanes (such as, for example, dichloromethane, dichloroethane (e.g., CH_2Cl-CH_2Cl), trichloromethane, and tetrachloromethane), (ii) arylhalides (such as, for example, chlorobenzene), (iii) DMSO, (iv) DMF, (v) THF, (vi) ethers (such as, for example, diethyl ether), and (vii) mixtures thereof, and preferably a haloalkane, and more preferably anhydrous dichloromethane.

In Process 1 and the embodiments of Process 1 described above, the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{3A}CH_2R^{4A}$ is usually about 1:0.8 to about 1:1.2, and preferably about 1:1.

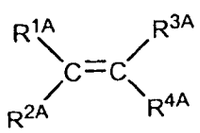
In Process 1 and the embodiments of Process 1 described above, the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{5A}S(O)_2R^{6A}$ is usually about 1:1 to about 1:4, and preferably about 1:1.

In Process 1 and the embodiments of Process 1 described above, the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{7A}C(O)R^{8A}$ is usually about 1:1 to about 1:4, and preferably about 1:1.

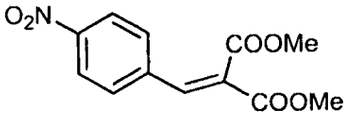
In Process 1 and the embodiments of Process 1 described above, the molar ratio of $R^{5A}S(O)_2R^{6A}$ to the basic amine (e.g., $NR^{9A}R^{10A}R^{11A}$, such as, for example, a trialkylamine, such as, for example, triethylamine or diisopropyl ethyl amine) is usually about 1:2 to about 1:3, and preferably about 1:2.

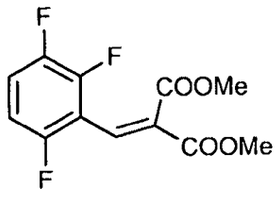
In Process 1 and the embodiments of Process 1 described above, the molar ratio of $R^{7A}C(O)R^{8A}$ to the basic amine (e.g., $NR^{9A}R^{10A}R^{11A}$, such as, for example, a trialkylamine, such as, for example, triethylamine or diisopropyl ethyl amine) is usually about 1:2 to about 1:3, and preferably about 1:2.

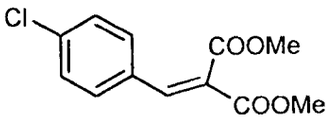
Examples of the compound of the formula:



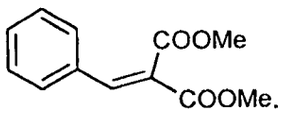
produced by the processes of this invention include, but are not limited to:



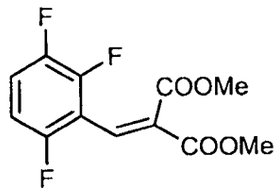
,


,


, and



Thus, another embodiment of the processes of this invention is directed to a process for preparing a compound of the formula:



said process comprising reacting:

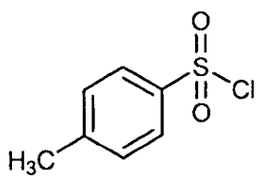
(1) a mixture comprising:

(a) 2,3,5-triflorobenzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) dichloromethane (preferably anhydrous); with

(2) mesyl chloride, i.e.,



;

wherein:

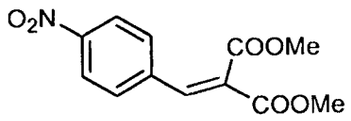
said process is carried out at a temperature within the range of about -40°C to about 40°C, and preferably about 0°C to about 30°C, and more preferably about 0°C to about 10°C;

the molar ratio of 2,3,5-triflorobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2, and preferably 1:1;

the molar ratio of 2,3,5-triflorobenzaldehyde to mesyl chloride is about 1:1 to about 1:4, and preferably 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3, and preferably about 1:2.

Another embodiment of the processes of this invention is directed to a process for preparing a compound of the formula:



said process comprising reacting:

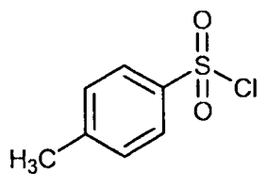
(1) a mixture comprising:

(a) 4-nitrobenzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) dichloromethane (preferably anhydrous); with

(2) mesyl chloride, i.e.,



;

wherein:

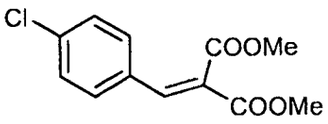
said process is carried out at a temperature within the range of about -40°C to about 40°C, and preferably about 0°C to about 30°C, and more preferably about 0°C to about 10°C;

the molar ratio of 4-nitrobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2, and preferably 1:1;

the molar ratio of 4-nitrobenzaldehyde to mesyl chloride is about 1:1 to about 1:4, and preferably 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3, and preferably about 1:2.

Another embodiment of the processes of this invention is directed to a process for preparing a compound of the formula:



said process comprising reacting:

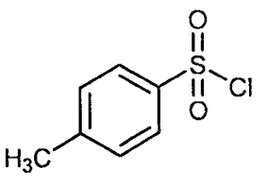
(1) a mixture comprising:

(a) 4-chlorobenzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) dichloromethane (preferably anhydrous); with

(2) mesyl chloride, i.e.,



;

wherein:

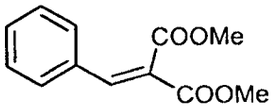
said process is carried out at a temperature within the range of about -40°C to about 40°C, and preferably about 0°C to about 30°C, and more preferably about 0°C to about 10°C;

the molar ratio of 4-chlorobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2, and preferably 1:1;

the molar ratio of 4-chlorobenzaldehyde to mesyl chloride is about 1:1 to about 1:4, and preferably 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3, and preferably about 1:2.

Another embodiment of the processes of this invention is directed to a process for preparing a compound of the formula:



said process comprising reacting:

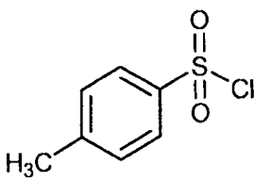
(1) a mixture comprising:

(a) benzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) dichloromethane (preferably anhydrous); with

(2) mesyl chloride, i.e.,



;

wherein:

said process is carried out at a temperature within the range of about -40°C to about 40°C, and preferably about 0°C to about 30°C, and more preferably about 0°C to about 10°C;

the molar ratio of benzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2, and preferably 1:1;

the molar ratio of benzaldehyde to mesyl chloride is about 1:1 to about 1:4, and preferably 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3, and preferably about 1:2.

The processes of this invention described above are generally carried out under an inert atmosphere, such as, for example N_2. Thus, for example the mixture of the compound $R^{1A}C(O)R^{2A}$, the the compound $R^{3A}CH_2R^{4A}$ (e.g., malonic acid dimethyl ether) and the organic solvent (preferably anhydrous, e.g., anhydrous dichloromethane) are under N_2, and then the basic amine (e.g., TEA) is added, and then the compound $R^{5A}S(O)_2R^{6A}$ (e.g., mesyl chloride, i.e., methanesulfonyl chloride) is added. The mixture of $R^{1A}C(O)R^{2A}$ and $R^{3A}CH_2R^{4A}$ is usually at a low temperature, such as, for example, the temperature resulting from the mixture being in an ice bath (e.g., 5°C). Thus, another embodiment of Process 1 is directed to any of the embodiments described above wherein the reaction is carried out under an inert atmosphere, preferably N_2.

The desired compound of the processes of this invention can be isolated by techniques well known in the art. For example, water can be added creating an organic and an aqueous layer. The layers can be extracted with a suitable organic solvent, preferably the organic solvent used in the process itself (e.g., dichloromethane). The organic layer can be washed with water, and then the resulting organic layer can be dried over a suitable drying agent, such as, for example, anhydrous sodium sulfate. The dried organic layer can then be concentrated to produce the desired product (usually as a solid).

EXAMPLES

The invention disclosed herein is exemplified by the following preparations and examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. The retention time and observed parent ion are given.

The following solvents, reagents, and conditions may be referred to by their abbreviations in parenthesis:

Acetyl (Ac), i.e., $CH_3C(O)$-
Butyl (Bu)
Cyclopropyl (Pr-c)
Dichloroethane (DCE)
Dichloromethane (DCM)
Diethyl ether (Et_2O)
Diisobutylaluminum hydride (DIBAL-H)
Dimethyl formamide (DMF)
Ethanol (EtOH)
Ethyl (Et)
Ethyl acetate (EtOAc)
High resolution mass spectrometry (HRMS)
Lithium Aluminum Hydride (LAH)
Lithium diisopropyl amide (LDA)
Liquid chromatography/mass spectrometry (LCMS)
m-Chloroperoxybenzoic acid (mCPBA)

Mesyl (Ms), i.e., $-S(O)_2CH_3$

Methanol (MeOH)

Methyl (Me)

Nuclear magnetic resonance spectroscopy (NMR)

Preparative thin-layer chromatography (PTLC)

Pyridine (Pyr)

Room temperature (RT)

Tert-butyldimethylsilyl (TBS)

Tetrabutyl ammonium fluoride (TBAF)

Tetrahydrofuran (THF)

Trifluoroacetic acid (TFA)

Trimethylsilyl (TMS)

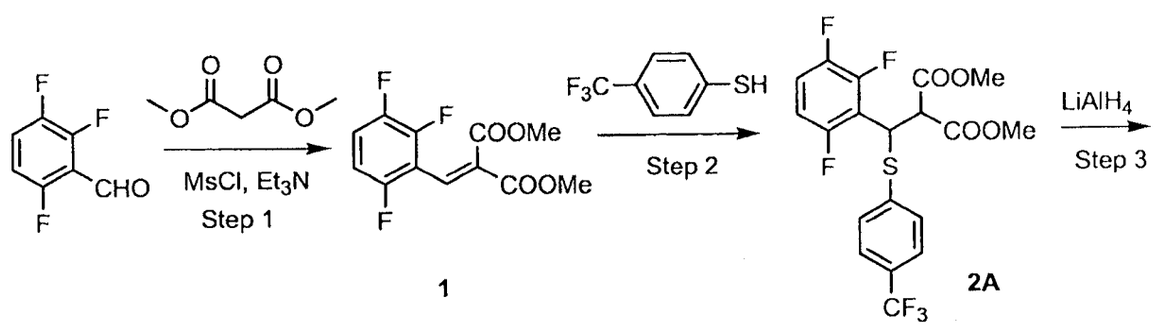
Trimethylsilyl chloride (TMSCl)

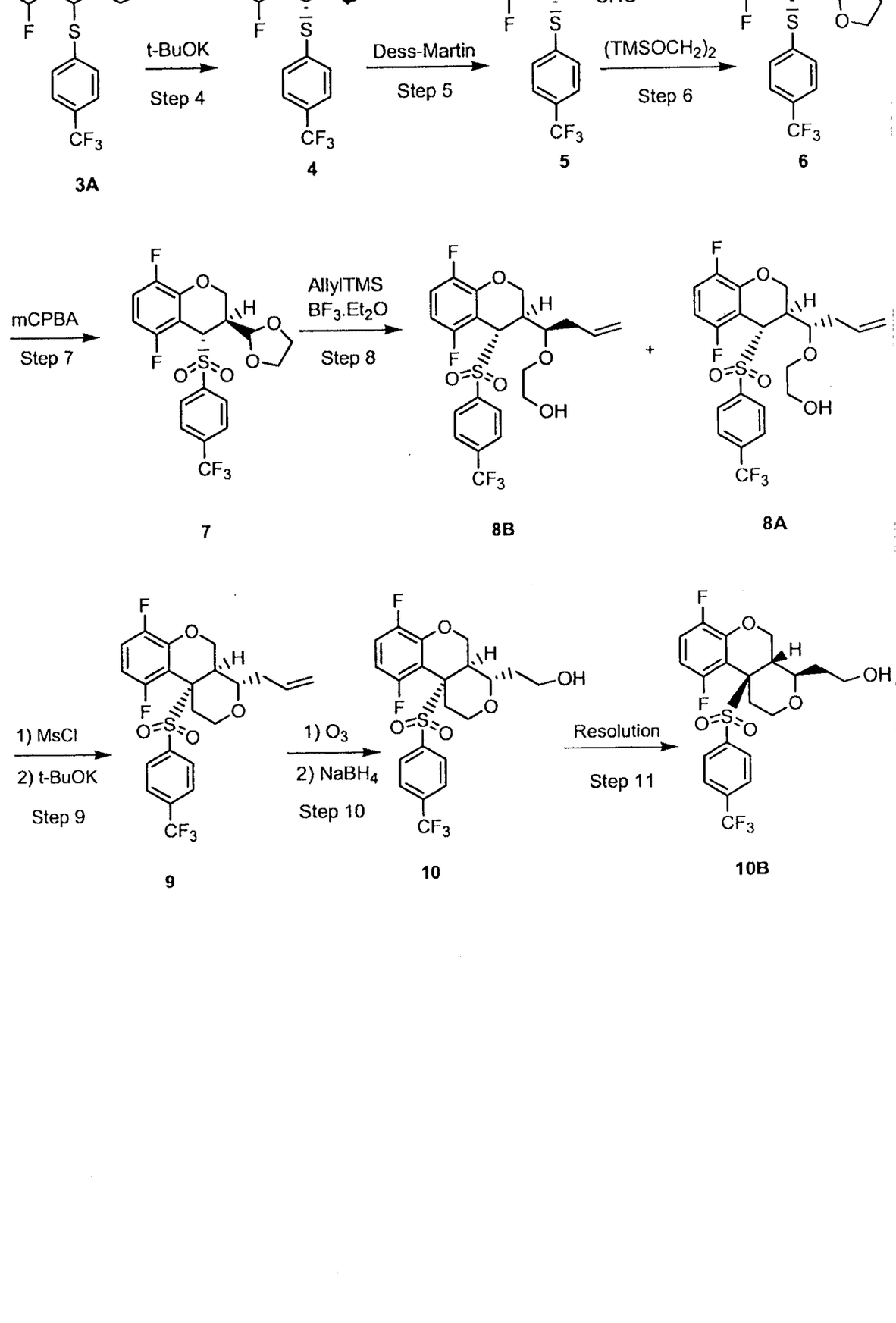
Triethylamine (NEt_3 or Et_3N or TEA)

Compounds of Formula (I) can be prepared by various methods well known to those skilled in the art, and by the methods described below.

Compounds of Formula (I) can be prepared according to the procedures described in Schemes 1 and 2.

Scheme 1

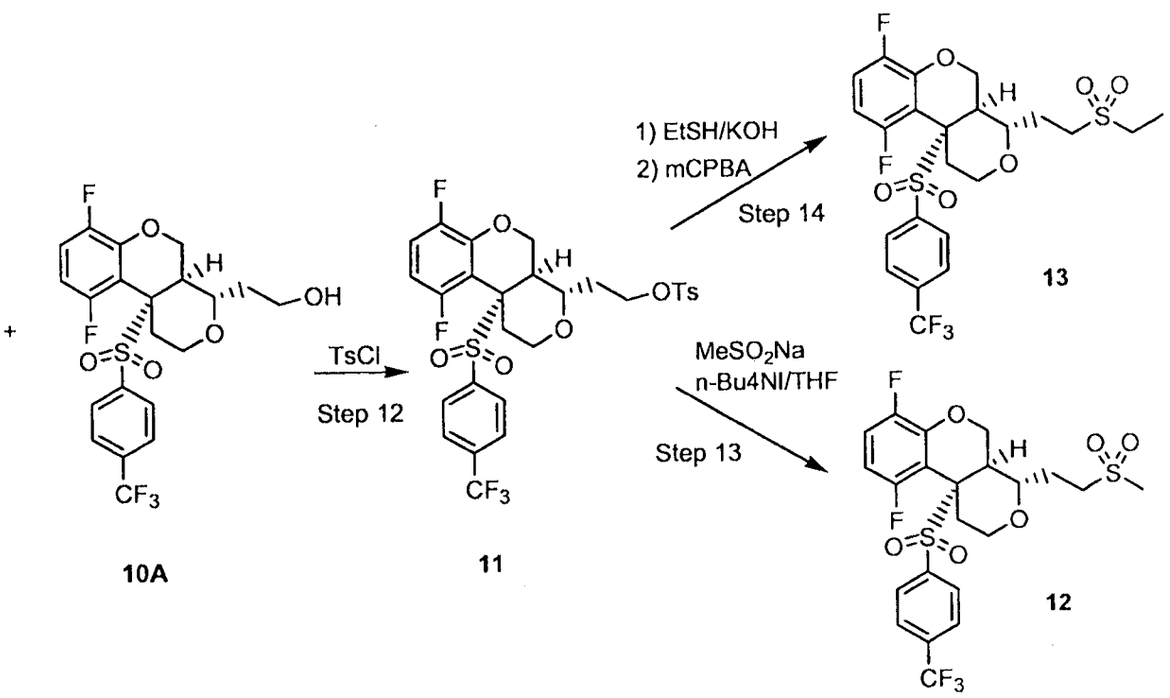




3A 4 5 6

7 8B 8A

9 10 10B



Step 1

To a stirred solution of 64 g (400 mmol) of 2,3,6-trifluorobenzoaldehyde and 53 g (400 mmol) of dimethyl malonate in 600 mL of dichloromethane was added 81 g (800 mmol) of triethylamine at 0 °C. A solution of 69 g (600 mmol) of methanesulfonyl chloride in 200 mL of dichloromethane was added over a period of 1.5 h, with the temperature maintained at 0 °C. An additional 20 g (200 mmol) of triethylamine was added, followed by the addition of a solution of 23 g (200 mmol) of methanesulfonyl chloride in 50 mL of dichloromethane. The reaction was quenched with 800 mL of water, extracted with three 500 mL portions of dichloromethane. The combined organic extracts were washed with 200 mL of saturated sodium bicarbonate and concentrated to give 128 g of crude compound **1**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.70 (s, 1 H), 7.20 (m, 2 H), 6.90 (m, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H). MS: Calcd. for $C_{12}H_{10}F_3O_4$ (MH^+), m/z = 275.1; found 275.2. Retention time: 4.00 min.

Step 2

To a solution of 124 g (400 mmol) of compound **1** and 71.3 g (400 mmol) of 4-(trifluoromethyl)thiophenol in 1500 mL of tetrahydrofuran was added 55.2 g (400 mmol) of potassium carbonate. The mixture was stirred at room temperature for 18 h. An additional 29 g (210 mmol) of potassium carbonate and 12 g (67 mmol) of 4-

trifluoromethyl thiophenol were added. After 2 h, it was quenched with 800 mL of water, extracted with three 600 mL portions of ethyl acetate. The combined organic extracts were concentrated and filtered. The filtrate was concentrated to give 205 g of crude compound **2A**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.50 (m, 4 H), 7.04 (m, 1 H), 6.78 (s, 1 H), 5.22 (d, J = 12 Hz, 1 H), 4.36 (d, J = 12 Hz, 1 H), 3.81 (s, 3 H), 3.66 (s, 1 H). MS: Calcd. for $C_{19}H_{15}F_6O_4S$ (MH^+), m/z = 453.1; found 453.2. Retention time: 5.11 min.

Step 3

To a stirred suspension of 32 g (842 mmol) of lithium aluminum hydride in 1000 mL of tetrahydrofuran was added at 0 °C a solution of 200 g (400 mmol) of compound **2A** in 500 mL of tetrahydrofuran over a period of 2 h. It was stirred at room temperature for 2 h and quenched with 100 mL of water (cooled with ice-water bath). After addition of 1500 mL of 6 N HCl, it was extracted with five 600 mL portions of dichloromethane. The combined organic extracts were concentrated, and the residue was purified by chromatography eluting with a gradient of 10% to 50% of ethyl acetate in hexanes to give 55 g of compound **3A**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.50 (m, 4 H), 7.03 (m, 1H), 6.78 (m, 1 H), 5.03 (d, J = 12 Hz, 1 H), 4.35 (m, 1 H), 4.20 (dd, J = 11, 2.4 Hz, 1 H), 3.87 (dd, J = 11, 2..4 Hz, 1 H), 3.50 (dd, J = 11, 4.8 Hz, 1 H), 2.46 (m, 1 H), 2.20 (br, 2 H). MS: Calcd. for $C_{17}H_{15}F_6O_2S$ (MH+), m/z = 397.1; found 397.2. Retention time: 4.31 min.

Step 4

To a stirred solution of 55 g (139 mmol) of compound **3A** in 600 mL of tetrahydrofuran cooled to 10 °C was added dropwise a solution of 20 g (179 mmol) of potassium tert-butoxide in 200 mL of tetrahydrofuran over a period of 1 h. It was stirred at room temperature for additional 1 h and quenched with 500 mL of water and 80 mL of 1 N HCl. It was separated, the aqueous layer was extracted with three 400 mL portions of dichloromethane. The combined organic extracts were concentrated, and the residue was purified by chromatography eluting with a gradient of 15% to 20% of ethyl acetate in hexanes to give 41 g of compound **4**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.58 (s, 4 H), 6.98 (m, 1H), 6.60 (m, 1 H), 4.75 (s, 1 H), 4.63 (dd, J = 12, 2.4 Hz, 1 H), 4.10 (dd, J = 10, 2.4 Hz, 1 H), 3.75 (m, 1 H), 3.55 (m, 1 H), 2.33 (m, 1 H).

MS: Calcd. for $C_{17}H_{14}F_5O_2S$ (MH^+), m/z = 377.1; found 377.2. Retention time: 4.81 min.

Step 5

To a stirred solution of 10 g (26.6 mmol) of compound **4** in 250 mL of dichloromethane was added 14.2 g (33.5 mmol) of Dess-Martin periodinane. The mixture was stirred at room temperature for 2 h and diluted with 400 mL of dichloromethane. It was stirred with 400 mL of saturated sodium bicarbonate and 200 mL of 10% sodium thiosulfate solution and separated. This procedure was repeated twice with 200 mL of saturated sodium bicarbonate and 200 mL of 10% sodium thiosulfate solution. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to give 10.1 g of crude aldehyde **5**. ^1H NMR ($CDCl_3$ 400 MHz) δ 9.74 (s, 1 H), 7.60 (m, 4 H), 6.97 (m, 1 H), 6.64 (m, 1 H), 5.08 (s, 1 H), 4.95 (d, J = 12 Hz, 1 H), 4.75 (dd, J = 12, 2..4 Hz, 1 H), 2.87 (s, 1 H). MS: Calcd. for $C_{17}H_{12}F_5O_2S$ (MH^+), m/z = 375.1; found 375.2. Retention time: 5.00 min.

Step 6

To a stirred solution of 10 g (26.5 mmol) of compound **5** in 150 mL of dichloromethane were added 7.14 g (33.5 mmol) of 1,2-bis(trimethylsiloxy)ethane and 0.69 g (3.1 mmol) of trimethylsilyl trifluoromethanesulfonate at -78 °C. After 30 min, it was warmed to room temperature and stirred for 30 min. The reaction was quenched with 200 mL of saturated sodium bicarbonate and extracted with three 200 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 2% to 30% of ethyl acetate in hexanes to give 9.4 g of compound **6**. ^1H NMR ($CDCl_3$ 400 MHz) δ 7.60 (m, 4 H), 7.00 (m, 1 H), 6.57 (m, 1 H), 4.90 (s, 1H), 4.79 (d, J = 7.6 Hz, 1 H), 4.60 (m, 1 H), 3.80-4.0 (m, 5 H), 2.18 (m, 1 H). MS: Calcd. for $C_{19}H_{16}F_5O_2S$ (MH^+), m/z = 419.1; found 419.2. Retention time: 5.20 min.

Step 7

To a stirred solution of 9.8 g (23.4 mmol) of compound **6** in 250 mL of dichloromethane was added 14.4 g (58.5 mmol) of 3-chloroperoxybenzoic acid at 0 °C. The mixture was stirred at room temperature overnight. It was diluted with 400

mL of dichloromethane and quenched at 0 °C with 200 mL of saturated sodium bicarbonate and 200 mL of 10% sodium thiosulfate. The dichloromethane layer was washed with 100 mL of 1 N NaOH, and dried over sodium sulfate. It was filtered, concentrated and the residue was purified by chromatography eluting with a gradient of 5% to 45% of ethyl acetate in hexanes to give 10.1 g of compound **7**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.96 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.03 (m, 1 H), 6.39 (m, 1 H), 4.89 (dd, J = 12, 4 Hz, 1 H), 4.67 (m, 2 H), 4.64 (dd, J = 6.4, 1.6 Hz, 1 H), 3.8 – 4.0 (m, 4 H), 2.92 (m, 1 H). MS: Calcd. for $C_{19}H_{16}F_5O_5S$ (MH^+), m/z = 451.1; found 451.2. Retention time: 4.43 min.

Step 8

A solution of 10.0 g (22.2 mmol) of compound **7**, 12.7 g (111 mmol) of allyltrimethylsilane and 15.8 g (111 mmol) of boron trifluoride etherate in 120 mL of dichloromethane was stirred at reflux for 1 day. Additional 5.0 g (44 mmol) of allyltrimethylsilane and 6.2 g (44 mmol) of boron trifluoride etherate were added, and the mixture was stirred at reflux for another day. The reaction was quenched with 200 mL of saturated sodium bicarbonate, and extracted with three 150 mL potions of dichloromethane. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 10% to 60% of ethyl acetate in hexanes to give 2.70 g of compound **8A** and 5.3 g of **8B**. **8A**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.97 (d, J = 8.4 Hz, 2 H), 7.82 (d, J = 8.4 Hz, 2 H), 7.03 (m, 1 H), 6.41 (m, 1 H), 5.80 (m, 1 H), 5.18 (d, J = 12.4 Hz, 1 H), 4.97 (s, 1 H), 4.92 (d, J = 9.6 Hz, 1 H), 4.67 (m, 1 H), 4.43 (d, J = 12.4 Hz, 1 H), 3.56 (m, 3 H), 3.24 (m, 1 H), 3.13 (m, 1 H), 2.97 (m, 1 H), 2.57 (m, 1 H), 2.36 (m, 1 H). MS: Calcd. for $C_{22}H_{22}F_5O_5S$ (MH^+), m/z = 493.1; found 493.3. Retention time: 4.33 min. **8B**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.95 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 8.0 Hz, 2 H), 7.05 (m, 1 H), 6.45 (m, 1 H), 5.70 (m, 1 H), 5.0 (m, 2 H), 4.86 (d, J = 5.6 Hz, 1 H), 4.67 (d, J = 11.6 Hz, 1 H), 4.53 (s, 1 H), 3.61 (m, 3 H), 3.47 (m, 1 H), 3.29 (m, 1 H), 2.94 (m, 1 H), 2.37 (m, 1 H), 2.06 (m, 1 H). MS: Calcd. for $C_{22}H_{22}F_5O_5S$ (MH^+), m/z = 493.1; found 493.3. Retention time: 4.21 min.

Step 9

To a solution of 2.68 g (5.44 mmol) of compound **8A** in 40 mL of dichloromethane were added 1.0 g (10 mmol) of triethylamine and 1.0 g (8.7 mmol) of methanesulfonyl chloride. The mixture was stirred at room temperature for 1 h. It was quenched with 80 mL of saturated sodium bicarbonate and extracted with two 80 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue was dissolved in 100 mL of tetrahydrofuran. To this solution was added 10 mL (10 mmol) of 1 N potassium tert-butoxide in THF. The mixture was stirred at room temperature for 15 min., quenched with 100 mL of water and extracted with two 150 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 2% to 30% of ethyl acetate in hexanes to give 2.46 g of compound **9**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.85 (d, J = 8.4 Hz, 2 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.10 (m, 1 H), 6.46 (m, 1 H), 5.60 (m, 1 H), 5.15 (m, 3 H), 4.47 (d, J = 12.4 Hz, 1 H), 3.93 (m, 1 H), 3.37 (m, 1 H), 3.16 (t, J = 11.6 Hz, 1 H), 2.60 (m, 2 H), 2.40 (m, 3 H). MS: Calcd. for $C_{22}H_{20}F_5O_4S$ (MH^+), m/z = 475.1; found 475.3. Retention time: 4.85 min.

Step 10

To a stirred solution of 6.01 g (12.7 mmol) of compound **9** in 125 mL of dichloromethane at – 78 °C was bubbled with O_3 until blue color sustained. It was bubbled with N_2 to remove excess O_3. To this solution were added 3.0 g (75 mmol) of sodium borohydride and 25 mL of methanol. The mixture was stirred at room temperature overnight. After addition of 0.7 g (2.67 mmol) of triphenylphosphine, the reaction was stirred for 1 day and diluted with 200 mL of water. It was extracted with three 150 mL portions of dichloromethane and the combined extracts were dried over sodium sulfate. The extracts were filtered, concentrated, and the residue was purified by chromatography eluting with a gradient of 5% to 50% of ethyl acetate in hexanes to give 5.5 g of compound **10**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.86 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.10 (m, 1 H), 6.40 (m, 1 H), 5.16 (d, J = 12.4 Hz, 1 H), 4.46 (d, J = 12.8 Hz, 1 H), 3.94 (m, 1 H), 3.80 (m, 2 H), 3.50(m, 1 H), 3.19 (t, J = 12 Hz, 1 H), 2.70 (d, J = 10 Hz, 1 H), 2.50 (d, J = 13.6 Hz, 1 H), 2.1 -2.40 (m, 3 H), 1.86 (m, 1 H). MS: Calcd. for $C_{21}H_{20}F_5O_5S$ (MH^+) m/z = 479.1; found 479.3. Retention time: 4.20 min.

Step 11

Compound **10** (2.1 g) was resolved on Chiral AS column eluting with 65% isopropanol in hexanes and 35 mL /min flow rate to give two enantiomers **10B** (0.95 g, retention time 33.5 -39.1 min, $[\alpha]_D^{20}$ +98.4°) and **10A** (0.98 g, retention time 41.3 – 49.3 min., $[\alpha]_D^{20}$ -91.4°).

Step 12

A solution of 0.98 g (2.05 mmol) of compound **10A**, 0.82 g (4.3 mmol) of *p*-toluenesulfonyl chloride and 0.6 g (6.0 mmol) of triethylamine in 20 mL of dichloromethane was stirred at room temperature for 18 h. It was quenched with 80 mL of saturated sodium bicarbonate, and extracted with three 80 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 2% to 45% of ethyl acetate in hexanes to give 1.33 g of compound **11**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.84 (d, J = 8.4 Hz, 2 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.14 (m, 1 H), 6.48 (m, 1 H), 5.11 (d, J = 10 Hz, 1 H), 4.32 (d, J = 12.4 Hz, 1 H), 4.16 (m, 2 H), 3.76 (m, 1 H), 3.27 (m, 1 H), 2.96 (t, J = 12 Hz, 1 H), 2.54 (m, 1 H), 2.46 (m, 1 H), 2.42 (s, 3 H), 2.20 (m, 2 H), 1.80 (m, 1 H). MS: Calcd. for $C_{28}H_{26}F_5O_7S_2$ (MH^+), m/z = 633.1; found 633.3. Retention time: 4.85 min.

Step 13

A mixture of 0.90 g (1.42 mmol) of compound **11** and 1.59 g (4.3 mmol) of tetrabutylammonium iodide in 50 mL of tetrahydrofuran was stirred at reflux for 3 h. After addition of 0.56 g (5.5 mmol) of sodium methanesulfinate, the mixture was stirred at reflux for 18 h and diluted with 80 mL of water. It was extracted with three 80 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 10% to 75% of ethyl acetate in hexanes to give 0.52 g of compound **12**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.86 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.12 (m, 1 H), 6.48 (m, 1 H), 5.18 (d, J = 10 Hz, 1 H), 4.48 (d, J = 12.8 Hz, 1 H), 3.88 (m, 1 H), 3.0-3.40 (m, 4 H), 2.98 (s, 3 H), 2.61 (d, J = 10 Hz, 1 H), 2.3 – 2.53 (m, 3 H), 2.05 (m, 1

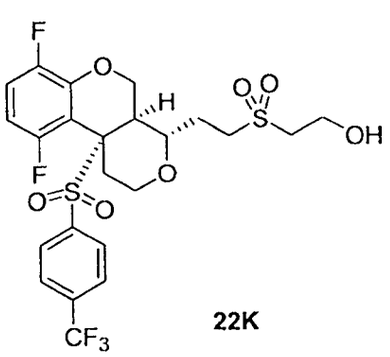
H). MS: Calcd. for $C_{22}H_{22}F_5O_6S_2$ (MH^+), m/z = 541.1; found 541.3. Retention time: 4.32 min.

Step 14

A mixture of 0.43 g (0.68 mmol) of compound **11**, 0.09 g (1.45 mmol) of 2-ethanethiol and 1 mL (1 mmol) of potassium hydroxide in ethanol in 50 mL of ethanol was stirred at 70 °C for 40 min. and concentrated. The residue was dissolved in 40 mL of water and extracted with two 50 mL portions of dichloromethane. The combined organic extracts were concentrated and the crude sulfide product was dissolved in 30 mL of dichloromethane. To this solution was added 0.42 g (1.7 mmol) of 70% 3-chloroperoxybenzoic acid. After stirring at room temperature for 1.5 h, it was diluted with 50 mL of dichloromethane, 40 mL of 10% sodium thiosulfate and 40 mL of saturated sodium bicarbonate. It was stirred for 8 min and separated. The organic layer was washed with 20 mL of 1N sodium hydroxide and concentrated. The residue was purified by chromatography eluting with a gradient of 10% to 60% of ethyl acetate in hexanes to give 0.35 g of compound **13**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.86 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.13 (m, 1 H), 6.48 (m, 1 H), 5.17 (d, J = 10 Hz, 1 H), 4.48 (d, J = 12.8 Hz, 1 H), 3.90 (m, 1 H), 3.36 (m, 1 H), 3.20 (m, 2 H), 2.95 (m, 3 H), 2.60 (d, J = 9.6 Hz, 1 H), 2.3 – 2.58 (m, 3 H), 2.05 (m, 1 H), 1.40 (t, J = 7.6 Hz, 3H). MS: Calcd. for $C_{23}H_{24}F_5O_6S_2$ (MH^+), m/z = 555.1; found 555.3. Retention time: 4.21 min.

The following compounds were prepared analogously:

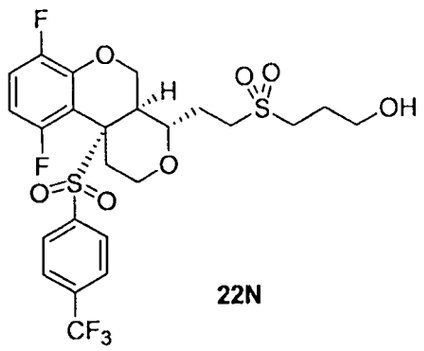
Compound **22K**



22K

Compound **22K** MS: Calcd. for $C_{23}H_{24}F_5O_7S_2$ $(M+1)^+$, m/z = 571.1; found 571.3. Retention time: 3.97 min.

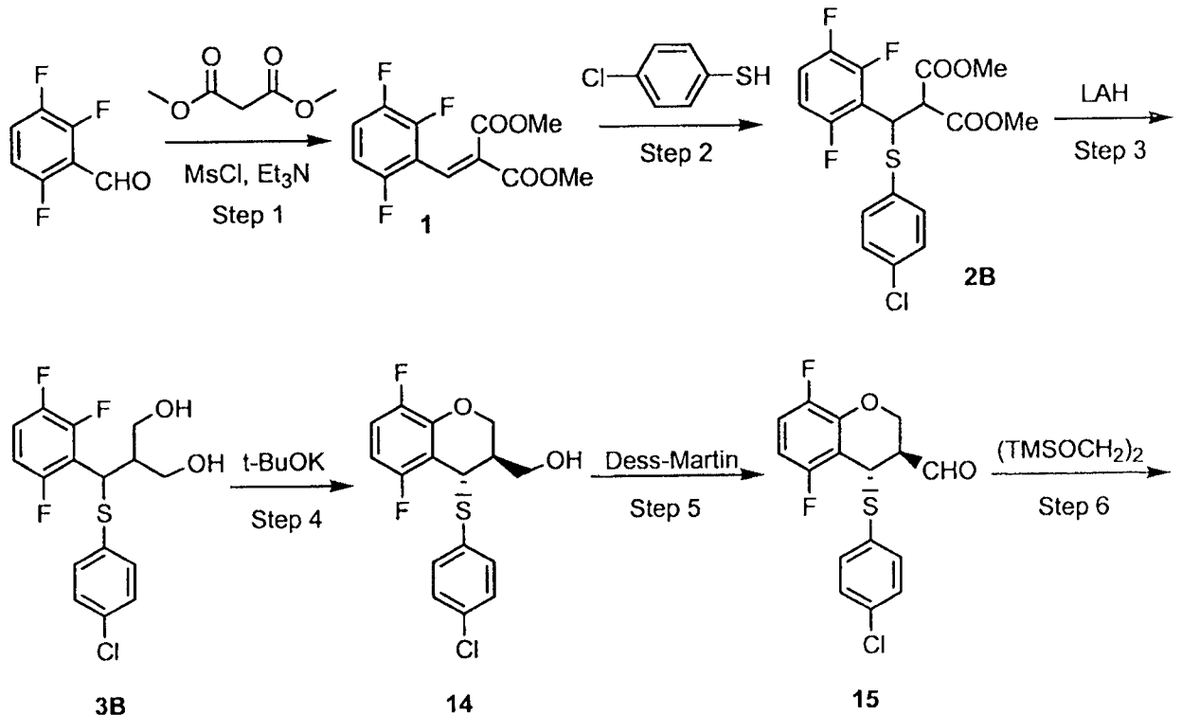
Compound **22N**



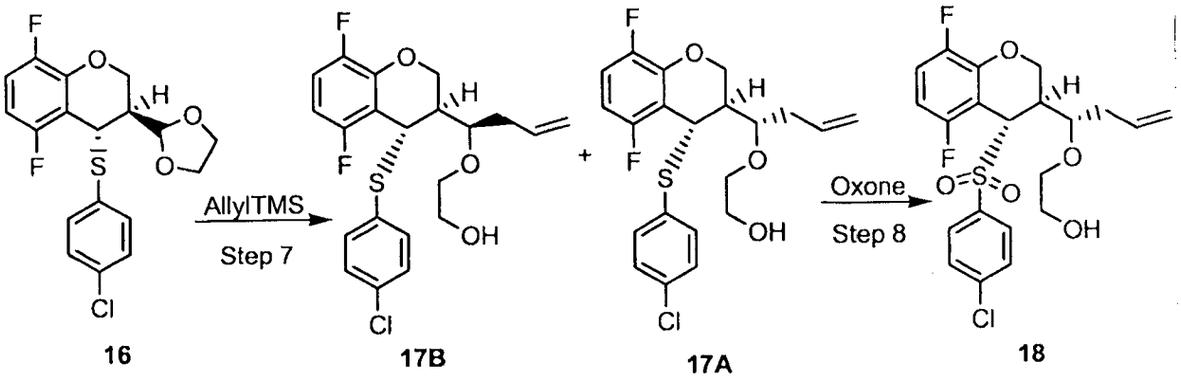
22N

Compound **22N** MS: Calcd. for $C_{24}H_{26}F_5O_7S_2$ $(M+1)^+$, m/z = 585.1; found 585.3. Retention time: 3.96 min.

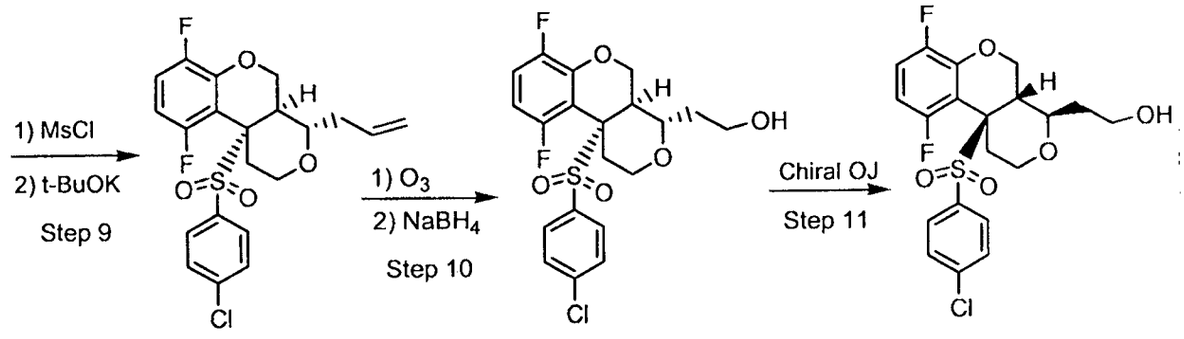
Scheme 2:



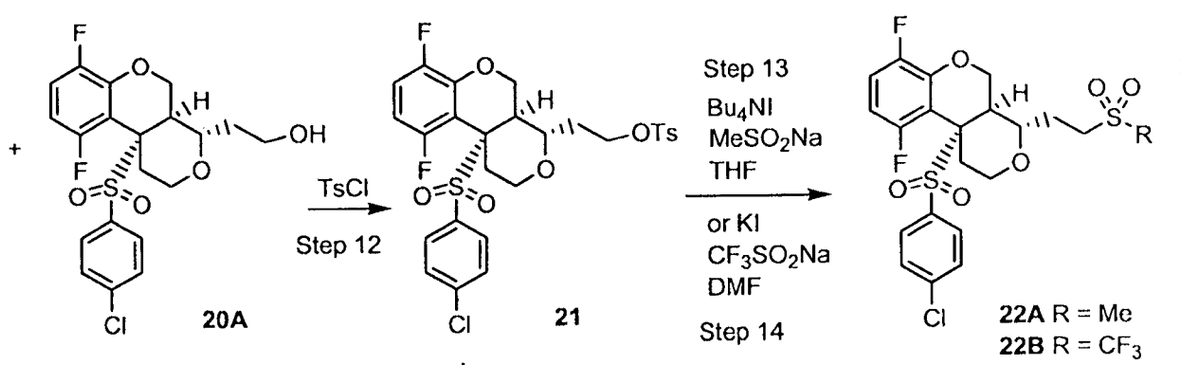
1 **2B** **3B** **14** **15**



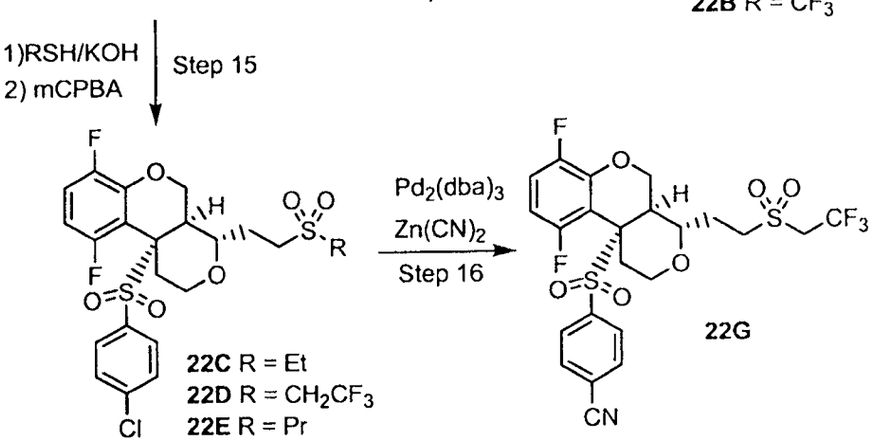
16 17B 17A 18



19 20 20B



20A 21



Step 1

To a stirred cold (0 °C) solution of 2,3,5-triflouro-benzaldehyde (400 g, 2.5 mol) and dimethylmalonate (280.5 g, 2.875 mol) in dichloromethane (7 L) was added triethylamine (455 g, 4.5 mol). The mixture was stirred at 0 to 5 °C for 40 min. Methanesulfonyl chloride (430 g, 3.75 mol) was added over 2.5 h maintaining reaction temperature below 6 °C. The reaction stirred for 30 min. at 0 °C. Additional triethylamine (126 g, 1.25 mol) was added. The reaction was stirred for 1hr at 0 °C. NMR indicated 91% product. Additional triethylamine (126 g, 1.25 mol) and methanesulfonyl chloride (86 g, 0.75 mol) were added. It was stirred at 0 °C for 1 h. The reaction was stirred with cold water (3 L) and separated. The aqueous layer was extracted with dichloromethane (2.5 L). The combined dichloromethane layers were washed with water (4 L), 1N HCl (2.5 L) and brine (2 L), dried over sodium sulfate and filtered. The filtrate was concentrated to give 771 g of the desired product **1** as a crude oil. ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.82 (s, 3H), 6.83 (m, 1H), 7.18 (m, 1H), 7.62 (s, 1H).

Step 2

To a solution of the above crude oil (771 g, 2.5 mol) and 4-chlorothiophenol (366 g, 2.53 mol) in THF (10 L) was added potassium carbonate (345 g, 2.5 mol) at room temperature. The mixture was stirred overnight. Additional 4-chlorothiophenol (37 g, 0.25 mol) and potassium carbonate (355 g, 0.25 mol) were added. The reaction was stirred 1h at room temperature. The reaction was stirred with ethyl acetate (4 L) and water (4 L) and separated. The aqueous layer was extracted with ethyl acetate (2 L). The combined organic layers were washed with brine (2 L), dried over sodium sulfate and filtered. The filtrate was concentrated to give 1152 g of the desired product **2B** as crude oil. ^{1}H NMR ($CDCl_3$): δ 3.58 (s, 3H), 3.80 (s, 3H), 4.35 (d, 2H), 5.08 (d, 2H), 6.75 (m, 1H), 7.00 (m, 1H), 7.22 (m, 4H)

Step 3

LAH pellets (100 g, 2.62 mol) were suspended and stirred in THF (5 L). To this cold suspension was added a solution of above crude oil **2B** (split into two batches, 560 g, 1.25 mol) in THF (800 ml) over 1h below 7 °C. The reaction was stirred at 0 °C for 3h. Water (200 ml) was dripped in slowly and the reaction was stirred for 30 min.

6N HCl (1 L) and hexane (4 L) were added and the reaction was stirred for 1h. The organic layer was decanted. Residual solid was stirred with hexane (3 L) and ethyl ether (2 L) and decanted. The combined organic layer was washed with water (2 x 3 L). The combined aqueous layers were extracted with hexane (2 L) and ethyl ether (1 L). The combined organic layers were washed with brine (1.5 L), dried over sodium sulfate and filtered. The filtrate was concentrated to give 430 g crude oil. This crude product was combined with the other batch prepared in the same scale. The combined crude products were purified by silica gel chromatography (5 Kg) eluting with a gradient from 10% to 50% of ethyl acetate in hexanes to give 505 g of the diol product **3B**. ^{1}H NMR ($CDCl_3$): δ 2.21 (m, 1H), 2.39 (m, 1H), 2.42 (m, 1H), 3.47 (m, 1H), 3.81 (m, 1H), 4.20 (m, 1H), 4.25 (m, 1H), 4.81 (d, 1H), 6.75 (m, 1H), 6.88 (m, 1H), 7.18 (m, 2H), 7.23 (m, 2H)

Step 4

To a solution of above diol **3B** (530 g, 1.19 mol) in THF was added 1M potassium tert-butoxide (1550 ml, 1.55 mol) in THF over 1h keeping the temperature below 8 °C. The reaction was stirred at room temperature for 105 min. Additional 1M potassium tert-butoxide (160 ml, 0.16 mol) was added. The reaction was stirred at room temperature for 1 h. Water (2 L) and hexane (4 L) were added to the reaction mixture in a ice bath and the layers were separated. The aqueous layer was extracted with ethyl acetate (1 L) and hexane (1 L). The combined organic layers were washed with brine (1 L), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (3 Kg) eluting with a gradient from 15% to 50% of ethyl acetate in hexanes to give 376 g of the desired bicyclic product **14**. ^{1}H NMR ($CDCl_3$): δ 2.22 (t, 1H), 3.45 (m, 1H), 3.63 (m, 1H), 4.40 (m, 1H), 4.48 (s, 1H), 4.60 (m, 1H), 6.58 (m, 1H), 6.95 (m, 1H), 7.29 (dd, 2H), 7.42 (dd, 2H).

Step 5

To a stirred solution of 9.1 g (26.5 mmol) of compound **14** in 200 mL of dichloromethane was added 14.6 g (34.5 mmol) of Dess-Martin periodinane. The mixture was stirred at room temperature for 2 h and diluted with 400 mL of dichloromethane. It was stirred with 400 mL of saturated sodium bicarbonate and 200 mL of 10% sodium thiosulfate solution and separated. This procedure was repeated

twice with 200 mL of saturated sodium bicarbonate and 200 mL of 10% sodium thiosulfate solution. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated to give 9.0 g of crude aldehyde **15**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 9.69 (s, 1 H), 7.45 (d, J = 8.6 Hz, 2 H), 7.34 (d, J = 8.8 Hz, 2 H), 6.95 (m, 1 H), 6.62 (m, 1 H), 4.91 (m, 2 H), 4.74 (dd, J = 12.5 Hz, 1 H), 2.83 (s, 1 H).

Step 6

To a stirred solution of 9.0 g (26.5 mmol) of compound **15** in 100 mL of dichloromethane were added 7.12 g (34.5 mmol) of 1,2-bis(trimethylsiloxy)ethane and 0.36 (1.6 mmol) of trimethylsilyl trifluoromethanesulfonate at -78 °C. After 30 min., it was warmed to room temperature and stirred for 30 min. It was diluted with 150 mL of dichloromethane and washed with three 200 mL portions of saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, concentrated, and the residue was purified by chromatography eluting with a gradient of 2% to 30% of ethyl acetate in hexanes to give 8.8 g of compound **16**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.42 (d, J = 9.0 Hz, 2 H), 7.31 (d, J = 8.6 Hz, 2 H), 6.95 (m, 1 H), 6.57 (m, 1 H), 4.74 (d, J = 7.4 Hz, 1 H), 4.70 (s, 1 H), 4.59 (s, 2 H), 3.80-3.92 (m, 4 H), 2.10 (m, 1 H). MS: Calcd. for $C_{18}H_{16}ClF_2O_3S(MH^+)$, m/z = 385.1; found 385.2. Retention time: 5.28 min.

Step 7

A solution of 2.9 (7.5 mmol) of compound **16**, 3.45 g (30.2 mmol) of allyltrimethylsilane and 4.3 g (30.2 mmol) of boron trifluoride diethyl etherate in 50 mL of dichloromethane was stirred at reflux for 1 day. It was quenched with 50 mL of water, and 50 mL of dichloromethane. The organic layer was washed with two 50 mL portions of saturated sodium bicarbonate, concentrated, and the residue was purified by chromatography eluting with a gradient of 1% to 30% of ethyl acetate in hexanes to give 1.1 g of compound **17A** and 0.63 g of **17B**. **17A**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.45 (d, J = 8.9 Hz, 2 H), 7.31 (d, J = 8.9 Hz, 2 H), 6.95 (m, 1 H), 6.60 (m, 1 H), 5.75 (m, 1 H), 5.10 (d, J = 5.7 Hz, 1 H), 5.07 (s, 1 H), 4.80(m, 1 H), 4.61 (d, J = 12.3 Hz, 1 H), 4.39 (d, J = 11.4 Hz, 1 H), 3.58 (m, 3 H), 3.24 (m, 2 H), 2.52 (m, 1 H), 2.34 (m, 1 H), 2.15 (m, 1 H), 1.60 (m, 1 H). MS: Calcd. for $C_{21}H_{22}ClF_2O_3S(MH^+)$, m/z = 427.1; found 427.1. Retention time: 5.04 min. **17B**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.48 (d, J = 8.1 Hz, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 6.97 (m, 1 H), 6.59 (m, 1 H), 5.50 (m, 1 H),

4.90 (d, J = 10.1 Hz, 1 H), 4.82(d, J = 16.9 Hz, 1 H), 4.63 (m, 2 H), 4.29 (s, 1 H), 3.64 (m, 3 H), 3.43 (m, 1 H), 3.20 (m, 1 H), 2.36 (m, 1 H), 1.90-2.18 (m, 3 H). MS: Calcd. for $C_{21}H_{22}ClF_2O_3S(MH^+)$, m/z = 427.1; found. Retention time: 4.32 min.

Step 8

A mixture of 3.6 g (8.4mmol) of compound **17A** and 20.7 g (33.6 mmol) of potassium peroxomonosulfate in 110 mL of acetone and 35 mL of water was stirred at 50 °C for 3 h. It was concentrated, and the residue was dissolved in 200 mL of water. It was extracted with three 150 mL portions of ethyl acetate. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 1% to 10% of ethyl acetate in dichloromethane to give 2.35 g of compound **18**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.75 (d, J = 8.6 Hz, 2 H), 7.52 (d, J = 8.1 Hz, 2 H), 7.05 (m, 1 H), 6.45 (m, 1 H), 5.83 (m, 1 H), 5.18 (d, J = 13.5 Hz, 2 H), 4.93 (m, 2 H), 4.40 (d, J = 12.4 Hz, 1 H), 3.55 (m, 3 H), 3.20 (m, 2 H), 2.93 (m, 1 H), 2.54 (m, 1 H), 2.38(m, 1 H), 1.64 (m, 1 H). MS: Calcd. for $C_{21}H_{22}ClF_2O_5S(MH^+)$, m/z = 459.1; found 459.3. Retention time: 4.39 min.

Step 9

To a solution of 2.33 g (5.1 mmol) of compound **18** in 100 mL of dichloromethane were added 0.7 g (7.0 mmol) of triethylamine and 0.87 g (7.6 mmol) of methanesulfonyl chloride. The mixture was stirred at room temperature for 1.5 h. It was diluted with 100 mL of dichloromethane and washed with two 80 mL portions of water, and 80 mL of saturated sodium bicarbonate. The organic layer was concentrated and the residue was dissolved in 100 mL of tetrahydrofuran. To this solution was added 12.7 mL (12.7 mmol) of 1 N potassium tert-butoxide in tetrahydrofuran. The mixture was stirred at room temperature for 30 min., quenched with 50 mL of water, and extracted with 250 mL portions of dichloromethane. The organic extract was concentrated and the residue was purified by chromatography eluting with a gradient of 1% to 30% of ethyl acetate in hexanes to give 1.59 g of compound **19**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 8.0 Hz, 2 H), 7.50 (d, J = 7.3 Hz, 2 H), 7.08 (m, 1 H), 6.46 (m, 1 H), 5.85 (m, 1 H), 5.15 (m, 3 H), 4.45 (d, J = 12.4 Hz, 1 H), 3.91 (m, 1 H), 3.37 (m, 1 H), 3.17 (t, J = 11.6 Hz, 1 H), 2.61 (m, 2 H), 2.25-

2.54 (m, 3 H). MS: Calcd. for $C_{21}H_{20}ClF_2O_4S(MH^+)$, m/z = 441.1; found 441.1. Retention time: 4.20 min.

Step 10

To a stirred solution of 5.0 g (11.4 mmol) of compound **19** in 150 mL of dichloromethane at – 78 °C was bubbled with O_3 until blue color sustained. It was bubbled with N_2 until the solution becomes colorless. To this solution were added 1.3 g (34.2 mmol) of sodium borohydride and 15 mL of methanol. The mixture was stirred at room temperature overnight. After addition of 3.0 g (11.4 mmol) of triphenylphosphine , it was stirred for 1 h and diluted with 200 mL of water. The mixture was extracted with three 150 mL portions of dichloromethane, and the combined extracts were dried over sodium sulfate. The combined organic extracts were filtered, concentrated, and the residue was purified by chromatography eluting with a gradient of 5% to 60% of ethyl acetate in hexanes to give 4.6 g of compound **20**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.64 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.9 Hz, 2 H), 7.12 (m, 1 H), 6.45 (m, 1 H), 5.16 (d, J = 10.0 Hz, 1 H), 4.43 (d, J = 13.5 Hz, 1 H), 3.92 (m, 1 H), 3.79 (m, 2 H), 3.51 (m, 1 H), 3.20 (t, J = 11.6 Hz, 1 H), 2.65 (d, J = 11.0 Hz, 1 H), 2.53 (d, J = 12.9 Hz, 1 H), 2.34 (m, 2 H), 2.15 (m, 1 H), 1.85 (m, 1 H). MS: Calcd. for $C_{20}H_{20}ClF_2O_5S(MH^+)$ m/z = 445.1; found 445.2 Retention time: 3.40 min.

Step 11

Compound **20** (1.8 g) was resolved on Chiral OJ column eluting with 70% isopropanol in hexanes and 28 mL/min flow rate to give two enantiomers **20A** (0.67 g, retention time 41 min, $[\alpha]_D^{20}$ -136.6°) and **20B** (0.70 g, retention time 50 min., $[\alpha]_D^{20}$ +132.5°).

Step 12

A solution of 1.5 g (3.37 mmol) of compound **20A**, 1.27 g (6.7 mmol) of p-toluenesulfonyl chloride and 0.68 g (6.7 mmol) of triethylamine in 30 mL of dichloromethane was stirred at room temperature for 65 h. It was quenched with 80 mL of saturated sodium bicarbonate, and extracted with three 100 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue

was purified by chromatography eluting with a gradient of 2% to 40% of ethyl acetate in hexanes to give 1.95 g of compound **21**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.74 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.12 (m, 1 H), 6.48 (m, 1 H), 5.10 (d, J = 12.8 Hz, 1 H), 4.29 (d, J = 12.8 Hz, 1 H), 4.19 (m, 2 H), 3.76 (m, 1 H), 3.24 (m, 1 H), 2.96 (t, J = 11.6 Hz, 1 H), 2.51 (m, 2 H), 2.42 (s, 3 H), 2.20 (m, 2 H), 1.80 (m, 1 H). MS: Calcd. for $C_{27}H_{26}ClF_2O_7S_2(MH^+)$, m/z = 599.1; found 599.3. Retention time: 4.82 min.

Step 13

A mixture of 3.15 g (5.26 mmol) of compound **21** and 5.83 g (15.8 mmol) of tetrabutylammonium iodide in 80 mL of tetrahydrofuran was stirred at reflux for 2 h. After addition of 2.15 g (21.0 mmol) of sodium methanesulfinate, the mixture was stirred at reflux overnight and diluted with 100 mL of water. It was extracted with three 100 mL portions of ethyl acetate. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 5% to 75% of ethyl acetate in hexanes to give 2.44 g of compound **22A**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.64 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 2 H), 7.10 (m, 1 H), 6.48 (m, 1 H), 5.18 (d, J = 13.2 Hz, 1 H), 4.45 (d, J = 12.4 Hz, 1 H), 3.90 (m, 1 H), 3.0-3.40 (m, 4 H), 2.92 (s, 3 H), 2.2 – 2.60 (m, 4 H), 2.05 (m, 1 H). MS: Calcd. for $C_{21}H_{22}ClF_2O_6S_2$ (MH^+), m/z = 507.1.; found 507.3. Retention time: 4.22 min.

Starting with racemic alcohol **20**, and proceding through Scheme 2, steps 12 and 13 provided racemic compound **22A-rac:** MS: Calcd. for $C_{21}H_{22}ClF_2O_6S_2$ (MH^+), m/z = 507.0; found 507.3. Retention time: 4.20 min.

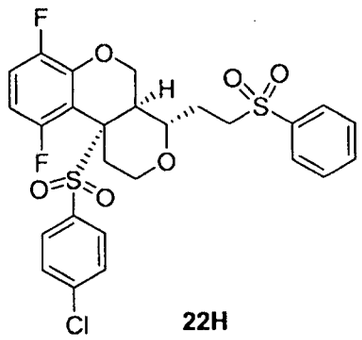
or Step 14

A mixture of 0.12 g (0.2 mmol) of compound **21**, 0.10 g (0.6 mmol) of potassium iodide and 0.10 g (0.6 mmol) of sodium trifluoromethylsulfinate in 6 mL of DMF was stirred at 120 °C for 6 h. It was diluted with 25 mL of water and extracted with three 40 mL portions of dichloromethane. The combined organic extracts were concentrated and the residue was purified by preparative TLC eluting with 30% of ethyl acetate in hexanes to give 0.045 g of compound **22B**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 2 H), 7.12 (m, 1 H), 6.48 (m, 1 H), 5.19 (d, J = 12.8 Hz, 1 H), 4.42 (d, J = 12.4 Hz, 1 H), 3.92 (m, 1 H), 3.1-3.54 (m, 4 H), 2.50

(m, 2 H), 2.30 (m, 2 H), 2.10 (m, 1 H). MS: Calcd. for $C_{21}H_{19}ClF_5O_6S_2$ (MH^+), m/z = 561.0; found 561.3. Retention time: 4.80 min.

The following compounds were prepared analogously:

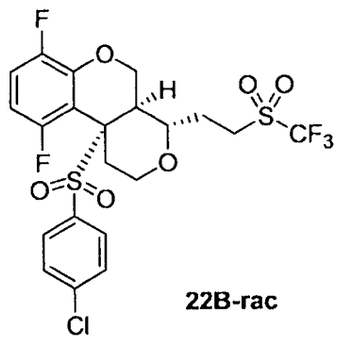
Compound **22H**



22H

Compound **22H**: MS: Calcd. for $C_{26}H_{24}ClF_2O_6S_2(MH^+)$, m/z = 569.1; found 569.3. Retention time: 4.71 min.

Compound **22B-rac**

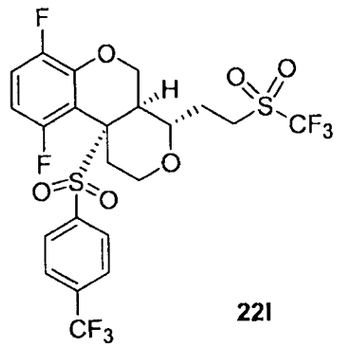


22B-rac

Starting with racemic alcohol **20**, and proceding through Scheme 2, steps 12 and 14 provided racemic compound **22B-rac:** MS: Calcd. for $C_{21}H_{19}ClF_5O_6S_2$ (MH^+), m/z = 561.0; found 561.3. Retention time: 4.89 min.

The following compounds were prepared analogously starting from compound **11** (Scheme 1) substituting Bu_4NI for KI:

Compound **22I**



22I

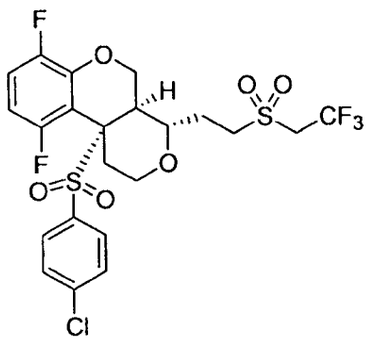
Compound **22I**: MS: Calcd. for $C_{22}H_{19}ClF_8O_6S_2(M+H)^+$, m/z = 595.0 found 595.3. Retention time: 5.06 min.

Step 15

A mixture of 0.2 g (0.33 mmol) of compound **21**, 0.04 g (0.67 mmol) of 2-ethanethiol 0.5 mL (1 mmol) of potassium hydroxide in ethanol in 5.5 mL of ethanol was stirred at 70 °C for 25 min. and concentrated The residue was dissolved in 15 mL of water and extracted with 30 mL of dichloromethane. The organic extract was concentrated and the crude sulfide product was dissolved in 10 mL of dichloromethane. To this solution was added 0.17 g (1.0 mmol) of 70% 3-chloroperoxybenzoic acid. After stirring at room temperature for 1 h, it was diluted with 30 mL of dichloromethane. It was washed with three 20 mL portions of saturated sodium bicarbonate. The organic layer was concentrated, the residue was purified by chromatography eluting with a gradient of 5% to 80% of ethyl acetate in hexanes to give 0.14 g of compound **22C**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 7.8 Hz, 2 H), 7.51 (d, J = 8.9 Hz, 2 H), 7.13 (m, 1 H), 6.47 (m, 1 H), 5.16 (d, J = 15.3 Hz, 1 H), 4.45 (d, J = 12.2 Hz, 1 H), 3.89 (d, J = 10.2, 1 H), 3.36 (m, 1 H), 3.20 (m, 2 H), 2.96 (m, 3 H), 2.5 (m, 2 H), 2.40 (m, 1 H), 2.29 (m, 1 H), 2.02 (m, 1 H), 1.40 (t, J = 7.4 Hz, 3 H). MS: Calcd. for $C_{22}H_{24}ClF_2O_6S_2(MH^+)$, m/z = 521.1; found 521.3 Retention time: 4.35 min.

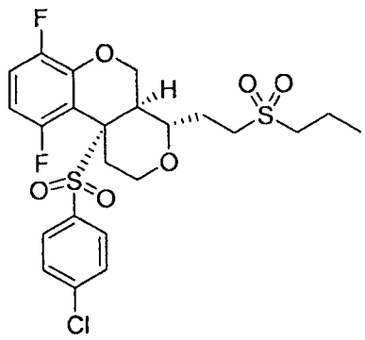
The following compounds were prepared analogously:

Compound **22D**



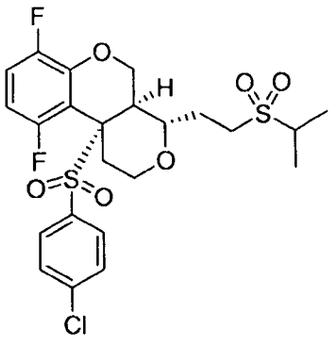
Compound **22D**: 7.62 (d, J = 8.0 Hz, 2 H), 7.54 (d, J = 8.4 Hz, 2 H), 7.13 (m, 1 H), 6.45 (m, 1 H), 5.19 (d, J = 15 Hz, 1 H), 4.42 (d, J = 12 Hz, 1 H), 3.92 (d, J = 10 Hz, 1 H), 3.79 (m, 2 H), 3.40 (m, 2 H), 3.19 (m, 2 H), 2.56 (m, 3 H), 2.34 (m, 1 H), 2.10 (m, 1 H). MS: Calcd. for $C_{22}H_{21}ClF_5O_6S_2(MH^+)$, m/z = 575.0; found 575.3. Retention time: 4.76 min.

Compound **22E**



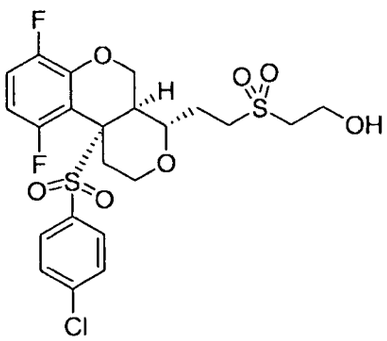
Compound **22E**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.62 (d, J = 8.0 Hz, 2 H), 7.52 (d, J = 8.4 Hz, 2 H), 7.10 (m, 1 H), 6.44 (m, 1 H), 5.18 (d, J = 15 Hz, 1 H), 4.42 (d, J = 12 Hz, 1 H), 3.88 (m, 1 H), 3.37 (m, 1 H), 3.18 (m, 2 H), 2.95 (m, 3 H), 2.55 (m, 1 H), 2.42 (m, 1 H), 2.28 (m, 1 H), 2.02 (m, 1 H), 1.88 (m, 2 H), 1.08 (t, J = 7.4 Hz, 3 H). MS: Calcd. for $C_{23}H_{26}ClF_2O_6S_2(MH^+)$, m/z = 535.1; found 535.3. Retention time: 4.53 min.

Compound **22F**



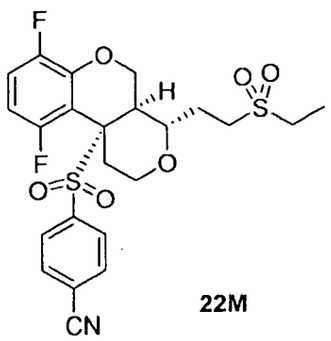
Compound **22F**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.64 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 8.6 Hz, 2 H), 7.13 (m, 1 H), 6.48 (m, 1 H), 5.17 (d, J = 15.3 Hz, 1 H), 4.47 (d, J = 8.5 Hz, 1 H), 3.89 (d, J = 10.2 Hz, 1 H), 3.36 (m, 1 H), 3.17 (m, 3 H), 2.92 (m, 1 H), 2.56 (d, J = 12.6 Hz, 2 H), 2.46 (m, 1 H), 2.29 (m, 1 H), 2.01 (m, 1 H), 1.40 (t, J = 8.0 Hz, 6H). MS: Calcd. for $C_{23}H_{26}ClF_2O_6S_2(MH^+)$, m/z = 535.1; found 535.3. Retention time: 4.23 min.

Compound **22L**



Compound **22L**: MS: Calcd. for $C_{22}H_{24}ClF_2O_7S_2(M+1)^+$, m/z = 537.1, found 537.3. Retention time: 3.86 min.

Compound **22M**



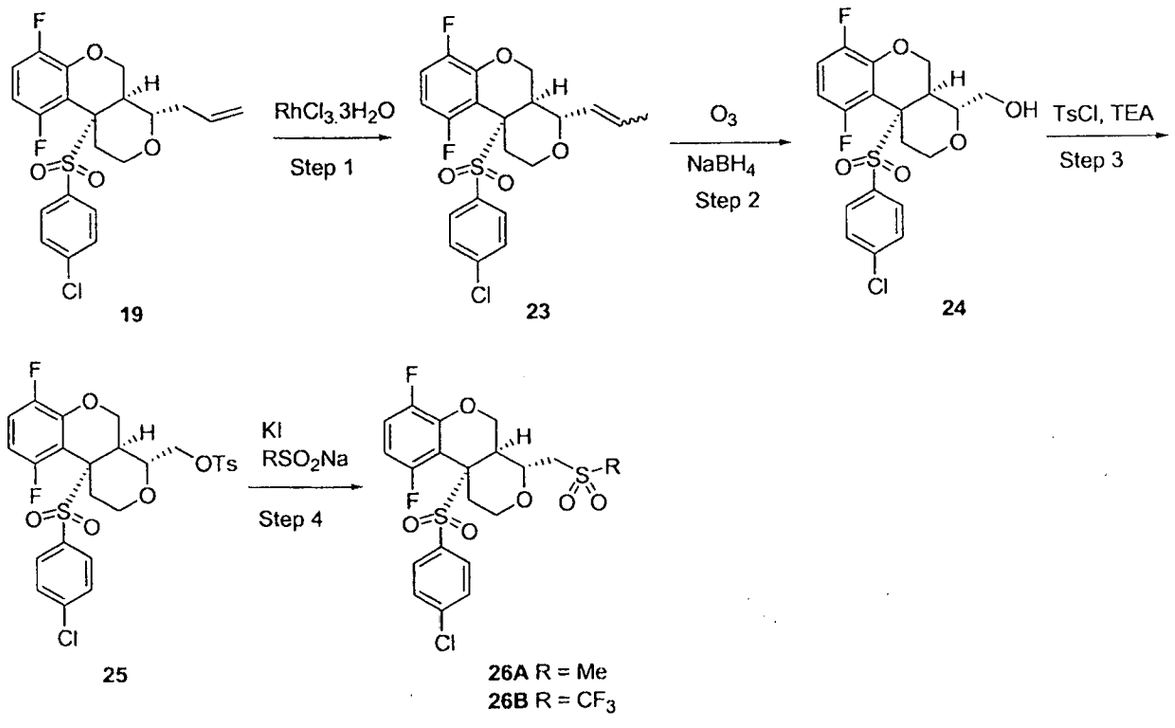
22M

Compound **22M** was prepared analogously starting with tosylate **30** (see Scheme 6): MS: Calcd. for $C_{23}H_{24}F_2NO_6S_2(M+1)^+$, m/z = 512.1, found 512.3. Retention time: 3.73 min.

Step 16

A mixture of 0.049 g (0.085 mmol) of compound **22D**, 0.007 g (0.009 mmol) of bis(dibenzylideneacetone) palladium ($Pd_2(dba)_3$), 0.008 g (0.013 mmol) of 1,1'-bis(diphenylphosphino)ferrocene (dppf), 0.010 g (0.085 mmol) of zinc cyanide and 0.002 g (0.03 mmol) of zinc power in 3 mL of N,N-dimethylacetamide in a sealed tube was heated at 150 °C for 1 h in microwave (Biotage). It was diluted with 20 mL of water, and extracted with 20 mL of dichloromethane. The organic extract was concentrated, the residue was purified by preparative TLC eluting with 30% ethyl acetate in hexanes to give 0.006 g of compound **22G**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.82 (s, 4 H), 7.12 (m, 1 H), 6.46 (m, 1 H), 5.16 (d, J = 10 Hz, 1 H), 4.46 (d, J = 12 Hz, 1 H), 3.92 (m, 1 H), 3.80 (m, 3 H), 3.40 (m, 2 H), 3.16 (m, 2 H), 2.63 (m, 1 H), 2.46 (m, 1 H), 2.32 (m, 1 H), 2.08 (m, 1 H). MS: Calcd. for $C_{23}H_{21}F_5NO_6S_2(MH^+)$, m/z = 566.1; found 566.3 Retention time: 4.66 min.

Scheme 3:



Step 1

A mixture of 2.2 g (5 mmol) of compound **19** and 0.052 (0.25 mmol) of $RhCl_3.3H_2O$ in 80 mL of ethanol was stirred at reflux for 3 h, then concentrated. The residue was purified by chromatography eluting with 10 - 40 % ethyl acetate in hexanes to give 2.1 g (95%) of olefin **23**. MS: Calcd for $C_{21}H_{20}ClF_2O_4S$ $(M+1)^+$ m/z = 441.1, found 441.2, Rt = 4.94 min.

Step 2

The ozonolysis of the olefin and subsequent reduction was accomplished using a procedure analogous to that shown in Step 10 of Scheme 2 to give alcohol **24**: MS: Calcd for $C_{19}H_{18}ClF_2O_5S$ $(M+1)^+$ m/z = 431.1, found 431.2, Rt = 3.93 min.

Step 3

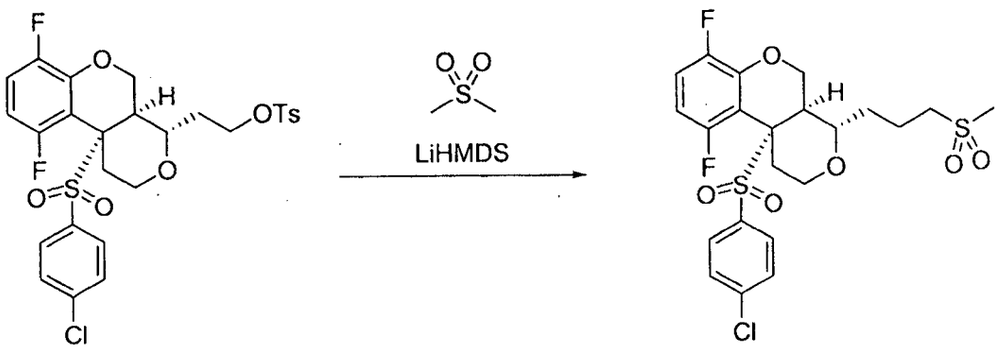
The tosylation of the alcohol was accomplished using a procedure analogous to that shown in Step 12 of Scheme 2 to give tosylate **25**: MS: Calcd for $C_{26}H_{24}ClF_2O_7S_2$ $(M+1)^+$ m/z = 585.1, found 585.3, Rt = 4.93 min.

Step 4

The displacement of the tosylate was accomplished using a procedure analogous to that shown in Step 13 of Scheme 2 using sodium methylsulfinate to give sulfone **26A** (R = Me): MS: Calcd for $C_{20}H_{20}ClF_2O_6S_2$ $(M+1)^+$ m/z = 493.0, found 493.3, Rt = 4.14 min.

The displacement of the tosylate was also accomplished using a procedure analogous to that shown in Step 14 of Scheme 2 using sodium trifluoromethylsulfinate to give sulfone **26B** (R = CF_3): MS: Calcd for $C_{20}H_{17}ClF_5O_6S_2$ $(M+1)^+$ m/z = 547.1, found 371.2 $(M\text{-}ClPhSO_2\text{-})^+$, Rt = 4.90 min.

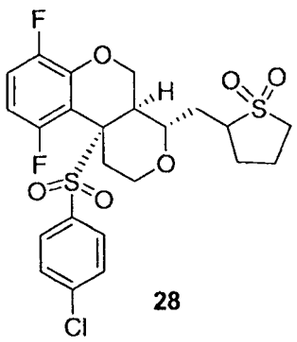
Scheme 4:



(±)-**21** **27**

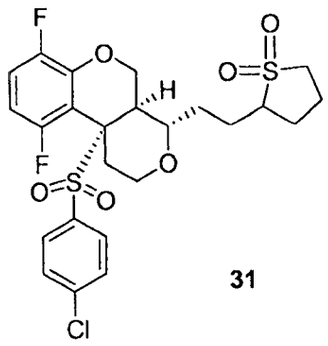
Step 1

To a solution of dimethylsulfone in 20 mL of THF was added LiHMDS in THF (1.0M) at -78 °C. After 30 min.,a solution of 0.12 g (0.2 mmol) of compound **21** in 5 mL of THF was added. The mixture was warmed to room temperature overnight. It was diluted with 50 mL of 1N HCl, extracted with three 50 mL portions of methylene chloride. the combined organic extracts were concentrated, the residue was purified by preparative TLC eluting with 50% ethyl acetate in hexanes to give 0.032 g of compound **27**. MS: Calcd for $C_{22}H_{23}ClF_2O_6S_2$ $(M+1)^+$ m/z = 521.1, found 521.3, Rt = 4.03 min.



28

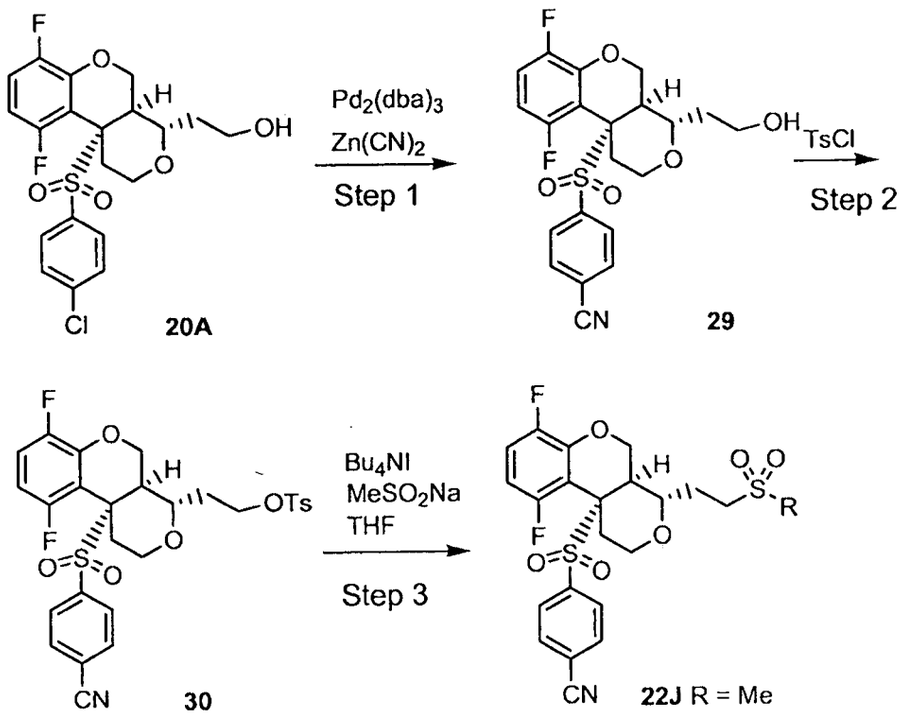
Using a similar procedure as Scheme 4, step 1 starting with compound **25** and sulfolane provided compound **28**: MS: Calcd for $C_{23}H_{24}ClF_2O_6S_2$ $(M+1)^+$ m/z = 533.1, found 533.3, Rt = 4.36 min.



31

Using a similar procedure as Scheme 4, step 1 starting with compound **30** and sulfolane provided compound **31**: MS: Calcd for $C_{24}H_{26}ClF_2O_6S_2$ $(M+1)^+$ m/z = 547.1, found 547.3, Rt = 4.23 min.

Scheme 5:



Step 1

Chlorophenylsulfone **20A** was converted to the cyanophenyl analog **29** using an anologous procedure to that used in Scheme 2, Step 16. MS: Calcd for $C_{21}H_{20}F_2NO_5S$ $(M+1)^+$ m/z = 436.1, found 436.3, Rt = 3.36 min.

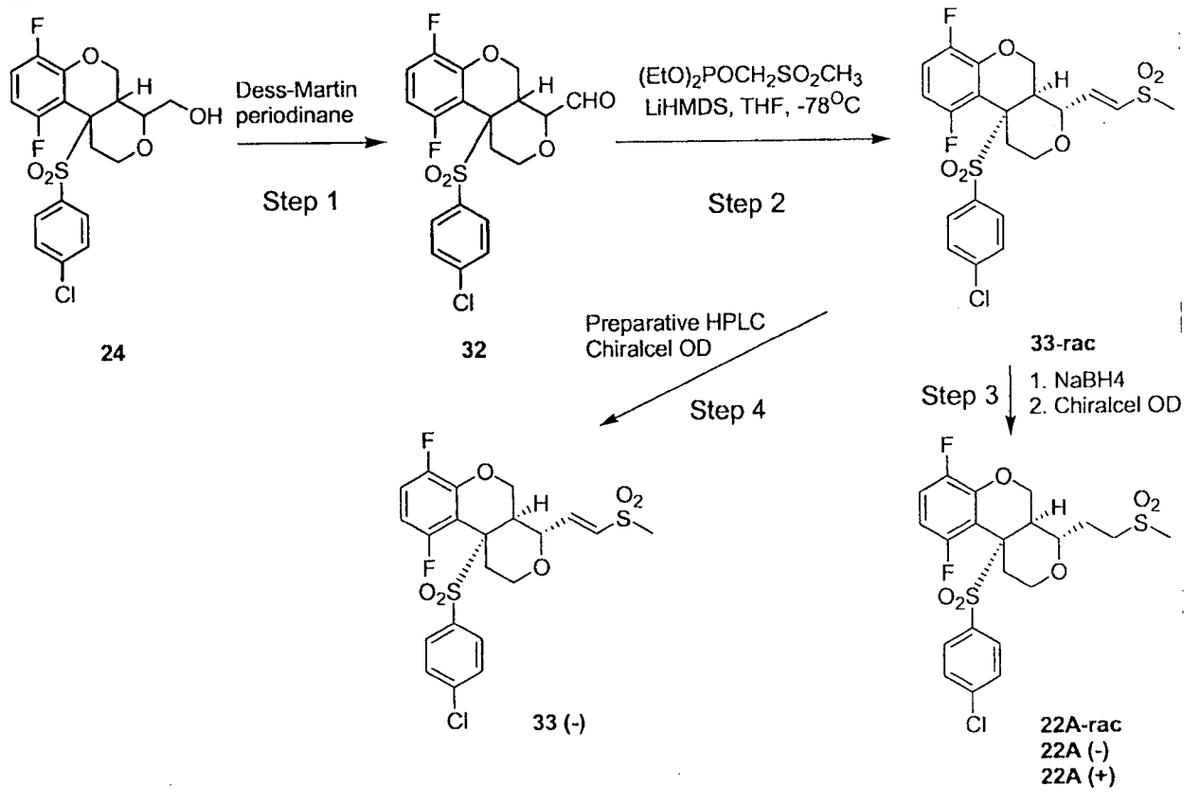
Step 2

Alcohol **29** was converted to the tosylate **30** using an anologous procedure to that used in Scheme 2, Step 12. MS: Calcd for $C_{28}H_{26}F_2NO_7S_2$ $(M+1)^+$ m/z = 590.1, found 590.3, Rt = 4.43 min.

Step 3

Tosylate **30** was converted to the methyl sulfone **22J** using an anologous procedure to that used in Scheme 2, Step 13. MS: Calcd for $C_{22}H_{22}ClF_2NO_6S_2$ $(M+1)^+$ m/z = 498.1, found 498.3, Rt = 3.85 min.

Scheme 6:



Step 1

The Dess-Martin periodinane (0.895 g, 2.11 mmol) was added in portions to a stirring solution of the hydroxymethyl compound **24** (0.700 g, 1.62 mmol) in dichloromethane (35 mL) at room temperature. The reaction was complete after 2.5 hrs (tlc: 30% EtOAc/hexane). The reaction was diluted with 100 mL of dichloromethane partitioned with 10% sodium thiosulfate/sat. sodium bicarbonate (3

80 mL portions of a 1:1 mixture). The dichloromethane was dried over anhydrous sodium sulfate and was concentrated in vacuo to yield compound **32** (0.680 g, 97%). MS: Calcd for $C_{19}H_{16}ClF_2O_5S$ $(M+1)^+$ m/z = 429.0, found 429, Rt = 4.10 min.

Step 2

To a solution of 34.5 g (150 mmol) of diethyl methylsulfonomethyl-phosphonate [ref:G. H. Posner and D. J. Brunelle *J. Org. Chem.* **1972**, *37*, 3547] in 500 mL of THF was added 145 mL (145 mmol) of LiHMDS in THF at -78 °C. After 40 min., a solution of 31.5 g (73.5 mmol) of the aldehyde **32** in 60 mL of THF was added, and the mixture was stirred at -78 °C for 5h. It was quenched with 200 mL of saturated aqueous NH_4Cl and 500 mL of water, and extracted with four 500 mL portions of ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give crude vinyl sulfone **33-rac**. MS: Calcd for $C_{21}H_{20}ClF_2O_6S_2$ $(M+1)^+$ m/z = 505.0, found 505, Rt = 4.20 min.

Step 3

To a solution of the above racemic intermediate **33-rac** in 400 mL of THF were added 5.0 g (132 mmol) of $NaBH_4$ and 100 mL of ethanol. The mixture was stirred at room temperature for 4 h. It was quenched with 200 mL of water, and the organic solvents were evaporated. To this residue were added 300 mL of water and 50 mL of 1N HCl. It was then extracted with four 500 mL portions of ethyl acetate. The organic extracts were dried over $NaSO_4$, filtered, and concentrated. The residue was stirred with 300 mL of ethyl acetate and filtered to give 17.1 g of compound **22A-rac**. MS: Calcd for $C_{21}H_{22}ClF_2O_6S_2$ $(M+1)^+$ m/z = 507.1, found 507.3, Rt = 4.23 min.

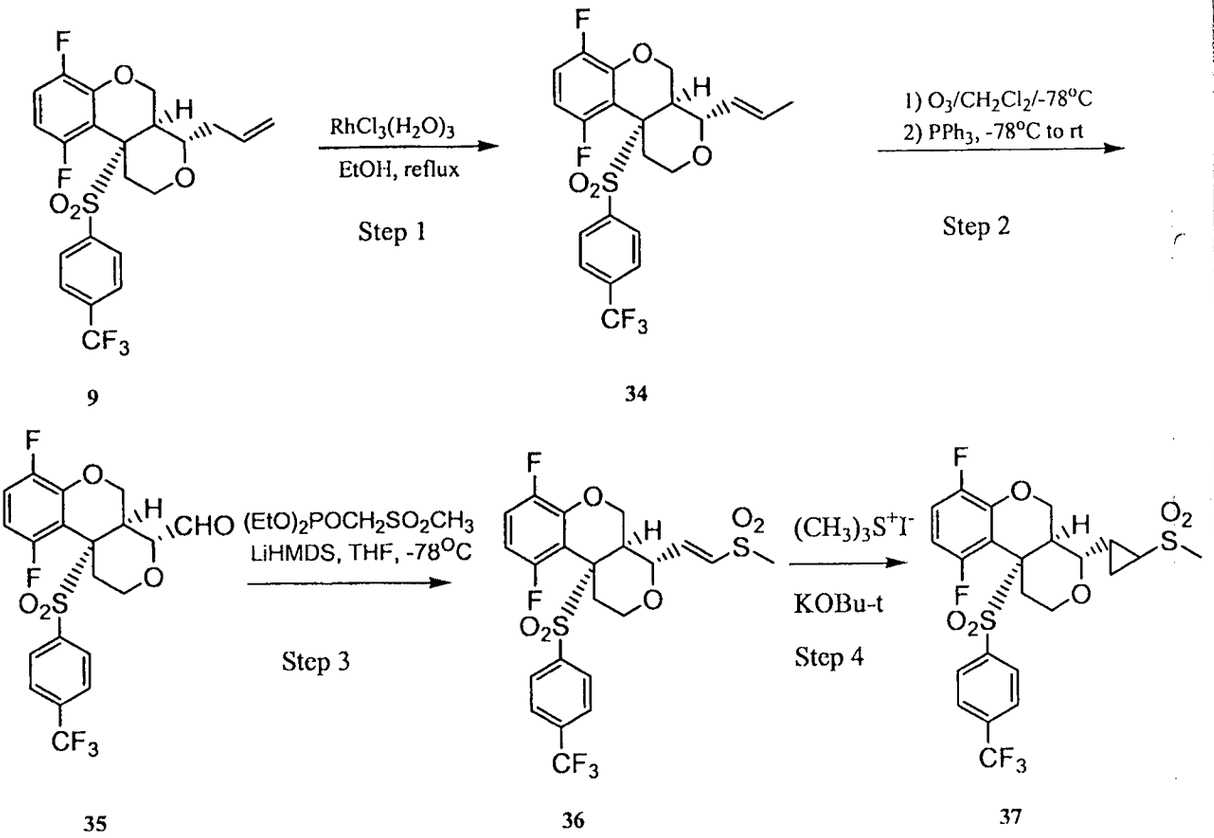
Racemate **22A-rac** could be resolved on a Chiralcel OD column eluting with 75% isopropyl alcohol in hexanes to give **22A (-)** (peak 1, retention time = 40.2 min, $[\alpha]_D^{20}$ -144.2°, conc = 1.000 M in dichloromethane) and **22A (+)** (peak 2, retention time = 47.4 min, $[\alpha]_D^{20}$ -139.3°, conc = 1.000 M in dichloromethane).

Step 4

The enantiomers of the vinyl sulfone were separated by preparative HPLC on a Chiralcel OD column eluting with 60% isopropanol/hexane at 40 mL/min to give **33 (-)**

(0.139 g). The desired isomer had a retention time of 56.6 min. MS: Calcd for $C_{21}H_{20}ClF_2O_6S_2$ $(M+1)^+$ m/z = 505.0, found 505.3, Rt = 4.33 min.

Scheme 7:



9 34 35 36 37

Step 1

The allyl derivative **9** was isomerized using $RhCl_3$ as per Scheme 3, step 1 to give the olefin **34**. Thus, a stirring mixture of the **9** (0.413 g, 0.87 mmol) and rhodium (III) chloride hydrate (0.020 g, 0.096 mmol) in 10 mL of ethanol was heated to reflux for 1 hr (tlc: 20% EtOAc/hexane). The EtOH was evaporated under vacuum to give 0.442 g crude product. This material was purified by flash column chromatography on silica gel, eluting with a solvent gradient from1% EtOAc/hexane to 40% EtOAc/hexane over 30 min to yield **34** (0.343 g, 85%). MS: Calcd for $C_{22}H_{20}F_5O_4S$ $(M+1)^+$m/z = 475.1, found 475.3, Rt = 5.05 min.

Step 2

A stirring solution of **34** (0.322 g, 0.678 mmol) in 50 mL of dichloromethane was cooled to -78 °C. A stream of O_3 was bubbled through the solution until a blue color of excess O_3 persisted. The mixture was stirred for an additional 5-10 min. A stream of N_2 was bubbled through the solution until it became colorless. Triphenylphosphine (0.268 g, 1.02 mmol) was added in one portion, and the reaction was stirred at -78 °C for 10 min and at room temperature for 16 hrs (tlc: 20% EtOAc/hexane). The solvent was evaporated to give an 0.730 g of an oil. The oil was purified by flash column chromatography on silica gel, eluting with a solvent gradient from 1% EtOAc/hexane to 40% EtOAc/hexane over 20 min to give aldehyde **35** (0.277 g, 88%). MS: Calcd for $C_{20}H_{16}F_5O_5S$ $(M+1)^+$m/z = 463.1, found 463.3, Rt = 4.05 min.

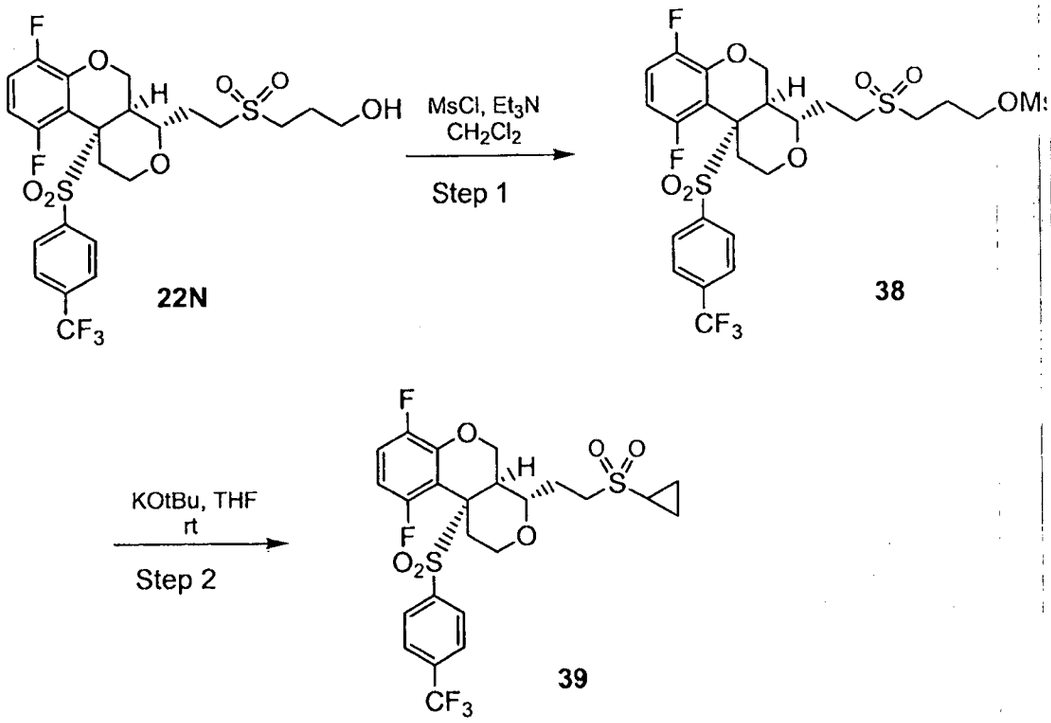
Step 3

The aldehyde **35** was converted to the vinyl sulfone **36** using an analogous procedure as that described in Scheme 6, step 2 (74% yield). MS: Calcd for $C_{22}H_{20}F_5O_6S_2$ $(M+1)^+$ m/z = 539.1, found 539.3, Rt = 4.36 min.

Step 4

To a stirring mixture of the KOtBu (0.014 g, 0.121 mmol) in 1.5 mL of DMSO was added the trimethyl sulfonium iodide (0.027 g, 0.121 mmol). The solution was stirred at room temperature under argon for 1 hr. A solution of the **36** (0.050 g, 0.093 mmol) in0.75 mL of DMSO was added dropwise. Stirring was continued overnight at room temperature (tlc: 40% EtOAc/hexane). The reaction was added to stirring water (40-50 mL) and was extracted with 2 40-mL portions of EtOAc. The combined EtOAc layers were washed with 20 mL of water and 20 mL of brine. The EtOAc layer was dried over anhydrous sodium sulfate and evaporated to give 0.050 g of the desired product. The product was purified by flash column chromatography on silica gel, eluting with a solvent gradient from 10% EtOAc/hexane to 80% EtOAc/hexane over 30 min to give 0.037 g of cyclopropylsulfone **37** (73%). MS: Calcd for $C_{23}H_{22}F_5O_6S_2$ $(M+1)^+$ m/z = 553.1, found 553.3, Rt = 4.28 min

Scheme 8:



Step 1

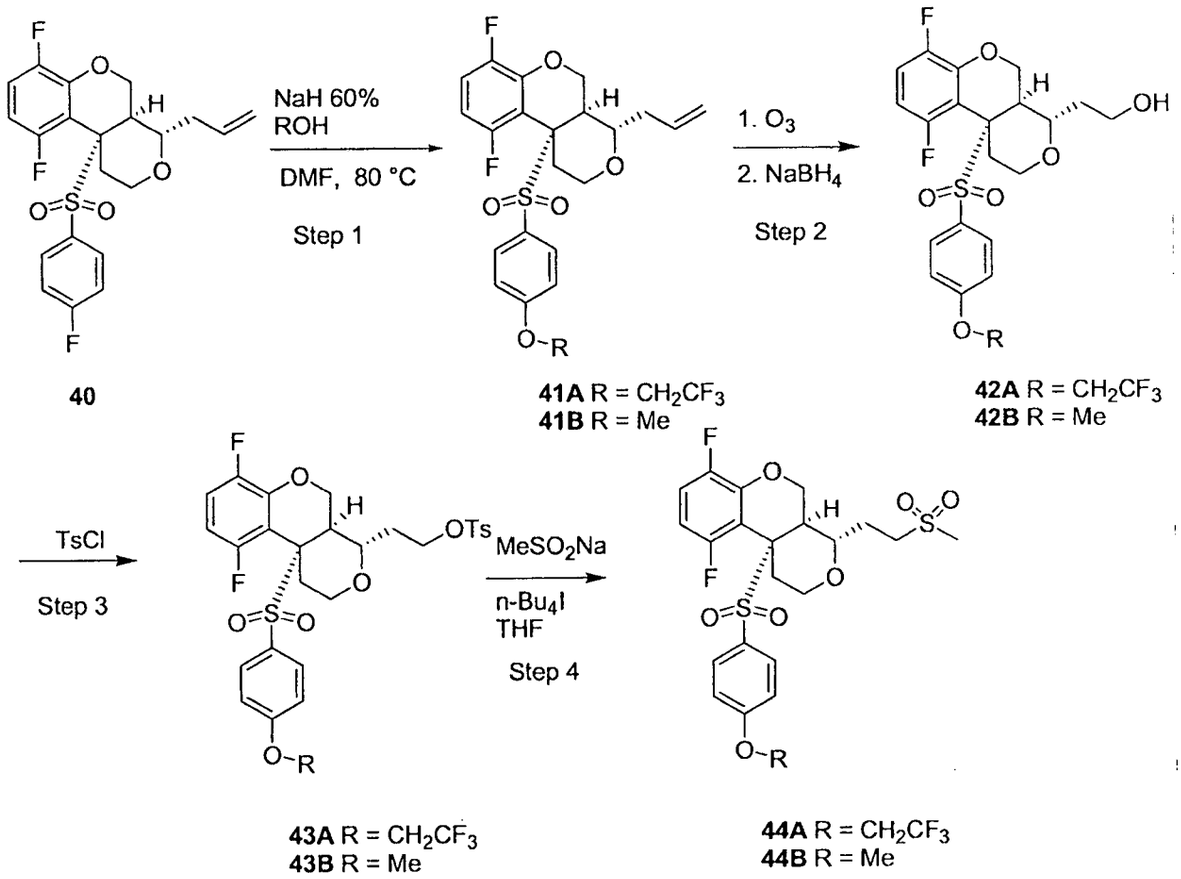
Triethylamine (0.012 g, 0.123 mmol) was added to a stirring solution of the **22N** (0.048 g, 0.082 mmol) and MsCl (0.014 g, 0.123 mmol) in 1 mL of dichloromethane at room temperature. After 1 hr the reaction was complete (tlc: 50%EtOAc/hexane). The reaction was diluted with 15 mL of dichloromethane and was washed with sat sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL). The dichloromethane layer was dried with anhydrous sodium sulfate and evaporated to give **38** (0.048 g, 90%). This material was used directly in the next reaction.

Step 2

1M KOtBu in THF (0.054 mLs, 0.054 mmol) was added dropwise to a stirring solution of the **38** (0.024 g, 0.036 mmol) in 50 mL of THF at room temperature. The reaction was complete after 30 min (tlc: 30% EtOAc/hexane). The reaction was quenched with the dropwise addition of water (1mL). The mixture was diluted with dichloromethane (20 mL) and partitioned with water (10 mL). The dichloromethane layer was dried over anhydrous sodium sulfate and evaporated to 0.020 g of the desired cyclopropyl compound. Purification by preparative tlc on silica gel (50%

EtOAc/hexane) gave 0.018 g of desired compound **39** (85%). MS: Calcd for $C_{24}H_{24}F_5O_6S_2$ $(M+1)^+$ m/z = 567.1, found 567.3, Rt = 4.60 min

Scheme 9:



40

41A R = CH_2CF_3
41B R = Me

42A R = CH_2CF_3
42B R = Me

43A R = CH_2CF_3
43B R = Me

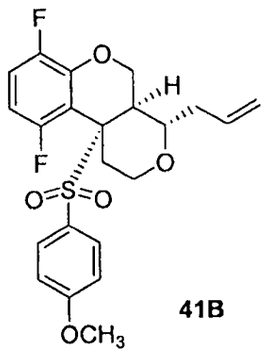
44A R = CH_2CF_3
44B R = Me

Step 1

A solution of trifluoroethanol (34 μL, 0.47 mmol) in 3 mL of DMF was treated with 60% NaH (5.0 mg, 0.23 mmol) and stirred for 20 min. 4-Allyl-7,10-difluoro-10-b-(4 fluoro-benzene sulfonyl)-1,4a,5,10b-tetrahydro-2*H*,4*H*-pyran[3,4-*c*] chromene **40** (100 mg, 0.23 mmol, prepared analogously to compound **19** from Scheme 2 using 4-fluorophenylsulfide in Step 2) 2 mL of DMF was added and the reaction was heated at 80 °C for 18 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with dichloromethane (3x). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with 15% EtOAc/hexanes to afford the desired compound **41A** (80%) ^1H NMR ($CDCl_3$ 400 MHz) δ 7.67 (d, J = 8.7 Hz, 2H), 7.13-

6.98 (m, 3H), 6.44 (m, 1H), 5.86 (m, 1H), 5.21-5.03 (m, 3H), 4.51-4.38 (m, 3H), 3.91 (m, 1H), 3.36 (m, 1H), 3.15 (t, J = 11.7 Hz, 1H), 2.66-2.47 (m, 3H), 2.45-2.24 (m, 2H).

The following compound (**41B**) was prepared analogously using methanol as the alcohol:

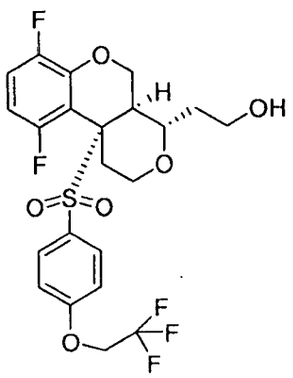


41B

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.60(d, J = 8.7 Hz, 2H), 7.06 (m, 1H), 6.97 (d, J = 8.05 Hz, 2H), 6.44 (m, 1H), 5.85 (m, 1H), 5.20-5.08 (m, 3H), 4.42 (d, J = 12.4 Hz, 1H), 3.88 (s, 4H), 3.35 (m, 1H), 3.15 (t, J = 11.7 Hz, 1H), 2.66-2.50 (m, 3H), 2.39 (m, 1H), 2.27 (m, 1H).

Step 2

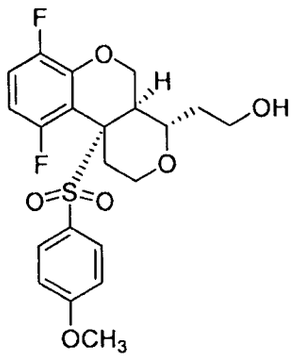
Alcohol **42A** was prepared analogously to Scheme 1, Step 10:



42A

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.67 (d, J = 8.7 Hz, 2H), 7.16-6.98 (m, 3H), 6.44 (m, 1H), 5.86 (d, J= 12.44 Hz, 1H), 4.50-4.36 (m, 3 H), 3.91 (m, 1H),3.81-3.74 (m, 2H), 3.49 (m, 1 H), 3.19 (t, J = 11.7 Hz, 1 H), 2.65-2.49 (m, 3H), 2.37-2.23 (m, 1 H),2.11 (m, 1H), 1.78 (m, 1H).

Analogously, alcohol **42B** was prepared analogously to Scheme 1, Step 10:

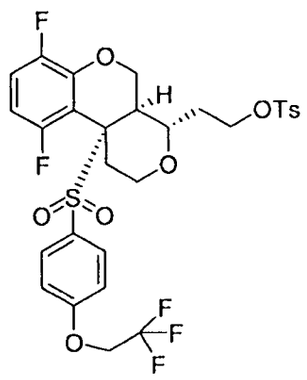


42B

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.60(d, J = 8.7 Hz, 2H), 7.06 (m, 1H), 6.97 (d, J = 8.05 Hz, 2H), 6.44 (m, 1H), 5.17 (d, J = 12.4 Hz, 1H), 4.40 (d, J = 12.4 Hz, 1H), 3.88 (s, 4H), 3.81-3.73 (m, 2H),3.49 (m, 1H), 3.19 (t, J = 11.7 Hz, 1H), 2.58 (d, J = 12.4 Hz, 2H), 2.37-2.24 (m, 2H), 2.10 (m, 1H), 1.81 (m, 1H).

Step 3

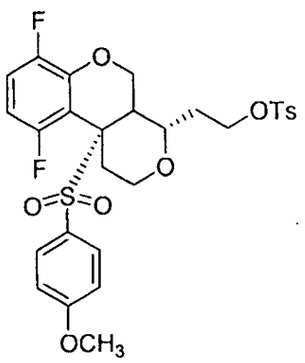
Tosylate **43A** was prepared analogously to the method described in Scheme 1, Step 12.



43A

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.72 (d, J = 8.7 Hz, 2H),7.64 (d, J = 8.7 Hz, 2H),7.29 (d, J = 8.05 Hz, 2H), 7.15-7.06 (m, 1 H), 7.03 (d, J = 9.5 Hz, 2H), 6.45 (m, 1H), 5.10 (d, J= 10.2 Hz, 1H), 4.50-4.38 (m, 2H), 4.27 (d, J = 13.2 Hz,1H), 4.22-4.07 (m, 2H), 3.75 (m, 1H), 3.23 (m, 1H), 2.97 (t, J = 12.4 Hz, 1H), 2.54-2.43 (m, 2H), 2.42 (s, 3 H), 2.26-2.10 (m, 2H), 1.78 (m, 1H).

Compound **43B** was prepared analogously to the method described in Scheme 1, Step 12.

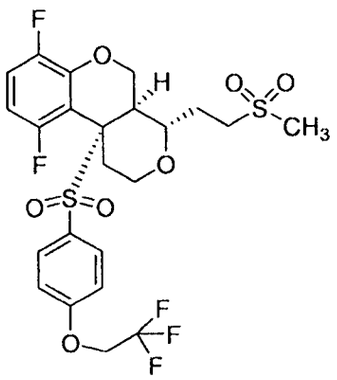


43B

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.72 (d, J = 8.7 Hz, 2H),7.64 (d, J = 8.7 Hz, 2H),7.29 (d, J = 8.05 Hz, 2H), 7.15-7.06 (m, 1 H), 7.03 (d, J = 9.5 Hz, 2H), 6.45 (m, 1H), 5.10 (d, J= 9.50 Hz, 1H), 4.25 (d, J = 13.2 Hz,1H), 4.21-4.07 (m, 3H), 3.88 (s, 3H), 3.74 (m, 1H), 3.22 (m, 1H), 2.94 (t, J = 12.4 Hz, 1H), 2.53 (d, J = 13.9 Hz, 2H), 2.47-2.37 (m, 2H), 2.26-2.09 (m, 2H), 1.78 (m, 1H).

Step 4

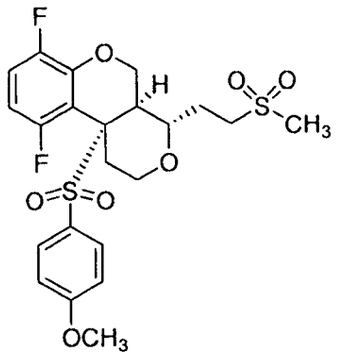
Sulfone **44A** was prepared analogously to the method described in Scheme 1, Step 13.



44A

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.64 (d, J = 8.7 Hz, 2H), 7.08 (m, 1H), 7.04 (d, J = 9.5 Hz, 2H), 6.45 (m, 1H), 5.19 (d, J= 10.25 Hz, 1H), 4.49-4.38 (m, 3H), 3.89 (m, 1H),3.38-3.21 (m, 2H), 3.19 (t, J = 11.7 Hz, 1H), 3.00 (m, 1H), 2.90 (s, 3H), 2.62-2.50 (m, 2H), 2.43 (m, 1H), 2.28 (m, 1H), 2.02 (m, 1H). MS: Calcd. for $C_{23}H_{23}F_5O_7S_2$ $(M+1)^+$, m/z = 571.3; found 571.3. Retention time 4.26 min.

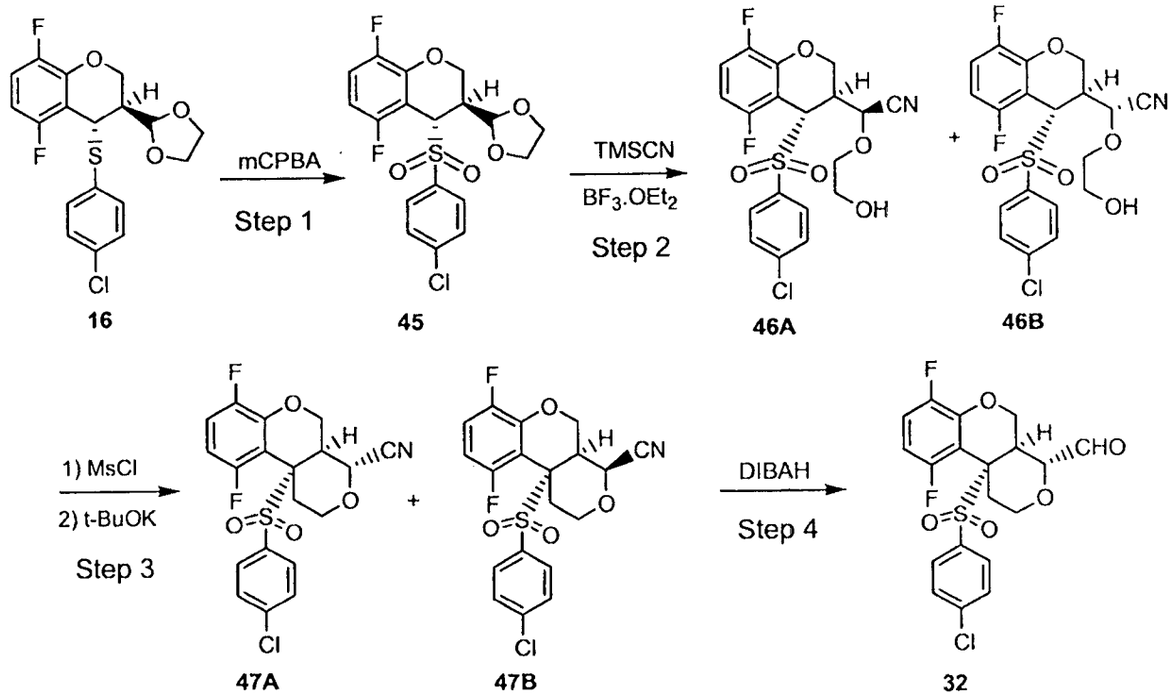
Sulfone **44B** was also prepared analogously to the method described in Scheme 1, Step 13.



44B

^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.7 Hz, 2H), 7.08 (m, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.46 (m, 1H), 5.20 (d, J= 10.25 Hz, 1H), 4.41 (d, J = 12.4 Hz, 1H), 3.90 (s, 4H), 3.47 (m, 1H), 3.37-3.22 (m, 2H), 3.14 (t, J = 11.7 Hz, 1H), 2.99 (m, 1H), 2.89(s, 3H), 2.60 (m, 1H), 2.49 (m, 1H), 2.27 (m, 1H), 2.01(m, 1H). MS: Calcd. for $C_{22}H_{24}F_2O_7S_2$ $(M+1)^+$, m/z = 503.3; found 503.3. Retention time 3.92 min.

Scheme 10:



16 **45** **46A** **46B** **47A** **47B** **32**

Step 1

To a stirred solution of 10.0 g (26.0 mmol) of compound **16** in 250 mL of dichloromethane was added 14.5 g (64.7 mmol) of 77% 3-chloroperoxybenzoic acid at 0 °C. The mixture was stirred at room temperature overnight. It was diluted with

400 mL of dichloromethane and quenched at 0 °C with 200 mL of saturated sodium bicarbonate and 200 mL of 10% sodium thiosulfate. The dichloromethane layer was washed with 100 mL of 1 N NaOH, and dried over sodium sulfate. It was filtered, concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 5% to 45% of ethyl acetate in hexanes to give 10.0 g of compound **45**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.74 (d, J = 8.0 Hz, 2 H), 7.51 (d, J = 8.0 Hz, 2 H), 7.01 (m, 1 H), 6.40 (m, 1 H), 4.88 (dd, J = 12, 4 Hz, 1 H), 4.60-4.75 (m, 3 H), 3.75-4.0 (m, 4 H), 2.89 (m, 1 H).). MS: Calcd. for $C_{18}H_{16}ClF_2O_5S$ (MH^+), m/z = 417.0; found 417.2. Retention time: 4.62 min.

Step 2

To a solution of 3.99 g (9.58 mmol) of compound **45** in 60 mL of dichloromethane at 0 °C were added 2.40 mL (17.95 mmol) of trimethylsilyl cyanide followed by 1.60 mL (12.5 mmol) of boron trifluoride etherate and the reaction was allowed to warm to room temperature and stirred 90 min. The final mixture was quenched with water, and extracted with three 50 mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 20% to 100% of ethyl acetate in hexanes to provide 3.80 g of **46A** and **46B** as a ~1:1 mixture. These compounds were used directly in the next reaction. . MS: Calcd. for $C_{19}H_{17}ClF_2NO_5S$ (MH^+), m/z = 444.0; found 444.2. Retention time: 3.93 min.

Step 3

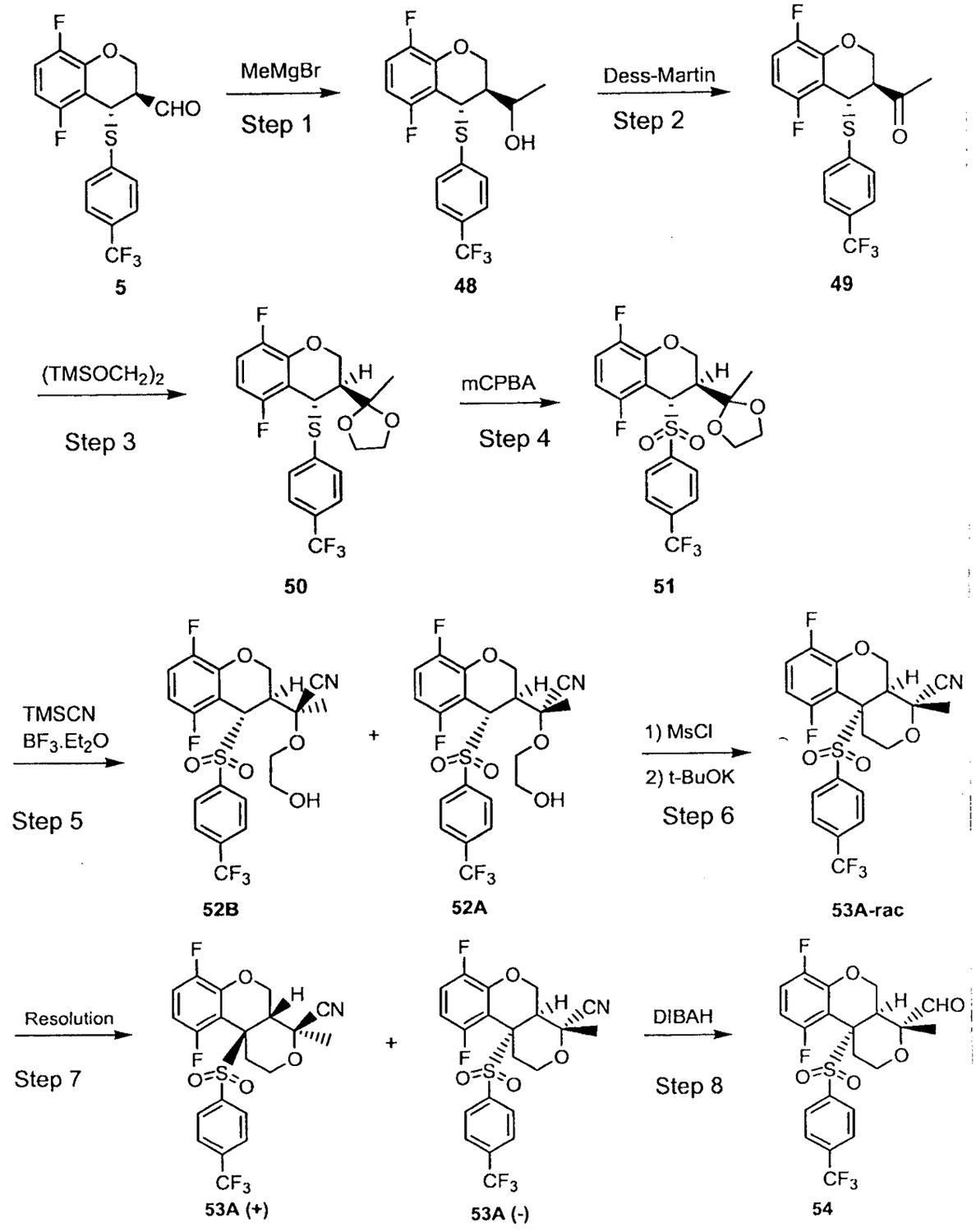
To a solution of 3.80 g (8.56 mmol) of ~1:1 mixture of compounds **46A** and **46B** in 20 mL of dichloromethane at 0 °C was added 0.76 mL (9.84 mmol) of methane sulfonyl chloride followed by 1.40 mL (10.0 mmol) of triethyl amine and the reaction was allowed to warm to room temperature overnight. The final mixture was concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 100% of ethyl acetate in hexanes to provide 4.14 g of methane sulfonyl intermediate as a ~1:1 mixture. A solution of 2.45 g (4.70 mmol) of this methane sulfonyl intermediate in 50 mL of tetrahydrofuran at 0 °C was treated with 5.0 mL (5.0 mmol) of a 1 N solution of potassium tert-butoxide in tetrahydrofuran. The mixture was slowly allowed to warm to room temperature and stirred at this

temperature for 2.5 h then quenched with 100 mL of water and extracted with three 50 mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 0% to 15% of ethyl acetate in dichloromethane to give 1.62 g of compound **47A** and 0.30 g of compound **47B**. **47A**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.63 (d, J = 8 Hz, 2 H), 7.53 (d, J = 8 Hz, 2 H), 7.15 (m, 1 H), 6.51 (m, 1 H), 5.25 (dd, J = 13, 3 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.15 (d, J = 11 Hz, 1 H), 4.00 (m, 1 H), 3.21 (t , J = 12 Hz, 1 H), 3.04 (br d, J = 12 Hz, 1 H), 2.58 (d, J = 14 Hz, 1 H), 2.38 (m, 1 H), MS: Calcd. for $C_{19}H_{15}ClF_2NO_4S$ (MH^+), m/z = 426.0; found 426.2. Retention time: 4.61 min. **47B**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.55 (d, J = 8 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H), 7.15 (m, 1 H), 6.46 (m, 1 H), 5.22 (dd, J = 12, 4 Hz, 1 H), 4.93 (d, J = 6 Hz, 1 H), 4.35 (d, J = 13 Hz, 1 H), 3.95 (m, 1 H), 3.61 (t, J = 12 Hz, 1 H), 3.20 (t, J = 5 Hz, 1 H), 2.63 (d, J = 14 Hz, 1 H), 2.44 (m, 1 H), MS: Calcd. for $C_{19}H_{15}ClF_2NO_4S$ (MH^+), m/z = 426.0; found 426.2. Retention time: 4.43

Step 4

To a solution of 0.75 g (1.76 mmol) of compound **47A** in 15 mL of dichloromethane at -78 °C was added 1.85 mL (1.85 mmol) of a 1 N solution of diisobutyl aluminum hydride in hexanes and the reaction was stirred 2 h at this temperature, then allowed to warm to room temperature over 1 h. The mixture was quenched with 0.3 mL of methanol then poured into 1 N hydrochloric acid and stirred 25 min. The mixture was then extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated to give 0.63 g of aldehyde **32**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 9.62 (s, 1 H), 7.63 (d, J = 8 Hz, 2 H), 7.51 (d, J = 8 Hz, 2 H), 7.11 (m, 1 H), 6.47 (m, 1 H), 5.07 (dd, J = 13, 2 Hz, 1 H), 4.67 (d, J = 12 Hz, 1 H), 4.02 (m, 1 H), 3.71 (d, J = 11 Hz, 1 H), 3.25 (t, J = 12 Hz, 1 H), 2.87 (d, J = 11 Hz, 1 H), 2.61 (d, J = 13 Hz, 1 H), 2.33 (m, 1 H). MS: Calcd. for $C_{19}H_{16}ClF_2O_5S$ (MH^+), m/z = 429.0; found 429.2. Retention time: 3.95 min.

Scheme 11:

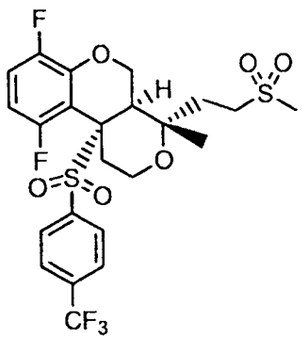

MeMgBr
Step 1
Dess-Martin
Step 2
(TMSOCH2)2
Step 3
mCPBA
Step 4
TMSCN
BF3.Et2O
Step 5
1) MsCl
2) t-BuOK
Step 6
Resolution
Step 7
DIBAH
Step 8
5
48
49
50
51
52B
52A
53A-rac
53A (+)
53A (-)
54

1. $(EtO)_2POCH_2SO_2CH_3$
LHMDS, THF

2. $NaBH_4$

as per Scheme 6, Steps 2 to 3

Steps 9-10



55

Step 1

To a suspension of 29.6 g (120 mmol) of cerium (III) chloride in 120 mL of tetrahydrofuran at 0 °C for 90 min was added 40 mL (120 mmol) of methylmagnesium bromide 3 N in diethylether and the reaction was stirred 1 h at 0 °C. A solution of 15.0 g (40.1 mmol) of compound **5** in 60 mL of tetrahydrofuran was added and the reaction was stirred 1 h at 10 °C. The final mixture was poured into saturated ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate and concentrated. The residue was purified by chromatography over silica gel eluting with a gradient of 1% to 40% of ethyl acetate in hexanes to give 12.1 g of compound **48**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.59 (m, 4 H), 6.98 (m, 1 H), 6.61 (m, 1 H), 5.15 (s, 1 H), 4.35-4.75 (m, 2 H), 3.74 (m, 1 H), 1.95 (m, 1 H), 1.36 and 1.16 (t, J = 7 Hz, 3 H), MS: Calcd. for $C_{18}H_{15}F_5O_2S$ (MH^+), m/z = 391.1; found 391.2. Retention time: 4.98 min.

Step 2

To a stirred solution of 12.1 g (30.9 mmol) of compound **48** in 150 mL of dichloromethane was added 15.7 g (37.0 mmol) of Dess-Martin periodinane. The mixture was stirred at room temperature for 1 h then filtered. The filtrate was concentrated and purified by chromatography over silica gel eluting with a gradient of 1% to 40% of ethyl acetate in hexanes to give 9.96 g of compound **49**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.59 (d, J = 8 Hz, 2 H), 7.54 (d, J = 8 Hz, 2 H), 6.98 (m, 1 H), 6.62 (m, 1 H), 5.12 (s, 1 H), 4.86 (d, J = 12 Hz, 1 H), 4.75 (d, J = 12 Hz, 1 H), 2.89 (s, 1 H), 2.28 (s, 3 H), MS: Calcd. for $C_{18}H_{14}F_5O_2S$ (MH^+), m/z = 389.1; found 389.2. Retention time: 5.14 min.

Step 3

To a solution of 6.98 g (18.0 mmol) of compound **49** in 60 mL of dichloromethane were added 7.90 mL (32.5 mmol) of 1,2-bis(trimethylsiloxy)ethane and 0.25 mL (1.50 mmol) of trimethylsilyl trifluoromethanesulfonate at -78 °C. After 30 min, the solution was warmed to room temperature and stirred for 48 h. The reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated, and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 100% of dichloromethane in hexanes to give 7.37 g of compound **50**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.60 (m, 4 H), 6.98 (m, 1 H), 6.58 (m, 1 H), 4.86 (s, 1 H), 4.60 (m, 2 H), 3.80-3.95 (m, 3 H), 3.59 (m, 1 H), 2.17 (s, 1 H), 1.20 (s, 3H), MS: Calcd. for $C_{20}H_{18}F_5O_3S$ (MH^+), m/z = 433.1; found 433.3. Retention time: 5.48 min.

Step 4

To a solution of 8.92 g (20.6 mmol) of compound **50** in 130 mL of dichloromethane was added 13.4 g (60.0 mmol) of 77% 3-chloroperoxybenzoic acid at 0 °C. The mixture was stirred at room temperature overnight then filtered, concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 100% of dichloromethane in hexanes to give 9.13 g of compound **51**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.95 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H), 7.01 (m, 1 H), 6.38 (m, 1 H), 4.81 (dd, J = 12, 5 Hz, 1 H), 4.74 (s, 1H), 4.66 (d, J = 12 Hz, 1 H), 2.93 (d, J = 4 Hz, 1 H), 1.13 (s, 3 H), MS: Calcd. for $C_{20}H_{18}F_5O_5S$ (MH^+), m/z = 465.1; found 465.3. Retention time: 4.74 min.

Step 5

To a solution of 9.13 g (19.6 mmol) of compound **51** in 100 mL of dichloromethane at 0 °C was added 4.10 mL of trimethylsilyl cyanide (30.8 mmol) followed by 2.55 mL (20.3 mmol) of boron trifluoride etherate dropwise and the reaction was allowed to warm to room temperature and stirred 2 h. The mixture was quenched with water and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 50% of

ethyl acetate in hexanes to provide 4.27 g of compound **52A** and 3.50 g of compound **52B**. **52A**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.96 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 2 H), 7.05 (m, 1 H), 6.42 (m, 1 H), 4.93 (dd, J = 13, 4 Hz, 1 H), 4.82 (s, 1 H), 4.74 (d, J = 13 Hz, 1 H), 3.71 (m, 2 H), 3.65 (m, 2 H), 3.37 (m, 1 H), 1.56 (m, 1 H), 1.42 (s, 3 H), MS: Calcd. for $C_{21}H_{19}F_5NO_5S$ (MH^+), m/z = 492.1; found 492.3. Retention time: 4.23 min. **52B**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.95 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 2 H), 7.07 (m, 1 H), 6.46 (m, 1 H), 4.86 (dd, J = 13, 5 Hz, 1 H), 4.82 (s, 1 H), 4.67 (d, J = 13 Hz, 1 H), 3.68 (m, 4 H), 3.22 (m, 1 H), 1.64 (br s, 1 H), 1.56 (s, 3 H), MS: Calcd. for $C_{21}H_{19}F_5NO_5S$ (MH^+), m/z = 492.1; found 492.3. Retention time: 4.22 min.

Step 6

To a solution of 4.27 g (8.69 mmol) of compound **52A** in 40 mL of dichloromethane were added 1.40 mL (10.0 mmol) of triethylamine and 0.78 mL (10.0 mmol) of methanesulfonyl chloride. The mixture was stirred at room temperature overnight then concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 50% of ethyl acetate in hexanes to provide 4.91 g of methanesulfonyl intermediate. A solution of 4.91 g (8.73 mmol) of this methane sulfonyl intermediate in 70 mL of tetrahydrofuran at 0 °C was treated with 10.5 mL (10.5 mmol) of a solution of potassium tert-butoxide 1 N in tetrahydrofuran. The mixture was slowly allowed to warm to room temperature and stirred at this temperature for 30 min then quenched with 100 mL of water and extracted with two 150 mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 50% of ethyl acetate in hexanes to provide 1.77 g of compound **53A-rac** and 0.42 g of recovered methanesulfonyl intermediate. **53A-rac**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.80 (m, 4 H), 7.13 (m, 1 H), 6.44 (m, 1 H), 5.20 (dd, J = 13, 4 Hz, 1 H), 4.64 (d, J = 13 Hz, 1 H), 3.95 (m, 1 H), 3.44 (m, 1 H), 3.36 (d, J = 4 Hz, 1 H), 2.60 (m, 2 H), 1.52 (s, 3 H), MS: Calcd. for $C_{21}H_{17}F_5NO_4S$ (MH^+), m/z = 474.1; found 474.3. Retention time: 4.78 min.

Step 7

Compound **53A-rac** (1.7 g) was resolved on Chiral OD column eluting with 60% isopropanol in hexanes and 35 mL /min flow rate to give two enantiomers **53A (-)**(0.82 g, $[\alpha]_D^{20}$ -94.4°) and **53A (+)** (0.88 g, $[\alpha]_D^{20}$ +90.3°).

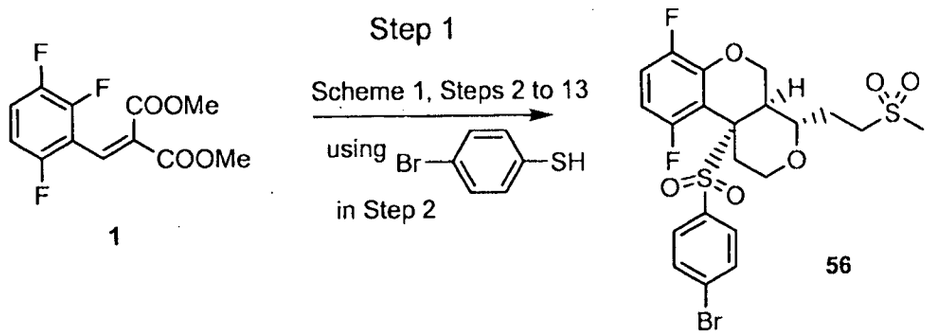
Step 8

To a solution of 200 mg (0.42 mmol) of compound **53A (-)** in 8 mL of dichloromethane at -78 °C was added 0.89 mL (0.89 mmol) of a 1 N solution of diisobutyl aluminum hydride in hexanes and the reaction was stirred 1 h at this temperature. The mixture was quenched with 0.2 mL of methanol then diluted with dichloromethane and brine. Celite was added and the slurry was stirred at room temperature for 15 min. The mixture was filtered over Celite then extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 50% of ethyl acetate in hexanes to provide 92 mg of compound **54 (-)**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 9.43 (s, 1 H), 7.78 (m, 4 H), 7.12 (m, 1 H), 6.42 (m, 1 H), 5.06 (dd, J = 12, 5 Hz, 1 H), 4.49 (d, J = 12 Hz, 1 H), 3.90 (m, 1 H), 3.49 (m, 1 H), 3.04 (d, J = 4 Hz, 1 H), 2.58 (m, 1 H), 2.42 (m, 1H), 1.13 (s, 3 H), MS: Calcd. for $C_{21}H_{18}F_5O_5S$ (MH^+), m/z = 477.1; found 477.3. Retention time: 4.46 min.

Steps 9-10

Compound **54 (-)** was subjected to conditions analogous to the ones described in Scheme 6, Steps 2 to 3, with the exclusion of the final chiral HPLC purification, to provide compound **55**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.76 (m, 4 H), 7.11 (m, 1 H), 6.40 (m, 1 H), 5.17 (dd, J = 13, 5 Hz, 1 H), 4.45 (d, J = 13 Hz, 1 H), 3.74 (m, 1 H), 3.37 (t, J = 12 Hz, 1 H), 3.23 (m, 1 H), 3.14 (m, 1 H), 2.95 (s, 3 H), 2.74 (d, J = 4 Hz, 1 H), 2.54 (d, J = 14 Hz, 1 H), 2.34 (m, 1 H), 2.24 (m, 1 H), 2.16 (m, 1 H), 1.01 (s, 3 H). MS: Calcd. for $C_{23}H_{24}F_5O_6S_2$ (MH^+), m/z = 555.1; found 555.3. Retention time: 4.50 min.

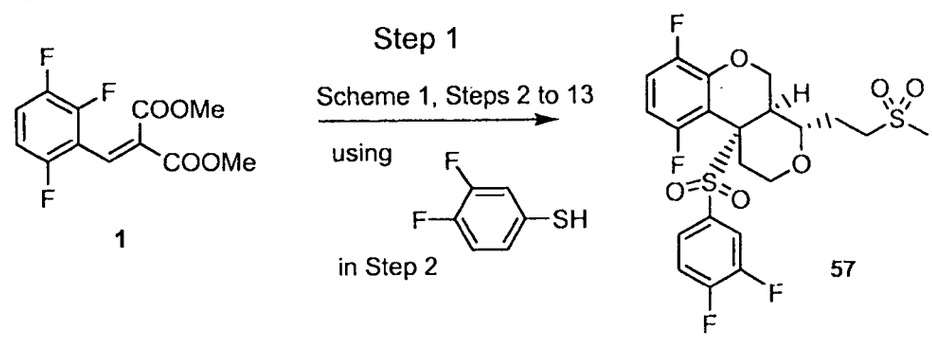
Scheme 12:



Step 1

Compound **1** was subjected to conditions analogous to the ones described in Scheme 1, Steps 2 to 13, and using 4-bromothiophenol instead of 4-chlorothiophenol in Step 2, to provide compound **56**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.68 (d, J = 8 Hz, 2 H), 7.55 (d, J = 8 Hz, 2 H), 7.10 (m, 1 H), 6.48 (m, 1 H), 5.17 (dd, J = 12, 2.4 Hz, 1 H), 4.44 (d, J = 12 Hz, 1 H), 3.90 (br d, J = 12 Hz, 1 H), 3.34 (m, 1 H), 3.27 (m, 1 H), 3.14 (m, 1 H), 3.02 (m, 1 H), 2.91 (s, 3 H), 2.50-2.60 (m, 2 H), 2.44 (m, 1 H), 2.29 (m, 1 H), 2.03 (m, 1 H). MS: Calcd. for $C_{21}H_{22}BrF_2O_6S_2$ (MH+), m/z = 551.0; found 551.3. Retention time: 4.34 min.

Scheme 13:

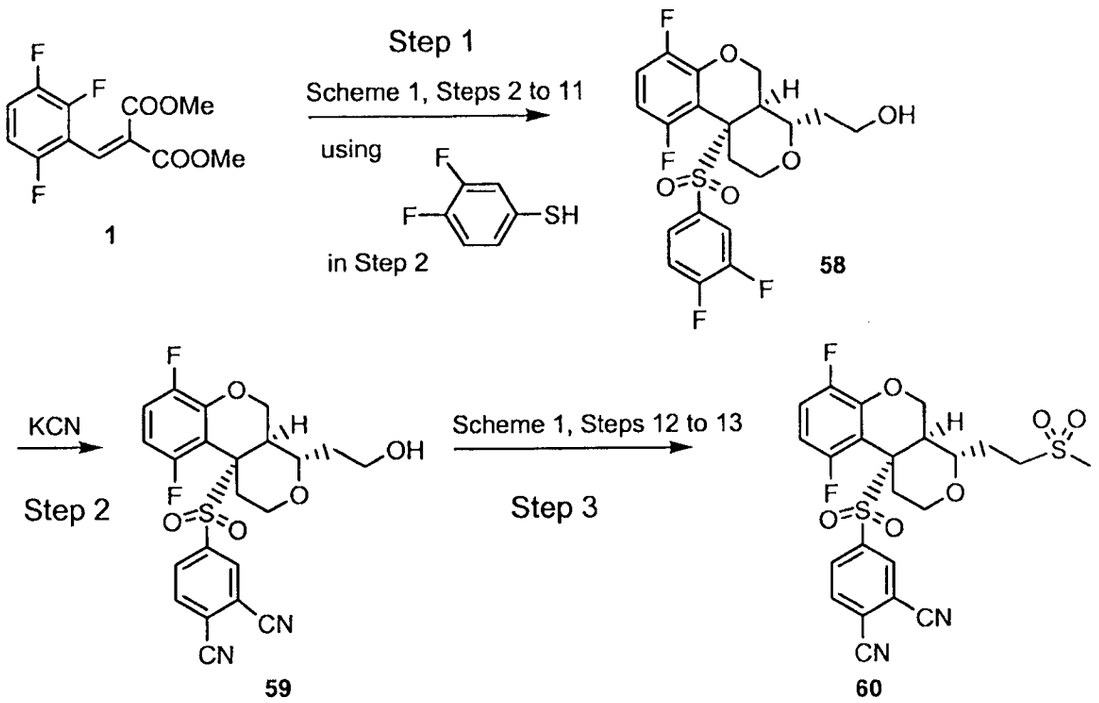


Step 1

Compound **1** was subjected to conditions analogous to the ones described in Scheme 1, Steps 2 to 13, and using 3,4-difluorothiophenol instead of 4-chlorothiophenol in Step 2, to provide compound **57**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.54 (m, 1 H), 7.48 (m, 1 H), 7.33 (m, 1 H), 7.11 (m, 1 H), 6.47 (m, 1 H), 5.15 (dd, J = 13, 3 Hz, 1 H), 4.45 (d, J = 12 Hz, 1 H), 3.91 (m, 1 H), 3.35 (m, 1 H), 3.27 (m, 1 H), 3.14 (t, J = 12 Hz, 1 H), 3.01 (m, 1 H), 2.91 (s, 3 H), 2.50-2.60 (m, 2 H), 2.44 (m, 1 H),

2.31 (m, 1 H), 2.04 (m, 1 H). MS: Calcd. for $C_{21}H_{21}F_4O_6S_2$ (MH+), m/z = 509.1; found 509.3. Retention time: 4.13 min.

Scheme 14:



Step 1

Compound **1** was subjected to conditions similar to the ones described in Scheme 1 Steps 2 to 11, and using 3,4-difluorothiophenol instead of 4-chlorothiophenol in Step 2, to provide compound **58**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.40-7.60 (m, 2 H), 7.34 (m, 1 H), 7.12 (m, 1 H), 6.47 (m, 1 H), 5.15 (dd, J = 12, 3 Hz, 1 H), 4.44 (d, J = 12 Hz, 1 H), 3.93 (m, 1 H), 3.80 (m, 2 H), 3.50 (m, 1 H), 3.20 (t, J = 12 Hz, 1 H), 2.67 (m, 1 H), 2.52 (d, J = 10 Hz, 1 H), 2.35 (m, 1 H), 2.26 (m, 1 H), 2.12 (m, 1 H), 1.85 (m, 1 H), 1.55 (s, 1 H), MS: Calcd. for $C_{20}H_{19}F_4O_5S$ (MH+), m/z = 447.1; found 447.2. Retention time: 3.93 min.

Step 2

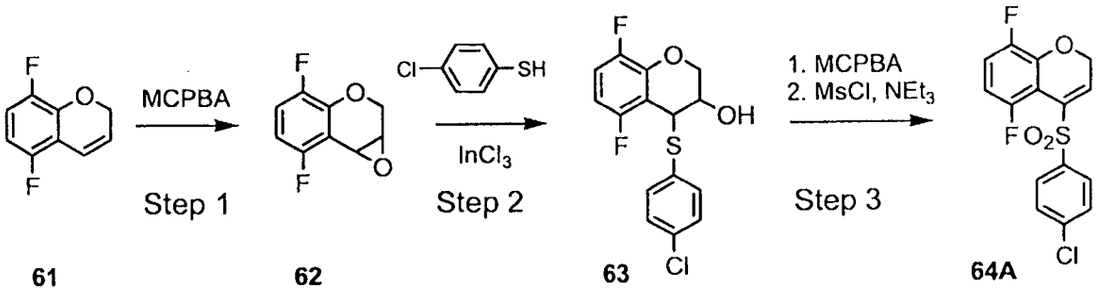
A solution of 100 mg (0.22 mmol) of compound **58** in 2 mL of acetonitrile was treated with 30 mg (0.44 mmol) of potassium cyanide and heated at reflux overnight. The mixture was diluted with water and dichloromethane and extracted with

dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated and the residue was purified by chromatography over silica gel eluting with a gradient of 1% to 50% of ethyl acetate in hexanes to provide 25 mg of compound **59** and 25 mg of starting **58.** **59**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.10 (s, 1 H), 8.05 (d, J = 8 Hz, 1 H), 7.99 (d, J = 8 Hz, 1 H), 7.16 (m, 1 H), 6.49 (m, 1 H), 5.08 (dd, J = 12, 3 Hz, 1 H), 4.48 (d, J = 13 Hz, 1 H), 3.93 (m, 1 H), 3.80 (m, 2 H), 3.52 (m, 1 H), 3.18 (m, 1 H), 2.74 (d, J = 10 Hz, 1 H), 2.68 (m, 1 H), 2.38 (m, 1 H), 2.24 (m, 1 H), 2.12 (m, 1 H), 1.86 (m, 1 H), 1.05 (s, 1 H), MS: Calcd. for $C_{22}H_{19}F_2N_2O_5S$ (MH+), m/z = 461.1; found 461.3. Retention time: 3.78 min.

Step 3

Compound **59** was subjected to conditions similar to the ones described in Scheme 1, Steps 12 to 13 to provide compound **60**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.10 (s, 1 H), 8.04 (d, J = 9 Hz, 1 H), 7.99 (d, J = 9 Hz, 1 H), 7.17 (m, 1 H), 6.50 (m, 1 H), 5.11 (dd, J = 12, 2.2 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 3.93 (br d, J = 12 Hz, 1 H), 3.38 (m, 1 H), 3.29 (m, 1 H), 3.14 (m, 1 H), 3.03 (m, 1 H), 2.93 (s, 3 H), 2.67 (d, J = 9 Hz, 1 H), 2.45-2.55 (m, 2 H), 2.08 (m, 1 H); MS Calcd. for $C_{23}H_{21}F_2N_2O_6S_2$ (MH+), m/z = 523.1; found 523.3. Retention time: 3.92 min.

Scheme 15:



Step 1: *5,8-Difluoro-2H-chromene oxide*

5,8-Difluoro-2H-chromene **61** (35g, 0.21 mol) was dissolved in 500 mL of dichloromethane and 93 g of MCPBA (77%, 0.42 mol) was added. The reaction was stirred at room temperature for 30 minutes. The reaction was quenched with a solution of 50 g $Na_2S_2O_3$ in 500 mL water. The organic layer was washed with two 500-mL portions of 2N NaOH solution, 200 mL of brine, dried over Na_2SO_4 and

concentrated. The residue was recrystalized from EtOAc/Hexane solution to give rise to 21.6 g pure product **62**. The residue from mother liquor was purified by column chromatography eluting with a gradient from hexanes to 25% EtOAc/hexanes over 55 minute to obtain an additional 1.4 g of **62**. Total Yield: 23 g, 60%. ^{1}H NMR ($CDCl_3$ 400 MHz δ 7.00 (m, 1H), 6.63 (m, 1H), 4.67 (d, J = 12.4 Hz, 1H), 4.27 (m, 2H), 3.84 (d, J = 4.4Hz, 1H).

Step 2: *4-(4-Chloro-phenylsulfanyl)-5,8-difluoro-chroman-3-ol*

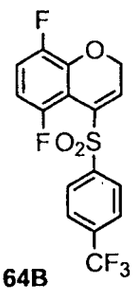
5,8-Difluoro-2H-chromene oxide **62** (23 g, 0.125 mol) and 4-chloro-benzenethiol (18.1 g, 0.125 mmol) were dissolved in 500 mL of dichloromethane and 2.9 g of $InCl_3$ (0.013 mol) was added. The reaction was stirred at room temperature overnight. The reaction was partitioned between 200 mL of dichloromethane and 200 mL of water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The product was purified by column chromatography eluting with a gradient from hexanes to 50% EtOAc/hexane over 55 minute to give 23.2 g of alcohol **63** (57%). ^{1}H NMR ($CDCl_3$ 400 MHz δ 7.48 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.01 (m, 1H), 6.64 (m, 1H), 4.63 (d, J = 11.7 Hz, 1H), 4.32-4.41 (m, 2H), 4.12 (m, 1H).

Step 3: *4-(4-Chloro-benzenesulfonyl)-5,8-difluoro-2H-chromene*

4-(4-Chloro-phenylsulfanyl)-5,8-difluoro-chroman-3-ol **63** (23.2 g, 71 mmol) was dissolved in 200 mL of dichloromethane and 31.7 g (77%, 142 mmol) of MCPBA was added. The reaction was stirred at room temperature for 3 hours, then quenched with a solution of 10 g of $Na_2S_2O_3$ in 50 mL water. The organic layer was washed with 2 100-mL portions of 1N NaOH solution, 100 mL of brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in 200 mL of dichloromethane, 16.1 g of mesyl chloride (142 mmol) and 14.3 g of triethylamine (142 mmol) were added. The reaction was stirred at room temperature for one hour. The reaction solution was washed with 100 mL of brine, dried over Na_2SO_4 and concentrated. The residue was recrystalized from EtOAc/Hexane solution to give 8.4 g pure vinyl sulfone product **64**. The residue from mother liquor was purified by column chromatography eluting with a gradient from hexanes to 25% EtOAc/hexane over 55 minute to give an additional 7.1 g vinyl sulfone **64A**. Total yield: 15.5 g, 64%. ^{1}H NMR ($CDCl_3$ 400 MHz δ 7.84 (dd, J

= 8.8 and 2.2 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 4.4Hz, 1H), 7.00 (m, 1H), 6.54 (m, 1H), 4.99 (d, J = 4.4 Hz, 2H).

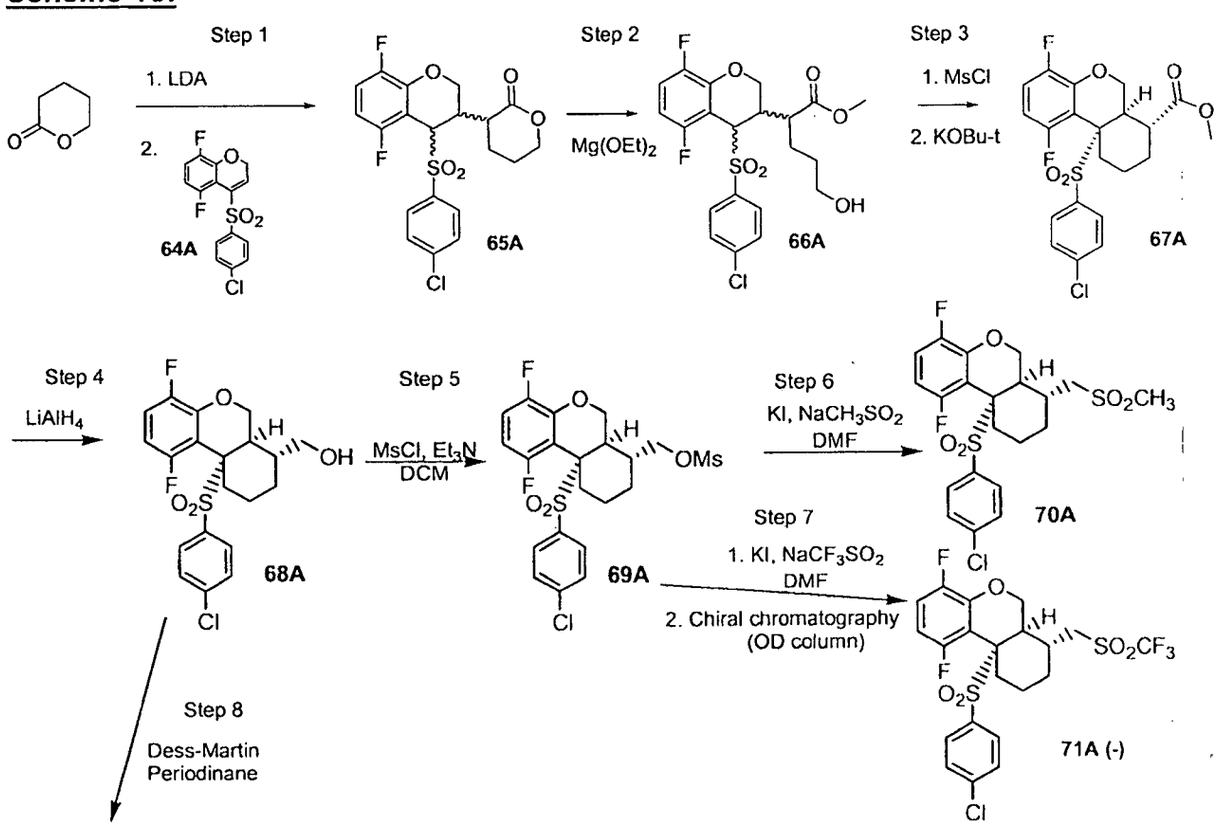
The following compound (**64B**) was prepared via an analogous three step route using 4-trifluoromethylphenylsulfide in Step 2:

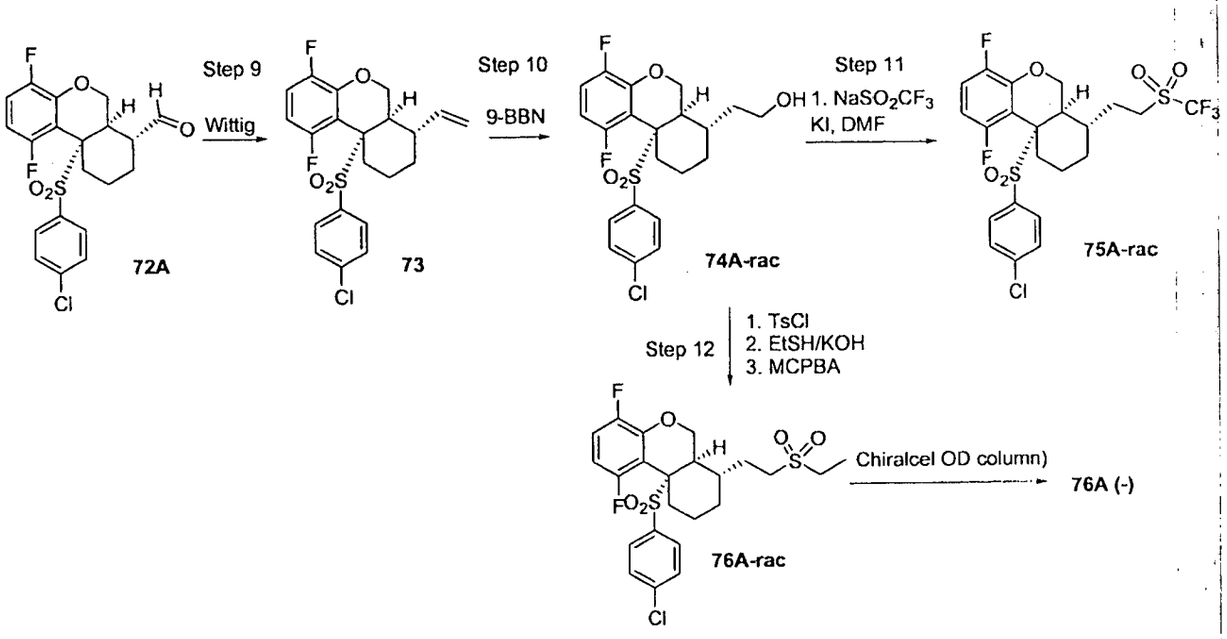


64B

^{1}HNMR (CDCl3)δ: 8.03 (d, 2H), 7.81 (d, 2H), 7.38 (m, 1H), 7.01 (m, 1H), 6.54 (m, 1H), 5.01 (d, 2H)

Scheme 16:





Step 1

To a solution of 8.25 mL (58.3 mmol) of diisopropylamine in 100 mL of THF at -40 °C was added 23.3 mL (58.3 mmol) of 2.5 M solution of n-butyl lithium in hexanes. The mixture was stirred for 20 min and cooled to -78 °C. A solution of 5.84 g (58.35 mmol) of delta-valerolactone in 10 mL of THF was added dropwise. The resulting viscous mixture was stirred at -78 °C over a period of 45 min, followed by the dropwise addition of a solution of 10.0 g (29.177 mmol) of alkene **64A** in 40 mL of THF. The mixture was stirred in the cold for 15 min, quenched with 50% saturated NH_4Cl, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was passed through a 120 g silica gel column using gradient of 0% to 40% of ethyl acetate in hexanes to furnish 11.53 g of product **65A** as a mixture of diastereomers. ^1H NMR ($CDCl_3$ 400 MHz) δ 7.91 (d, J = 8.8 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.75 (d, J = 8.8 Hz, 1 H), 7.53 (d, J = 8.8 Hz, 1 H), 7.10-7.01 (ser. m., 1 H), 6.59-6.47 (ser. m., 1 H), 5.09 (s, 0.5 H), 4.95 (dd, J = 12.3, 8.6 Hz, 0.5 H), 4.81 (dd, J = 12.6, 2.6 Hz, 0.5 H), 4.60 (dt, J = 12.3, 1.8 Hz, 0.5 H), 4.47 (dt, J = 12.6, 1.8 Hz, 0.5 H), 4.46 (s, 0.5 H), 4.29-4.14 (ser. m., 2H), 3.34 (m, 0.5 H), 3.08 (dm, J = 9.8 Hz, 0.5 H), 2.64-2.52 (ser. m, 0.5 H), 2.39-2.29 (m, 0.5 H), 2.28-2.19 (m, 0.5 H), 1.96-1.87 (ser m, 1.5 H), 1.70-1.62 (ser. m., 1.5 H), 1.39-1.28 (m, 0.5 H).

Step 2

To a mixture of 11.00 g (24.88 mmol) of compound **65A** in 120 mL of methanol was added 3.20 g (29.86 mmol) of magnesium ethoxide. The resulting mixture was stirred overnight and taken into 1200 mL of ethyl acetate. The mixture washed sequentially with 600 mL of 1M NaOH, twice with 1 L of water, and 600 mL of brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to furnish 11.0 g of alcohol **66A**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.77 (d, J = 8.8 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 1 H), 7.52 (d, J = 8.8 Hz, 1 H), 7.10-7.00 (m, 1 H), 6.53-6.40 (ser. m, 1 H), 4.90 (td, J = 12.5, 3.1 Hz, 1H), 4.56-4.46 (ser. m., 1 H), 4.31-4.24 (ser. m., 1 H), 3.65 (s, 1.5 H), 3.67-3.48 (ser. m., 2 H), 3.51 (s, 1.5 H), 3.12 (d, J = 11.5 Hz, 0.5 H), 2.96 (d, J = 9.7 Hz, 0.5 H), 2.43-2.28 (ser. m., 1 H), 1.97-1.29 (ser. m., 5 H).

Step 3

A mixture of alcohol **66A** obtained in the previous step and triethylamine (10.49 mL, 74.65 mmol) in 120 mL of dichloromethane was chilled with ice/water and treated dropwise with 2.89 mL (37.23 mmol) of methanesulfonyl chloride. The reaction mixture was stirred for 1 h, washed with equal volume of 1M HCl, dried over Na_2SO_4, concentrated and pumped on a high vacuum overnight to furnish 12.16 g of crude mesylate which was used without further purification. To a solution of 11.16 g (20.18 mmol) of this material in 200 mL of THF was added in portions 2.94 g (20.18 mmol) of potassium tert-butoxide. The reaction mixture was stirred for 40 min and quenched with equal volumes of 50% sat. NH_4Cl and ethyl acetate. The organic phase was separated, dried over $MgSO_4$, and concentrated. The product was purifed by column chromatography over silica gel using a gradient from 0-30% of ethyl acetate in hexanes as solvent to furnish 6.0 g of ester **67A**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.61 (d, J = 8.7 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 7.12-7.04 (m, 1 H), 6.47-6.40 (m, 1 H), 5.19 (dd, J = 12.5, 2.7 Hz, 1 H), 4.20 (d, J = 12.2 Hz, 1 H), 3.72 (s, 3 H), 2.98 (d, J = 9.9 Hz, 1 H), 2.64 (d, J = 11.2 Hz, 1 H), 2.46 (td, J = 11.9, 4.2 Hz, 1 H), 1.98-1.87 (m, 2 H), 1.81-1.74 (m, 1 H), 1.58-1.49 (m, 2 H), 1.17-1.06 (m, 1 H).

Step 4

To a solution of 2.70 g (5.91 mmol) of ester **67A** in 59 mL of THF at 0 °C was added 6.50 mL (6.50 mmol) of 1M lithium aluminum hydride solution in THF. The reaction mixture was stirred over 15 min and quenched by careful dropwise addition of 1M HCl, untill no more gas was evolving. The mixture was partitioned between 1M HCl and ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated to furnish 2.40 g of alcohol **68A** which was used without further purification. δ 7.62 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.09-7.02 (m, 1 H), 6.46-6.39 (m, 1 H), 5.17 (dd, J = 12.1, 2.5 Hz, 1 H), 4.63 (d, J = 12.6 Hz, 1 H), 3.88 (dd, J = 11.0, 4.4 Hz, 1 H), 3.71 (dd, J = 11.2, 2.9 Hz, 1 H), 2.70 (d, J = 11.0 Hz, 1 H), 2.57 (d, J = 14.6 Hz, 1 H), 1.94-1.83 (m, 1 H), 1.78-1.66 (m, 2 H), 1.57-1.41 (m, 3 H), 1.17-1.04 (m, 1 H).

Step 5

To alcohol **68A** (1.794 g, 4.18 mmol) in dichloromethane (50 mL) was added Et_3N (1.17 mL, 0.846 g, 8.36 mmol,) and MsCl (0.48 mL, 0.719 g, 6.27 mmol,) respectively, the mixture was stirred at 0 °C for 30 mins, and quenched with water. It was washed with 1N HCl, and extracted with dichloromethane. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude **69A** (2.257 g, quantitative) was used for the next step directly. ^{1}H-NMR (CDCl3 400 MHz) δ: 7.61 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.12-7.03 (m, 1H), 6.50-6.40 (m, 1H), 5.21 (d, J = 13.0 Hz, 1H), 4.55-4.46 (m, 2H), 4.20 (dd, J = 2.4, 10.4 Hz, 1H), 3.06 (s, 3H), 2.68 (d, J = 11.6 Hz, 1H), 2.57 (d, J = 13.2 Hz, 1H), 1.96-1.84 (m, 1H), 1.82-1.66 (m, 3H), 1.58-1.46 (m, 1H), 1.18-1.04 (m, 1H).

Step 6:

To compound **69A** (0.131 g, 0.26 mmol) in DMF was added 0.129 g of KI (0.78 mmol) and 0.079 g of sodium methanesulfinate (0.78 mmol), the mixture was at 120 °C for 1 hr., and quenched with water. It was extracted with dichloromethane, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude **70A** was purified by prep-TLC, followed by reverse phase HPLC. ^{1}H-NMR (CDCl3 400 MHz) δ: 7.62 (d, J

= 8.5 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.15-7.03 (m, 1H), 6.54-6.41 (m, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 12.2 Hz, 1H), 3.36 (d, *J* = 14.7 Hz, 1H), 3.02-2.88 (m, 1H), 2.95 (s, 3H), 2.57 (d, *J* = 11.6 Hz, 2H), 2.27 (d, *J* = 12.4 Hz, 1H), 2.10-1.95 (m, 1H), 1.96-1.81 (m, 1H), 1.79-1.66 (m, 1H), 1.48-1.33 (m, 1H), 1.17-1.02 (m, 1H). LCMS $[M+H]^+$: 491.3 (4.44 min)

Step 7: Sulfone **71A** was obtained by an analogous procedure to that described in the general procedure from preparation of sulfone **70A** (Step 6 above, using sodium trifluoromethylsulfinate). The racemic form of **71A** was separated by preparative Chiracel OD column chromatography to give two enantiomers:**71A (-)** $[\alpha]_D$ = -122.6° (c = 1.00, dichloromethane) and **71A (+)** $[\alpha]_D$ = +132.5 (c = 1.00, dichloromethane). ^{1}H-NMR (CDCl3 400 MHz) δ: 7.62 (d, *J* = 9.2 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.15-7.05 (m, 1H), 6.53-6.44 (m, 1H), 5.27 (d, *J* = 13.2 Hz, 1H), 4.44-4.40 (d, *J* = 13.0 Hz, 1H), 3.50 (d, *J* = 14.0 Hz, 1H), 3.23 (dd, *J* = 8.2, 14.4 Hz, 1H), 2.72-2.52 (m, 2H), 2.28-2.10 (m, 2H), 1.98-1.85 (m, 1H), 1.78 (d, *J* = 14.8 Hz, 1H), 1.60-1.48 (m, 1H), 1.20-1.04 (m, 1H). LCMS $[M+H]^+$: 545.3 (5.08 min).

Step 8

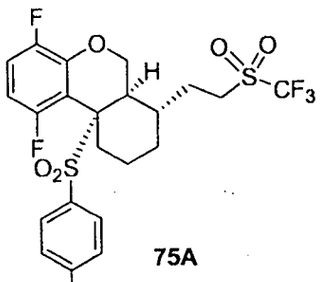
Alcohol **68A** was dissolved in 60 mL of dichloromethane and treated at with 2.50 g (5.91 mmol) of Dess-Martin reagent. After 30 min, completion of reaction was confirmed by TLC (30% ethyl acetate in hexanes was used as solvent) The reaction was quenched with a solution of 1 g sodium thiosulfate in 10 mL of water, followed by 10 mL of sat $NaHCO_3$. The bi-phasic mixture was stirred vigorously for 30 min, and extracted with dichloromethane. The organic phase was dried over Na_2SO_4, concentrated, and the residue chromatographed over silica gel eluting with 0-20% ethyl acetate in hexanes as solvent to furnish 2.356 g of aldehyde **72A**. ^{1}H-NMR (CDCl3 400 MHz) δ 9.67 (s, 1 H), 7.62 (d, J = 8.6 Hz, 2 H), 7.50 (d, J = 8.6 Hz, 2 H), 7.12-7.05 (m, 1 H), 6.49-6.41 (m, 1 H), 5.17 (dd, J = 12.3, 2.7 Hz, 1 H), 4.33 (d, J = 12.1 Hz, 1 H), 3.02 (d, J = 11.7 Hz, 1 H), 2.68 (d, 11.7 Hz, 1 H), 2.53 (m, 1 H), 1.96 (m, 1 H), 1.92-1.81 (m, 2 H), 1.33-1.09 (ser. m., 2 H).

Step 9

To a stirring suspension of 14.42 g (40.36 mmol) of methyl triphenylphosphonium bromide in 200 mL of THF at -40 °C was added dropwise 15.52 mL (38.8 mmol) of 2.5 M solution of n-butyl lithium in hexanes, after which the reaction was stirred in an ice bath for 45 min. To this yellow mixture of Wittig reagent was added a solution of the 6.62 g (15.52 mmol) of aldehyde **72A** in 75.0 mL of THF. The mixture was stirred 1 hr at 0 °C, then cooling was removed and stirring continued for additional 2 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by column chromatography over silica gel eluting with a gradient of 0-20% ethyl acetate in hexanes as solvent to furnish 5.560 g of alkene **73A**. ^{1}H-NMR (CDCl3 400 MHz) δ 7.60 (d, J = 8.6 Hz, 2 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.10-7.03 (m, 1 H), 6.44-6.37 (m, 1 H), 5.62 (dt, J = 18.0, 8.9 Hz, 1 H), 5.18 (s, 1 H), 5.15 (d, J = 5.8 Hz, 1 H), 5.06 (dd, J = 11.8, 2.8 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 2.59 (d, J = 13.2 Hz, 1 H), 2.38 (d, J = 12.2 Hz, 1 H), 2.09-1.97 (m, 1 H), 1.96-1.87 (m, 1 H), 1.75-1.64 (m, 2 H), 1.38-1.25 (m, 1 H), 1.17-1.04 (m, 1 H)

Step 10

To a solution of 1.90 g (4.47 mmol) of alkene **73A** in 10 mL of THF under nitrogen was added 17.88 mL (8.94 mmol) of 0.5 M solution of 9-BBN-THF. The flask was equipped with a reflux condenser and placed in a pre-heated oil bath at 80 °C for 1 hr. The reaction mixture was cooled down to 0 °C and treated dropwise with 7.96 g of 35% aqueous solution of hydrogen peroxide and then dropwise with 13.4 mL of 2M NaOH. The milky mixture was stirred for 1 hr at ambient temperature. Water (50 mL) was added and the mixture was extracted 3x100 mL portions of ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo, with bath temperature not exceeding 40 °C. The residue was purified by column chromatography over silica gel eluting with a gradient of 0-40 ethyl acetate in hexanes to furnish 1.8 g of alcohol **74A-rac**. ^{1}H-NMR (CDCl3 400 MHz) δ 7.61 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.09-7.02 (m, 1 H), 6.45-6.38 (m, 1 H), 5.17 (dd, J = 12.5, 2.3 Hz, 1 H), 4.61 (d, J = 12.5 Hz, 1 H), 3.80-3.71 (m, 1 H), 3.71-3.63 (m, 1 H), 2.56 (d, J = 13.7 Hz, 1 H), 2.41 (d, J = 10.0 Hz, 1 H), 2.04-1.67 (ser. m., 4 H), 1.19-1.00 (ser. m., 5 H).



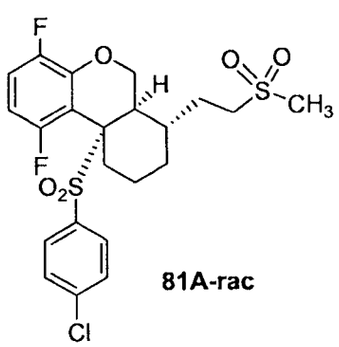
75A

Step 11

Starting from alcohol **74A-rac** and using an analogous procedure as described in Step 7 above, sulfone **75A-rac** was obtained. MS: Calcd. for $C_{22}H_{21}ClF_5O_5S_2$ (MH^+), m/z = 559.04.; found 559.3. Retention time: 5.08 min.

The following compounds were prepared analogously:

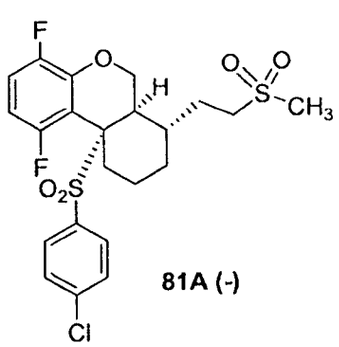
Compound **81A-rac**



81A-rac

MS: Calcd. for $C_{22}H_{23}ClF_2O_5S_2$ (MH^+), m/z = 505.1.; found 505.3. Retention time: 4.47 min. Resolution of this compound using Chiralcel OD chromatography gave:

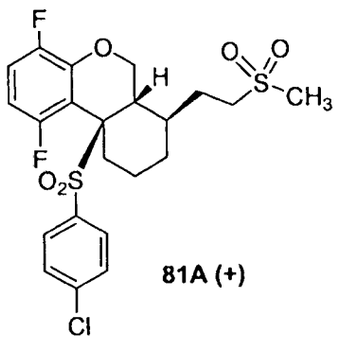
Compound **81A(-)**



81A (-)

MS: Calcd. for $C_{22}H_{23}ClF_2O_5S_2$ (MH^+), m/z = 505.1.; found 505.3. Retention time: 4.47 min.

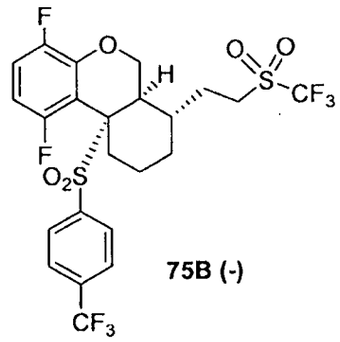
Compound **81A(+)**



81A (+)

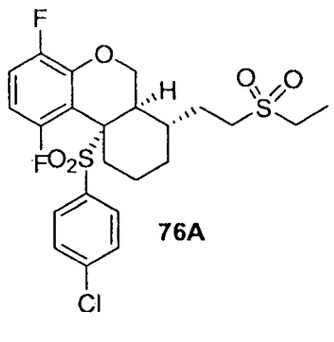
MS: Calcd. for $C_{22}H_{24}ClF_2O_5S_2$ (MH^+), m/z = 505.1.; found 505.3. Retention time: 4.47 min.

Compound **75B(-)**



75B (-)

^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H), 7.78 (d, 2H), 7.06-7.12 (m, 1H), 6.41-6.47 (m, 1H), 5.17 (dd, 1H), 4.58 (d, 1H), 3.63 (m, 1H), 3.47-3.54 (m, 1H), 2.52 (d, 1H), 2.44 (d, 1H), 2.21-2.29 (m, 1H), 1.92 (tt, 1H), 1.67-1.84 (m, 3H), 1.55-1.63 (m, 1H), 1.02 (m, 2H).



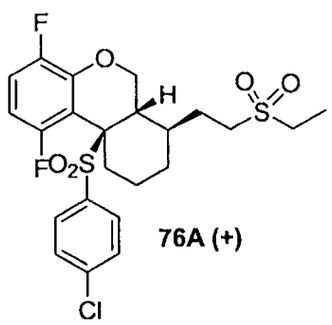
76A

Step 12

Alcohol **74A-rac** was tosylated using an analogous procedure to that described in Scheme 1, Step 12 and converted to sulfone **76A** using an analogous procedure to that described in Scheme 1, Step 14. **76A-rac:** MS: Calcd. for $C_{23}H_{26}ClF_2O_5S_2$ $(M+1)^+$,m/z = 519.09; found 519.3. Retention time: 4.58 min. Using chiral chromatography on a Chiralcel OD column, **76A (-)** was isolated $[\alpha]_D^{20}$ -163.18° (c=1, dichloromethane).

The following compounds were prepared analogously:

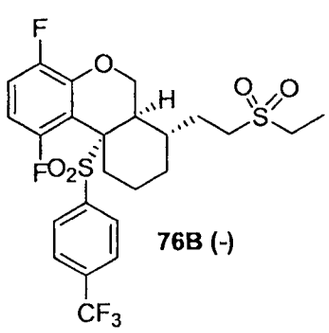
Compound **76A(+)**



76A (+)

MS: Calcd. for $C_{23}H_{26}ClF_2O_5S_2$ $(M+1)^+$,m/z = 519.09; found 519.3. Retention time: 4.58 min.

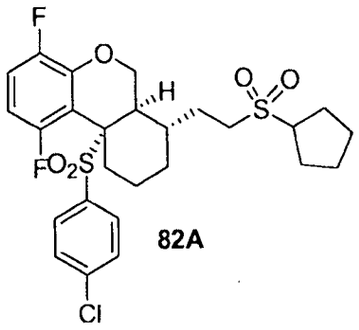
Compound **76B(-)**



76B (-)

MS: Calcd. for $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$,m/z = 553.1; found 553.3. Retention time: 4.64 min.

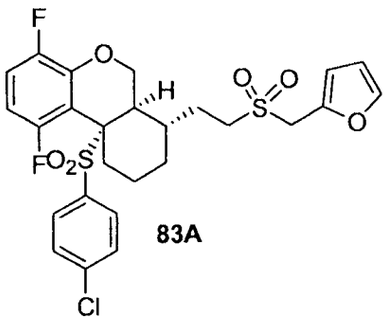
Compound **82A**



82A

MS: Calcd. for $C_{26}H_{30}ClF_2O_5S_2$ $(M+1)^+$,m/z = 559.1; found 559.3. Retention time: 4.92 min.

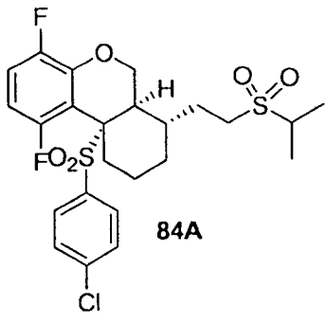
Compound **83A**



83A

MS: Calcd. for $C_{26}H_{26}ClF_2O_6S_2$ $(M+1)^+$,m/z = 571.1; found 571.3. Retention time: 4.81 min.

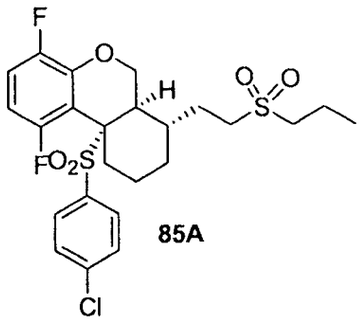
Compound **84A**



84A

MS: Calcd. for $C_{24}H_{28}ClF_2O_5S_2$ $(M+1)^+$,m/z = 533.1; found 533.1. Retention time: 4.70 min.

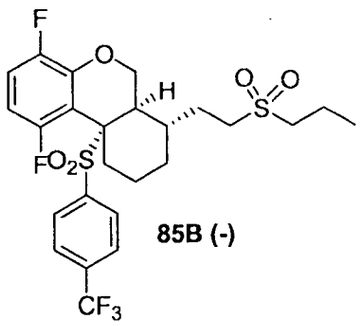
Compound **85A**



85A

MS: Calcd. for $C_{24}H_{28}ClF_2O_5S_2$ $(M+1)^+$,m/z = 533.1; found 533.3. Retention time: 4.76 min.

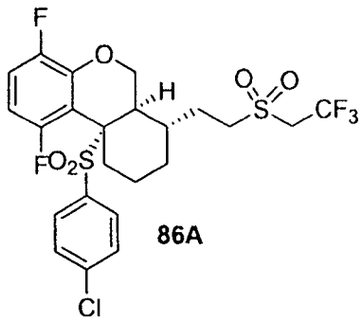
Compound **85B**



85B (-)

MS: Calcd. for $C_{25}H_{28}F_5O_5S_2$ $(M+1)^+$,m/z = 567.1; found 567.3. Retention time: 4.79 min.

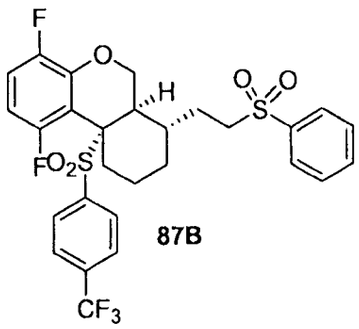
Compound **86A**



86A

MS: Calcd. for $C_{23}H_{23}ClF_5O_5S_2$ $(M+1)^+$,m/z = 573.1; found 573.3. Retention time: 4.86 min.

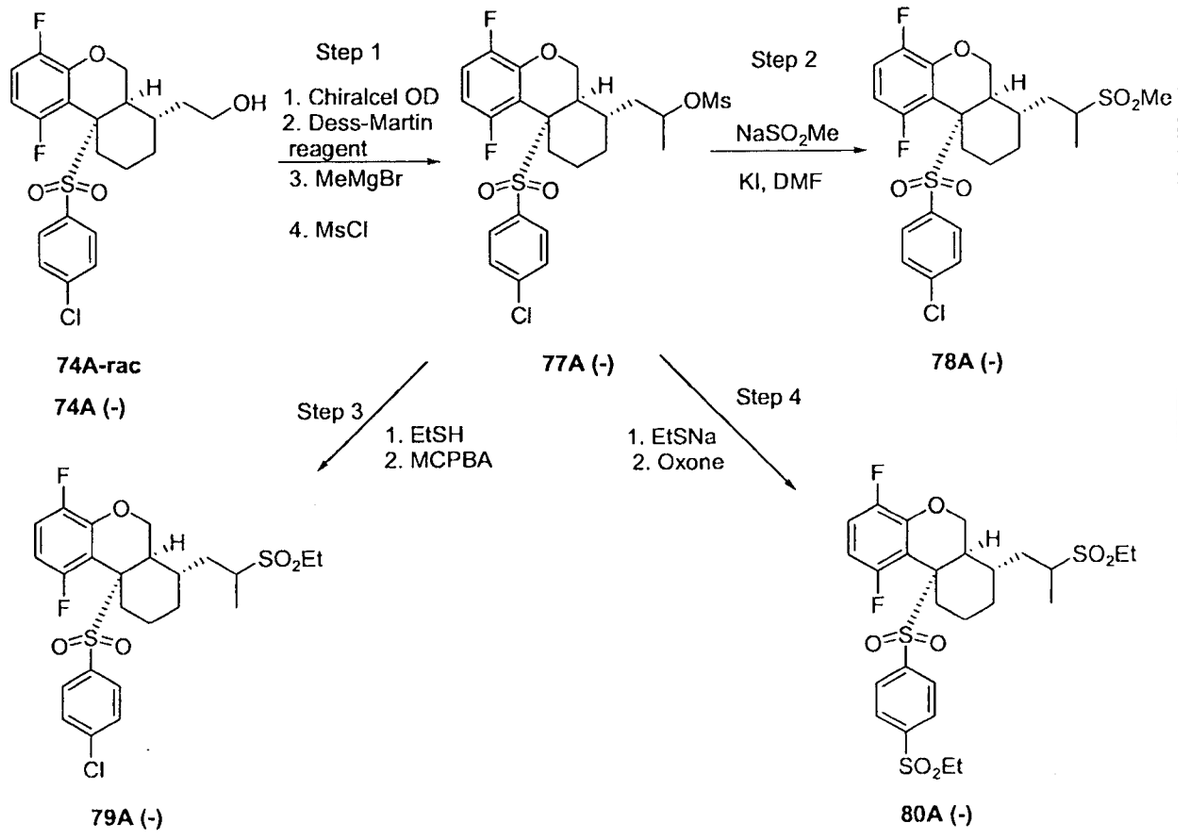
Compound **87B**



87B

MS: Calcd. for $C_{28}H_{26}F_5O_5S_2$ $(M+1)^+$,m/z = 601.1; found 601.3. Retention time: 4.95 min.

Scheme 17:



Step 1

Alcohol 10 was resolved using a Chiracel OD column eluting with 30% isopropyl alcohol in hexanes. First eluting peak **74A (+)** has positive optical rotation, $[\alpha]_D^{20}$

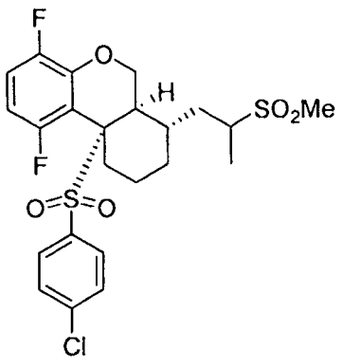
+1.71° (c=0.6, dichloromethane). Second eluting peak **74A (-)** has negative optical rotation, $[\alpha]_D^{20}$ -1.69° (c=0.5, dichloromethane). For subsequent chemistry, **74 (-)** was used.

Alcohol **74 (-)** was oxidized to an aldehyde using a procedure analogous to that of Scheme 16, Step 8. ^{1}H-NMR (CDCl3 400 MHz) δ 9.76 (dd, J = 2.5, 1.1 Hz, 1 H), 7.61 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.13-7.05 (m, 1 H), 6.49-6.41 (m, 1 H), 5.21 (dd, J = 12.6, 2.5 Hz, 1 H), 4.43 (d, J = 12.5 Hz, 1H), 2.79 (dd, J = 16.8, 2.5 Hz, 1 H), 2.57 (d, J = 12.6 Hz, 1 H), 2.50 (d, J = 11.5 Hz, 1 H), 2.40 (ddd, J = 17.0, 8.8, 2.7 Hz, 1 H), 2.02-1.67 (ser. m., 4 H), 1.19-1.07 (m, 2 H).

The resulting aldehyde (100 mg, 0.227 mmol) was dissolved in 2.0 mL of THF, cooled to 0 °C and treated with 0.113 mL (0.34 mmol) of a 3M solution of methylmagnesium bromide in ether. After 10 min of stirring, the mixture was quenched with water and extracted with ethyl acetate to furnish 40 mg of the secondary alcohol. ^{1}H-NMR (CDCl3 400 MHz) δ 7.61 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.10-7.01 (m, 1 H), 6.46-6.39 (m, 1 H), 5.16 (dd, J = 12.6, 2.5 Hz, 1 H), 4.61 (d, J = 13.0 Hz, 1H), 3.89 (m, 1 H), 2.57 (d, J = 14.8 Hz, 1 H), 2.34 (d, J = 12.8 Hz, 1 H), 1.94-1.68 (ser. m., 3 H), 1.30-1.19 (ser. M., 2 H), 1.23 (d, J = 6.0 Hz, 3 H), 1.14-1.05 (ser. m., 2 H).

The secondary alcohol was mesylated according to the procedure of Scheme 16, Step 5 to give intermediate mesylate **77A (-)**: ^{1}H-NMR (CDCl3 400 MHz) δ 7.61 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.10-7.01 (m, 1 H), 6.46-6.39 (m, 1 H), 5.16 (dd, J = 12.5, 2.5 Hz, 1 H), 4.87 (m, 1 H), 4.55 (d, J = 12.1 Hz, 1H), 2.97 (s, 3 H), 2.57 (d, J = 13.3 Hz, 1 H), 2.34 (d, J = 12.1 Hz, 1 H), 2.09 (m, 1 H), 2.00-1.83 (ser. m., 2 H), 1.74-1.65 (m, 1 H), 1.46 (d, J = 6.2 Hz, 3 H), 1.40-1.31 (ser. m., 2 H), 1.13-1.02 (m, 2 H).

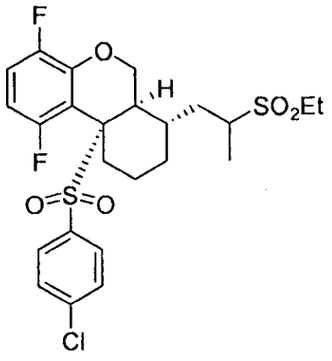
Step 2



78A (-)

Mesylate **77A (-)** was converted to sulfone **78A (-)** using a procedure analogous to that used in Scheme 16, Step 6. MS: Calcd. for $C_{23}H_{26}ClF_2O_5S_2$ $(M+1)^+$, m/z = 519.09.; found 519.3. Retention time: 4.38 min.

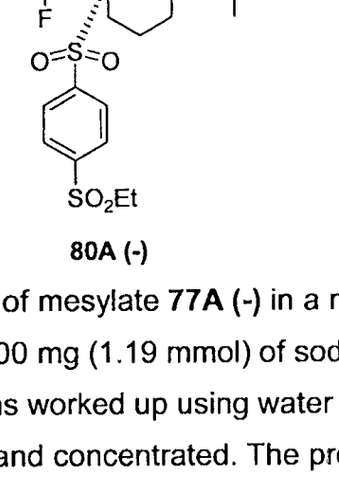
Step 3



79A (-)

Mesylate **77A (-)** was converted to sulfone **79A (-)** using a procedure analogous to that used in Scheme 16, Step 12. MS: Calcd. for $C_{24}H_{28}ClF_2O_5S_2$ $(M+1)^+$, m/z = 533.10; found 533.3. Retention time: 4.66 min.

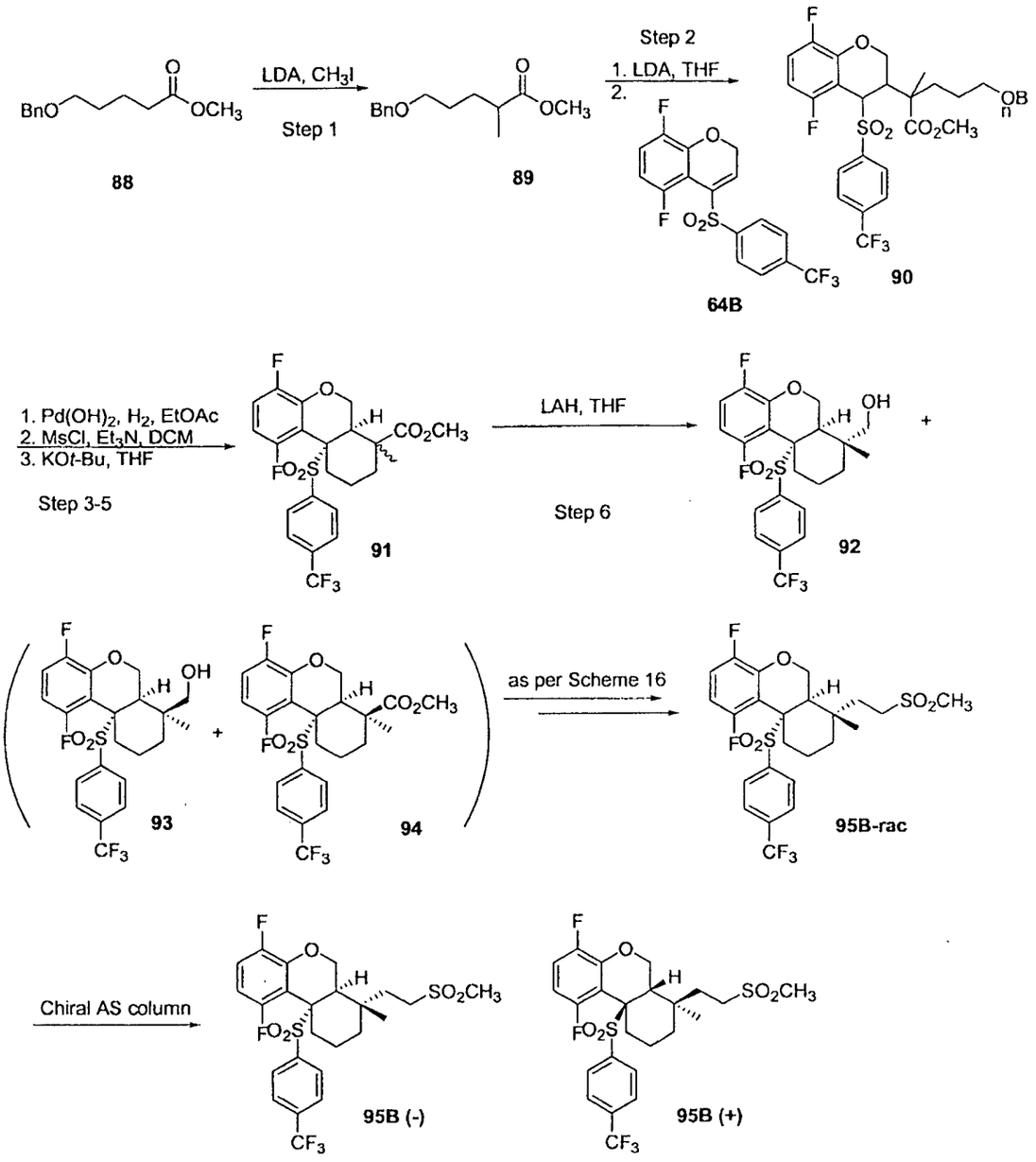
Step 4



80A (-)

A solution of 0.088 mmol of mesylate **77A (-)** in a mixture of 1.0 mL THF and 1.0 mL of DMF was treated with 100 mg (1.19 mmol) of sodium ethylthiolate. After 1 hr of stirring the reaction mixture was worked up using water and ethyl acetate. Organic phase was dried over $MgSO_4$ and concentrated. The product was re-dissolved in a mixture 0.88 mL of acetone and 0.22 mL of water and treated with 215 mg (0.35 mmol) of oxone. After 2 hrs of stirring the solids were filtered out and the product was placed on a preparative TLC plate and eluted with a mixture of 80% of ethyl acetate and 20% hexanes to furnish 9.0 mg of sulfone **80A (-)**. MS: Calcd. for $C_{26}H_{33}F_2O_7S_3$ $(M+1)^+$, m/z = 591.14; found 591.3. Retention time: 4.11 min.

Scheme 18:



Step 1

At 0 °C, to diisopropylamine (15 g, 1.1 equiv.) in 300 mL of THF was added 60 mL of *n*-BuLi (2.5 M in toluene, 0.15 mol, 1.1 equiv.) dropwise within 10 mins, and the reaction mixture was stirred for an additional 10 mins. The reaction was cooled to -78 °C and methyl ester **88** in 100 mL of THF was added within 20 minutes. The reaction was stirred for 30 minutes, followed by the addition of 21 g of iodomethane (0.15 mol, 1.1 equiv.) in 100 mL of THF dropwise over 30 mins. The reaction mixture was stirred

for an hour with temperature slowly rising to r.t. The reaction was quenched with 500 mL of brine, and diluted with 1 L of EtOAc. The organic layer was separated, washed with 200 mL of brine, dried over Na_2SO_4 and concentrated. The crude reaction mixture was purified by the column chromatography over silica gel eluting with a gradient from 100% hexanes to 25% EtOAc/Hexane over 45 mins to give 20.0 g of compound **89** (63% yield). ^{1}H-NMR (CDCl3 400 MHz) δ: 7.40-7.20 (m, 5H), 4.49 (s, 2H), 3.66 (s, 3H), 3.46 (t, J = 6.59, 2H), 2.52-2.40 (m, 1H), 1.78-1.46 (m, 4H), 1.16 (d, J = 6.4 Hz, 2H).

Step 2

At 0 °C, to diisopropylamine (6.1g, 60 mmol, 3.0 equiv.) in 200 mL of THF was added dropwise 37.5 mL of 1.6 N *n*-BuLi in hexanes (60.0 mmol, 3.0 equiv.). The reaction was stirred for 10 mins, followed by the addition of 14.1 g of **89** (60 mmol, 3.0 equiv.) in 60 mL of anhydrous THF. The reaction was stirred at 0 °C for another 30 minutes before cooling to -78 °C. Vinyl sulfone **64B** (6.9 g, 20 mmol, 1.0 equiv.) in 70 mL of THF was cooled to -78 °C, and added to the above reaction mixture. The cooling bath was removed and the mixture was stirred for 20 mins, quenched with 400 mL of water, and diluted with 300 mL of EtOAc. The organic layer was washed with 2 200-mL portions of 1N HCl solution, 100 mL of brine, dried over Na_2SO_4 and concentrated. The crude reaction mixture was purified by the column chromatography over silica gel eluting with a gradient from hexanes to 20% EtOAc/Hexane over 45 mins to give 9.7 g of compound **90** (78% yield) as a mixture of diastereomers. This material was used directly in the next reaction.

Steps 3-5

To 9.7 g of **90** (16 mmol, 1.0 equiv.) in 200 mL of EtOAc was added 1 g of $Pd(OH)_2$ and the mixture was stirred under 1 atm of H_2 at r.t. for 30 mins. The catalyst was filtered through a pad of celite, and solvent was removed in vacuo. The crude reaction mixture was dissolved in 200 mL of dichloromethane, followed by the addition of 8 mL Et_3N and 5 mL of methanesulfonyl chloride. The reaction was stirred at r.t. for 10 mins, and quenched with 200 mL of water and diluted 100 mL of dichloromethane. The organic layer was separated, washed with 200 mL of 1N HCl solution, 200 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The residue

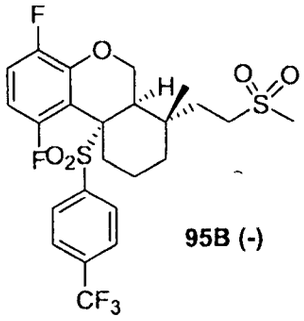
was dissolved in 200 mL of anhydrous THF, followed by the addition of 40 mL of KO*t*-Bu (1M in *t*-BuOH). The mixture was stirred at r.t. for 10 mins and 300 mL of EtOAc was added. The organic layer was washed with 2 100-mL portions of brine, dried over Na_2SO_4 and concentrated. The crude reaction mixture was purified by column chromatography over silica gel eluting with a gradient from hexanes to 25% EtOAc/Hexane over 45 mins, to give 7.3 g of a mixture of two diastereomers **91** (14.4 mmol, 90% yield for three steps). MS: Calcd for $C_{23}H_{22}F_5O_5S$ $[M\text{-}HSO_2C_6H_4CF_3+H]^+$: m/z = 295.2 (5.01 min), 295.2 (5.12 min).

Step 6

To 7.3 g of the mixture **91** (14.4 mmol, 1.0 equiv.) in 200 mL of THF was added 0.7 g LAH (18.4 mmol, 1.3 equiv.). The reaction was stirred at r.t. for 35 mins and the TLC showed starting material and two new spots. The reaction was quenched with 100 mL of 1N HCl and diluted with 300 mL of EtOAc. The organic layer was separated, washed with 200 mL of 1N HCl, 100 mL of brine, dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by column chromatography over silica gel three times eluting with a gradient from hexanes to 40% EtOAc/Hexane over 30 mins to give three different compounds: recovered *trans*-isomer **94**, *trans*-isomer **93** and 3.5 g of alcohol **92** (7.3 mmol). Alcohol **92:** ^{1}H-NMR ($CDCl_3$ 400 MHz) δ: 7.82-7.66 (m, 4H), 7.10-7.03 (m, 1H), 6.42-6.32 (m, 1H), 5.14 (dd, *J* = 4.8, 12.8 Hz, 1H), 4.71 (d, *J* = 12.4 Hz, 1H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.29 (d, *J* = 12.0 Hz, 1H), 3.00 (d, *J* = 4.8 Hz, 1H), 2.59 (d, *J* = 13.2 Hz, 1H), 2.01-1.90 (m, 1H), 1.79-1.62 (m, 2H), 1.39-1.18 (m, 2H), 0.65 (s, 3H). MS: Calcd for $C_{22}H_{22}F_5O_4S$ $(M+1)^+$ m/z = 477.1, found 477.3, Rt = 4.69 min

Using procedures analogous to those in Scheme 16, compound **95B-rac** was prepared. MS: Calcd for $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$ m/z = 553.1, found 533.3, Rt = 4.60 min. This compound was resolved on a Chiralpak AS column to give the following enantiomers:

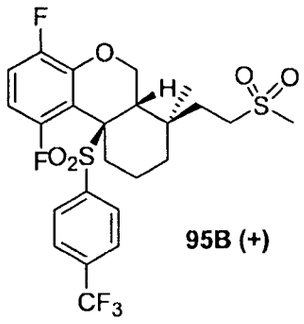
Compound **95B(-)**



95B (-)

MS: Calcd for $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$ m/z = 553.1, found 533.3, Rt = 4.65 min.

Compound **95B(+)**

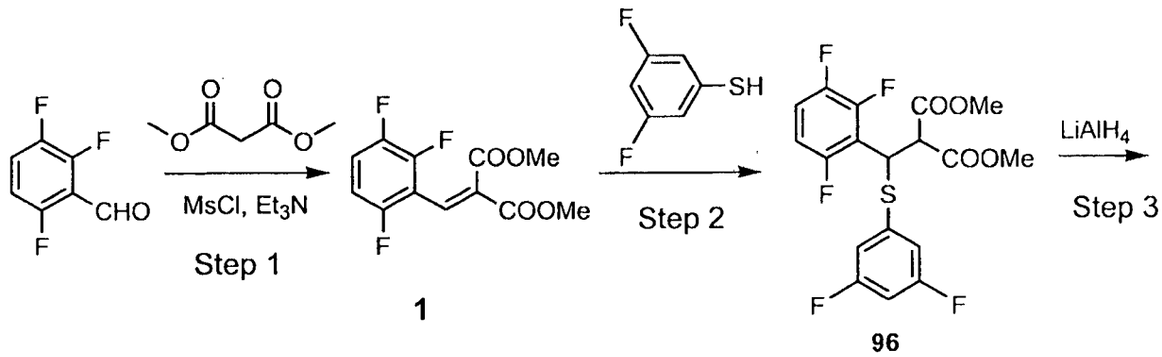


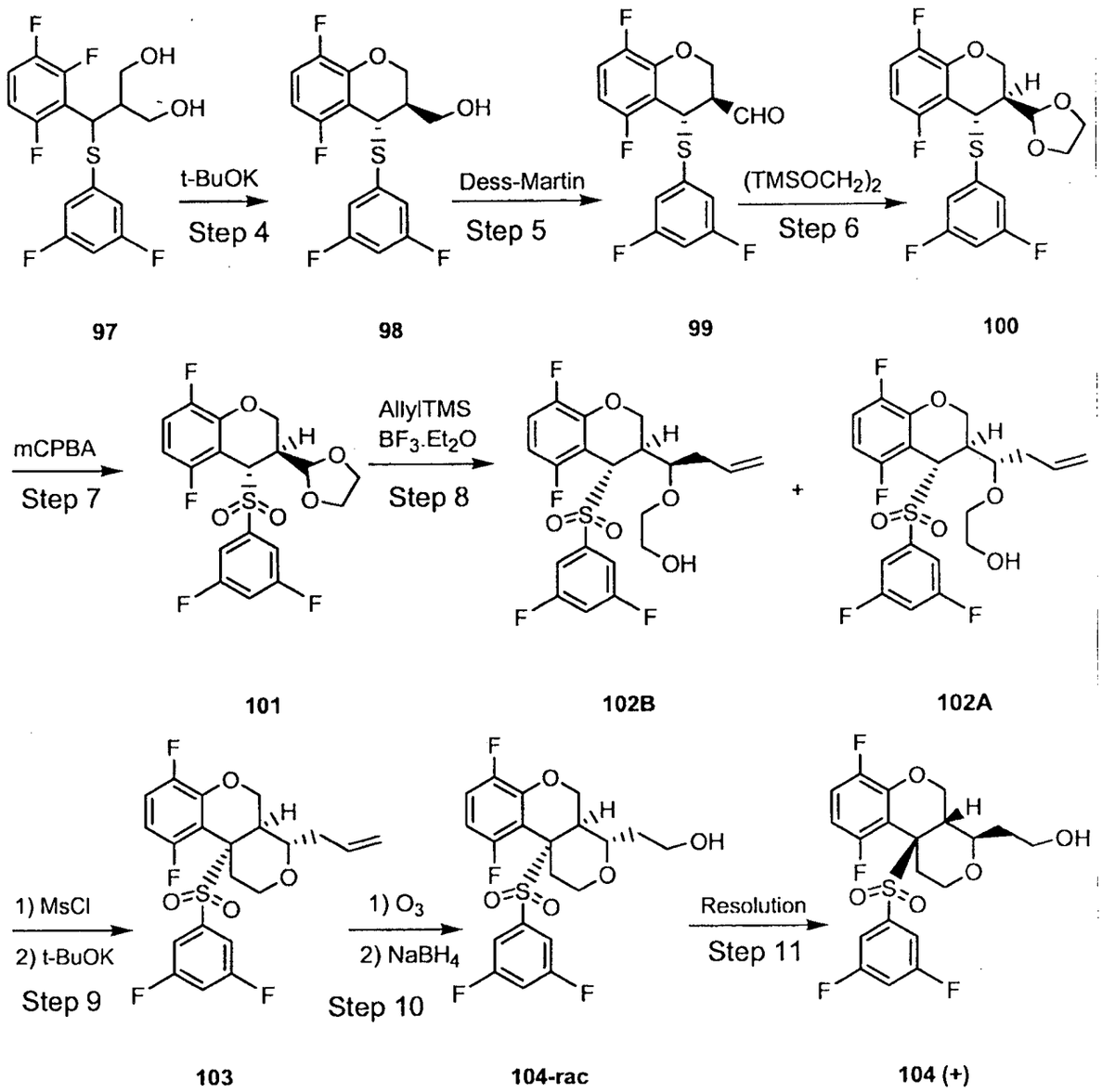
95B (+)

MS:

Calcd for $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$ m/z = 553.1, found 533.3, Rt = 4.65 min.

Scheme 19:

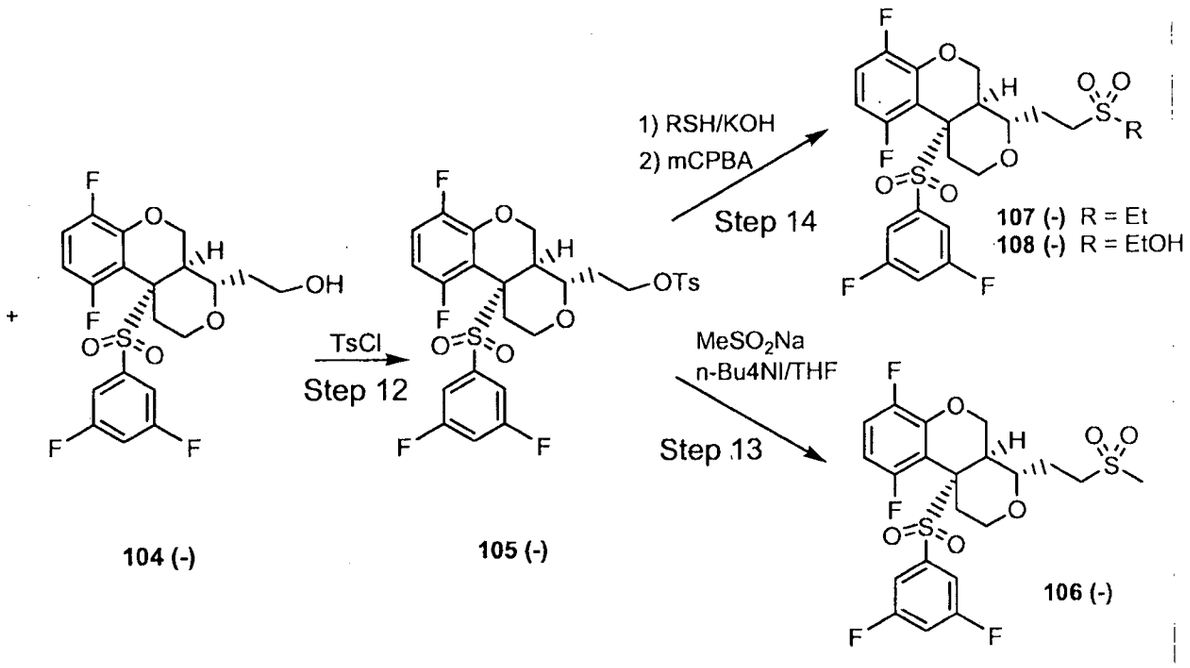




97 98 99 100

101 102B 102A

103 104-rac 104 (+)



Step 1

See Process Example 2 below.

Step 2

To a solution of 20 g (72.9 mmol) of compound **1** and 10.7 g (72.9 mmol) of 3,5-difluorothiophenol in 500 mL of tetrahydrofuran was added 10.1 g (72.9 mmol) of potassium carbonate. After 5 h, it was quenched with 300 mL of water, extracted with two 300 mL portions of ethyl acetate. The combined organic extracts were washed with brine, concentrated and filtered. The filtrate was concentrated to give 31 g of crude compound **96**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.03 (m, 1 H), 6.93 (m, 2 H), 6.79 (m, 2 H), 5.15 (d, J = 12 Hz, 1 H), 4.35 (d, J = 12 Hz, 1 H), 3.84 (s, 3 H), 3.57 (s, 3 H).

Step 3

To a stirred suspension of 6.5 g (170 mmol) of lithium aluminum hydride in 600 mL of tetrahydrofuran was added at 0 °C a solution of 34 g (80.8 mmol) of compound **96** in 100 mL of tetrahydrofuran over a period of 1 h. It was stirred at room temperature for 2 h and quenched with 15 mL of water (cooled with ice-water bath). After addition of 500 mL of 6 N HCl, it was extracted with two 500 mL portions of ethyl ether followed by two 500 mL portions of ethyl acetate. The combined organic

extracts were washed with brine, concentrated, and the residue was purified by chromatography eluting with a gradient of 8% to 90% of ethyl acetate in hexanes to give 9.1 g of compound **97**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.05 (m, 1 H), 6.90 (m, 2H), 6.80 (m, 1 H), 6.66 (m, 1 H), 4.99 (d, J = 12 Hz, 1 H), 4.33 (m, 1 H), 4.21 (d, J = 11 Hz, 1 H), 3.85 (dd, J = 11, 2..4 Hz, 1 H), 3.50 (m, 1 H), 2.46 (m, 1 H), 2.20 (br s, 2 H).

Step 4

To a stirred solution of 9.1 g (25 mmol) of compound **97** in 50 mL of tetrahydrofuran cooled to 0 °C was added a solution of 27.5 mL (27.5 mmol) of potassium tert-butoxide (1.0M in THF). It was stirred at room temperature for 1.5 h and quenched with 100 mL of 1 N HCl. The reaction mixture was extracted with three 100 mL portions of dichloromethane. The combined organic extracts were concentrated, and the residue was purified by chromatography eluting with a gradient of 5% to 40% of ethyl acetate in hexanes to give 6.0 g of compound **98**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.04 (m, 3 H), 6.71 (m, 1H), 6.59 (m, 1 H), 4.68 (s, 1 H), 4.57 (dd, J = 11, 2.2 Hz, 1 H), 4.44 (d, J = 11.7 Hz, 1 H), 3.76 (m, 1 H), 3.58 (m, 1 H), 2.32 (m, 1 H), 1.62 (s, 1 H).

Step 5

To a stirred solution of 6 g (17.4 mmol) of compound **98** in 100 mL of dichloromethane was added 8.9 g (21 mmol) of Dess-Martin periodinane. The mixture was stirred at room temperature for 2 h, concentrated in vacuo and diluted with 100 mL of ethyl ether. It was stirred with 100 mL of saturated sodium bicarbonate and 100 mL of 10% sodium thiosulfate solution and extracted twice with ethyl ether. The combined organic extracts were washed three times with saturated sodium bicarbonate, dried over magnesium sulfate and filtered. The filtrate was concentrated to give 6.0 g of aldehyde **99**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 9.74 (d, J = 1.5 Hz, 1 H), 7.02 (m, 3 H), 6.78 (m, 1 H), 6.64 (m, 1 H), 5.00 (s, 1 H), 4.94 (d, J = 11.7 Hz, 1 H), 4.74 (d, J = 11.7 Hz, 1 H), 2.88 (s, 1 H).

Step 6

To a stirred solution of 6.0 g (17.4 mmol) of compound **99** in 90 mL of dichloromethane were added 4.31 g (20.9 mmol) of 1,2-bis(trimethylsiloxy)ethane and

0.39 g (1.75 mmol) of trimethylsilyl trifluoromethanesulfonate at -78 °C. After 30 min, it was warmed to room temperature and stirred for 12 h. The reaction was diluted with dichloromethane and washed with three 100 mL portions of saturated sodium bicarbonate, and water. The organic phase was concentrated to give 6.1 g of compound **100**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.01 (m, 3 H), 6.68 (m, 1 H), 6.59 (m, 1 H), 4.83 (s, 1H), 4.81 (dd, J = 7.3, 2.2 Hz, 1 H), 4.60 (dd, J = 11.7, 2.2 Hz, 1 H), 4.56 (dd, J = 11.7, 2.2 Hz, 1 H), 3.94 (m, 5 H), 2.18 (d, J = 7.3 Hz, 1 H).

Step 7

To a stirred solution of 6.1 g (15.8 mmol) of compound **100** in 150 mL of dichloromethane was added 7.9 g (32 mmol) of 3-chloroperoxybenzoic acid. After 2 h, the reaction mixture was diluted with 200 mL of dichloromethane and washed with four 200 mL portions of saturated sodium bicarbonate. It was filtered, concentrated and the residue was purified by chromatography eluting with a gradient of 12% to 100% of dichloromethane in hexanes to give 4.7 g of compound **101**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.39 (m, 2 H), 7.14 (m, 1 H), 7.02 (m, 1 H), 6.41 (m, 1 H), 4.86 (dd, J = 11.7, 3.7 Hz, 1 H), 4.73 (m, 2 H), 4.66 (dd, J = 11.7, 1.5 Hz, 1 H), 3.99-3.79 (m, 3 H), 2.89 (m, 1 H).

Step 8

A solution of 4.7 g (11.2 mmol) of compound **101**, 6.4 g (56 mmol) of allyltrimethylsilane and 7.9 g (56 mmol) of boron trifluoride etherate in 75 mL of dichloromethane was stirred at room temperature for 1 day. Additional 3.2 g (28 mmol) of allyltrimethylsilane and 4.0 g (28 mmol) of boron trifluoride etherate were added, and the mixture was stirred at reflux for another day. An Additional 3.2 g (28 mmol) of allyltrimethylsilane and 4.0 g (28 mmol) of boron trifluoride etherate were added, and the mixture was stirred at reflux for another two days. The reaction was cooled (ice bath) and quenched dropwise with 50 mL of saturated sodium bicarbonate, and extracted with two 100 mL potions of dichloromethane followed by two 100 mL portions of ethyl acetate. The combined organic extracts were concentrated and the residue was purified by chromatography eluting with a gradient of 8% to 66% of ethyl acetate in hexanes to give 2.3 g of compound **102A** and 1.3 g of **102B**. **102A**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.39 (m, 2 H), 7.14 (m, 1 H), 7.07 (m, 1

H), 6.49 (m, 1 H), 5.82 (m, 1 H), 5.20 (d, J = 11.7 Hz, 1 H), 4.97 (s, 1 H), 4.86 (dd, J = 12.4, 2.9 Hz, 1 H), 4.53 (s, 1 H), 4.43 (dd, J = 12.4, 1.5 Hz, 1 H), 3.67 (m, 3 H), 3.22 (m, 1 H), 3.13 (m, 1 H), 2.90 (m, 1 H), 2.54 (m, 1 H), 1.57 (m, 1 H). **102B**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.35 (m, 2 H), 7.14 (m, 1 H), 7.06 (m, 1 H), 6.48 (m, 1 H), 5.72 (m, 1 H), 5.11 (d, J = 10.3 Hz, 1 H), 5.07 (d, J = 16.8 Hz, 1 H), 4.80 (dd, J = 12.4, 2.9 Hz, 1 H), 4.67 (d, J = 11.7 Hz, 1 H), 4.53 (s, 1 H), 3.67 (m, 3 H), 3.50 (m, 1 H), 3.30 (m, 1 H), 2.92 (m, 1 H), 2.35 (m, 1 H), 1.85 (m, 1 H).

Step 9

To a solution of 2.3 g (5.37 mmol) of compound **102A** in 50 mL of dichloromethane were added 1.04 g (10.2 mmol) of triethylamine and 0.92 g (8.06 mmol) of methanesulfonyl chloride. The mixture was stirred at room temperature for 1 h. It was quenched with 80 mL of 1N HCl and extracted with two 100 mL portions of dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate, concentrated and the residue was dissolved in 50 mL of tetrahydrofuran and cooled to 0 °C. To this solution was added 12 mL (12 mmol) of 1 N potassium tert-butoxide in THF. The mixture was stirred at room temperature for 15 min., quenched with 100 mL of saturated ammonium chloride and extracted with two 100 mL portions of ethyl acetate. The combined organic extracts were washed with brine, concentrated and the residue was purified by chromatography eluting with a gradient of 2% to 20% of ethyl acetate in hexanes to give 0.90 g of compound **103**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.24 (m, 2 H), 7.11 (m, 2 H), 6.47 (m, 1 H), 5.85 (m, 1 H), 5.11 (m, 3 H), 4.46 (d, J = 13.2 Hz, 1 H), 3.93 (m, 1 H), 3.37 (m, 1 H), 3.15 (dd, J = 11.6, 11.6 Hz, 1 H), 2.65 (m, 3 H), 2.40 (m, 1 H), 2.31 (m, 1 H).

Step 10

To a stirred solution of 900 mg (2.03 mmol) of compound **103** in 20 mL of 1:1 dichloromethane/methanol at – 78 °C was bubbled with O_3 until blue color sustained. It was bubbled with N_2 to remove excess O_3. To this solution was added 230 mg (6.0 mmol) of sodium borohydride and warmed to 0 °C. The mixture was stirred at room temperature. After 30 min, and additional 300 mg (7.94 mmol) of sodium borohydride was added. After 14 h, the reaction mixture was quenched with 20 mL saturated ammonium chloride and concentrated. The residue was extracted with two 100 mL

portions of dichloromethane and the combined extracts were washed with saturated sodium bicarbonate and dried over magnesium sulfate to give 800 mg of compound **104-rac**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.25 (m, 2 H), 7.16 (m, 2 H), 6.49 (m, 1 H), 5.11 (dd, J = 12.4, 2.2 Hz, 1 H), 4.46 (d, J = 12.4 Hz, 1 H), 3.93 (m, 1 H), 3.79 (t, J = 5.9 Hz, 2 H), 3.50 (ddd, J = 12.4, 9.5, 2.9 Hz, 1 H), 3.20 (dd, J = 11.7, 11.7 Hz, 1 H), 2.68 (d, J = 11 Hz, 1 H), 2.55 (d, J = 13.2 Hz, 1 H), 2.34 (m, 3 H), 2.11 (m, 1 H), 1.83 (m, 2 H).

Step 11

Compound **104-rac** (800 mg) was resolved on Chiral OD column eluting with 20% isopropanol in hexanes and 40 mL /min flow rate to give two enantiomers **104 (+)** (310 mg, retention time 49-68 min, $[\alpha]_D^{20}$ +95.5°) and **104 (-)** (310 mg, retention time 71-88 min., $[\alpha]_D^{20}$ -89.9°).

Step 12

A solution of 305 mg (0.683 mmol) of compound **104 (-)**, 195 mg (1.02 mmol) of *p*-toluenesulfonyl chloride and 138 mg (1.4 mmol) of triethylamine in 7 mL of dichloromethane was stirred at room temperature for 6 h. Dimethylaminopyridine (10 mg) was added and the reaction stirred for 14 h. It was quenched with 80 mL of saturated ammonium chloride and extracted with two 80 mL portions of dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate, concentrated and the residue was purified by chromatography eluting with a gradient of 8% to 66% of ethyl acetate in hexanes to give 348 mg of compound **105 (-)**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.73 (dd, J = 8.8, 2.2 Hz, 2 H), 7.31 (dd, J = 8.8, 1.5 Hz, 2 H), 7.23 (m, 2 H), 7.14 (m, 2 H), 6.51 (m, 1 H), 5.05 (dd, J = 13.2, 2.9 Hz, 1 H), 4.31 (d, J = 12.4 Hz, 1 H), 4.18 (m, 2 H), 3.78 (m, 1 H), 3.27 (m, 1 H), 2.97 (dd, J = 12.4, 11.7 Hz, 1 H), 2.51 (d, J = 11.7 Hz, 1 H), 2.42 (s, 3 H), 2.26 (m, 1 H), 2.18 (m, 1 H), 1.79 (m, 1 H).

Step 13

A mixture of 75 mg (0.124 mmol) of compound **105 (-)** and 138 mg (0.375 mmol) of tetrabutylammonium iodide in 4 mL of tetrahydrofuran was stirred at reflux for 1.5 h. After addition of 50 mg (0.50 mmol) of sodium methanesulfinate, the mixture was

stirred at reflux for 18 h and diluted with 80 mL of saturated ammonium chloride. It was extracted with 80 mL of ethyl acetate, and the organic extract was washed with saturated sodium bicarbonate, brine, concentrated and the residue was purified by chromatography eluting with a gradient of 8% to 66% of ethyl acetate in hexanes to give 54 mg of compound **106 (-)**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.24 (m, 2 H), 7.13 (m, 2 H), 6.50 (m, 1 H), 5.13 (dd, J = 12.4, 2.9 Hz, 1 H), 4.48 (d, J = 12.4 Hz, 1 H), 3.94 (m, 1 H), 3.36 (m, 1 H), 3.28 (m, 1 H), 3.15 (dd, J = 12.4, 11.7 Hz, 1 H), 3.01 (m, 1 H), 2.91 (s, 3 H), 2.57 (m, 2 H), 2.44 (m, 1 H), 2.32 (m, 1 H), 2.04 (m, 1 H). MS: Calcd. for $C_{21}H_{21}F_4O_6S_2$ (MH^+), 509.6; found 509.3. Retention time: 4.20 min.

Step 14

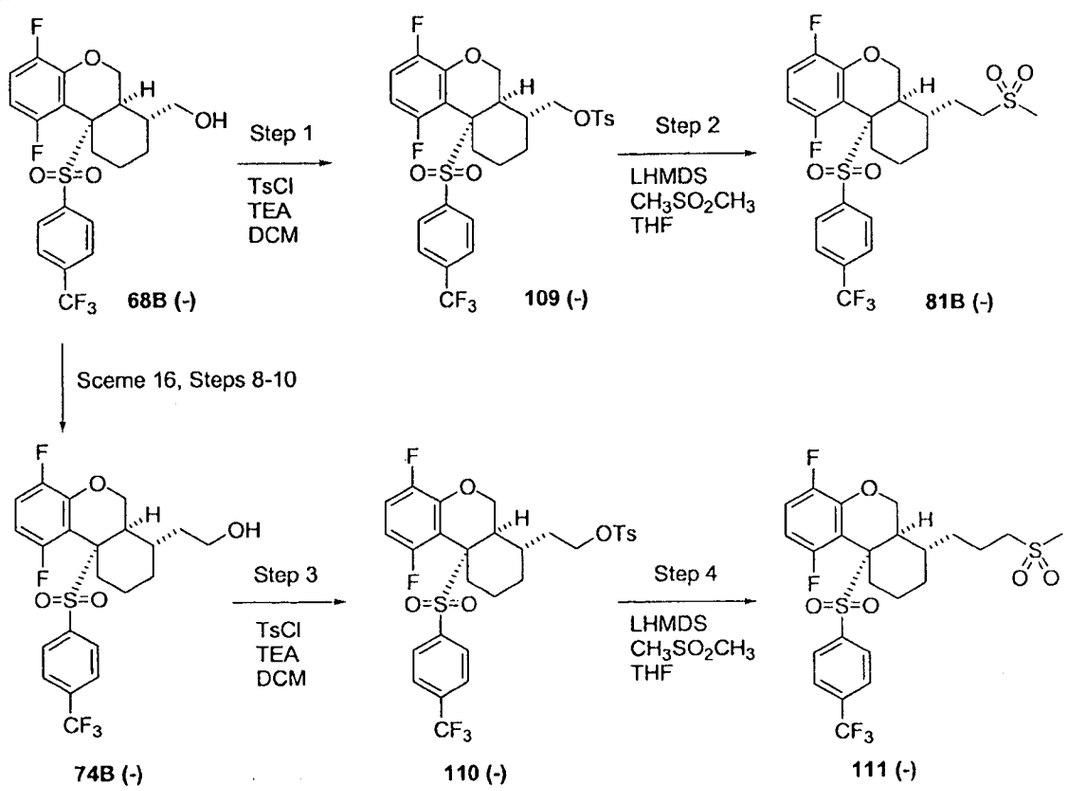
A mixture of 50 mg (0.08 mmol) of compound **105 (-)** and 10.6 mg (0.17 mmol) of ethanethiol and 8 mg (0.15 mmol) of potassium hydroxide was stirred at 50 °C for 1 h and diluted with saturated ammonium chloride. The reaction mixture was extracted with three 20 mL portions of dichloromethane. The combined organic extracts were concentrated and the crude sulfide product was dissolved in 1 mL of dichloromethane. To this solution was added 50 mg (0.29 mmol) of 70% 3-chloroperoxybenzoic acid. After stirring at room temperature for 14 h, it was diluted with 20 mL of saturated sodium carbonate and extracted with three 20 mL portions of ethyl acetate. The combined organic extracts were washed with brine and concentrated. The residue was purified by preparative thin layer chromatography eluting with 33% of ethyl acetate in hexanes to give 35.8 mg of compound **107 (-)**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.26 (m, 2 H), 7.16 (m, 2 H), 6.50 (m, 1 H), 5.16 (d, J = 13.2, Hz, 1 H), 4.48 (d, J = 12.4 Hz, 1 H), 3.91 (m, 1 H), 3.36 (m, 1 H), 3.22 (m, 1 H), 3.15 (dd, J = 12.4, 11.7 Hz, 1 H), 3.01 (m, 3 H), 2.59 (d, J = 13.2 Hz, 2 H), 2.45 (m, 1 H), 2.32 (m, 1 H), 2.02 (m, 1 H), 1.40 (t, J = 7.3 Hz, 3 H). MS: Calcd. for $C_{22}H_{23}F_4O_6S_2$ (MH^+), 523.1; found 523.3. Retention time: 4.29 min.

Step 14 (alternate)

A mixture of 50 mg (0.08 mmol) of compound **105 (-)** and 105 mg (0.280 mmol) of tetrabutylammonium iodide in 2 mL of tetrahydrofuran was stirred at reflux for 3.5 h. The reaction mixture was diluted with 50 mL of ethyl ether, washed with 1N HCl, saturated sodium bicarbonate, dried and concentrated. The residue was dissolved in

1 mL of ethanol and 26 μL (0.37 mmol) of β-mercaptoethanol and 10 mg (0.18 mmol) of potassium hydroxide was stirred at 50 °C for 1 h and diluted with saturated ammonium chloride. The reaction mixture was extracted with three 20 mL portions of dichloromethane. The combined organic extracts were concentrated and the crude sulfide product was dissolved in 1 mL of dichloromethane. To this solution was added 60 mg (0.35 mmol) of 70% 3-chloroperoxybenzoic acid. After stirring at room temperature for 14 h, it was diluted with 20 mL of saturated sodium carbonate and extracted with three 20 mL portions of dichloromethane. The combined organic extracts were concentrated. The residue was purified by preparative thin layer chromatography eluting with 67% of ethyl acetate in hexanes to give 39.4 mg of compound **108 (-)**. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.24 (m, 2 H), 7.14 (m, 2 H), 6.50 (m, 1 H), 5.11 (d, J = 12.4, Hz, 1 H), 4.49 (d, J = 12.4 Hz, 1 H), 4.11 (m, 2 H), 3.90 (d, J = 11.7 Hz, 1 H), 3.36 (m, 2 H), 3.21 (m, 2 H), 3.14 (m, 2 H), 2.57 (m, 2 H), 2.45 (m, 1 H), 2.31 (m, 1 H), 2.06 (m, 1 H). MS: Calcd. for $C_{22}H_{23}F_4O_7S_2$ (MH^+), 539.1; found 539.3. Retention time: 3.88 min.

Scheme 20:



Compound **68B (-)** was prepared similar to Scheme 16, Steps 1-4 starting with vinyl sulfone **64B** and resolved on a Chiralcel OD column.

Step 1

To a solution of 0.165 g of alcohol **68B (-)** (0.357 mmol) in dichloromethane (10 mL) was added 0.15 mL of Et_3N (0.1 mmol,) and 0.137 g of TsCl (0.718 mmol,) respectively. The mixture was stirred at room temperature overnight. Tosyl chloride (0.14 g) was added and stirred at room temperature overnight. The solvent was removed in vacuo and the product was isolated by silica gel chromatography eluting with a gradient from hexanes to 40% ethyl acetate/hexane to afford 0.21 g of compound **109 (-)**. ^{1}H-NMR ($CDCl_3$ 400 MHz) δ 7.80 (m, 6H), 7.39 (d, 2H), 7.08 (m, 1H), 6.42 (m, 1H), 5.03 (d, 1H), 4.24 (d, 1H), 4.18 (d, 1H), 4.01 (d, 1H), 2.65 (d, 1H), 2.47 (s, 3H), 1.86 (m, 1H), 1.71 (m, 1H), 1.51 (m, 4H), 1.05 (m, 1H).

Step 2

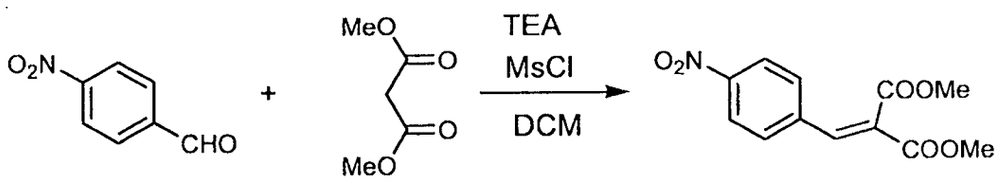
To a solution of 0.18 g of dimethyl sulfone (1.9 mmol) in 20 mL of THF at -78°C was added 1.9 mL of LHMDS (1M solution in THF, 1.9 mmol) and the reaction was stirred for 20 minutes. A solution of 0.12g of **109 (-)** (0.19 mmol) in 5 mL of THF was added. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched by the addition of 50 mL of 1N HCl solution and extracted with dichloromethane. The solvent was removed in vacuo and the product was isolated by silica gel chromatography eluting with a gradient from hexanes to 50% ethyl acetate/hexane to afford 0.029 g of compound **81B (-)**. ^{1}H-NMR ($CDCl_3$ 400 MHz) δ 7.79 (m, 4H), 7.07 (m, 1H), 6.44 (m, 1H), 5.20 (d, 1H), 4.48 (d, 1H), 3.07 (m, 1H), 2.98 (m, 1H), 2.96 (s, 3H), 2.55 (d, 1H), 2.44 (d, 1H), 2.25 (m, 1H), 1.89 (m, 3H), 1.60 (m, 2H), 1.16 (m, 2H). MS: Calcd. for $C_{23}H_{24}F_5O_5S_2$ (MH^+), m/z = 539.10; found 539.3. Retention time: 4.56 min.

The primary alcohol **74B (-)** was prepared analogously to the reactions in Scheme 16, Steps 8-10 from compound **68B (-)**. It was tosylated according to the procedure Scheme 20 (this scheme), Step 1 to give tosylate **110 (-)**: ^{1}H-NMR ($CDCl_3$ 400 MHz) δ 7.83 (m, 6H), 7.40 (d, 2H), 7.08 (m, 1H), 6.46 (m, 1H), 5.05 (d, 1H), 4.34 (d, 1H), 4.28 (d, 1H), 4.11 (d, 1H), 2.65 (d, 1H), 2.48 (s, 3H), 1.9 (m, 3H), 1.71 (m, 1H), 1.51 (m, 4H), 1.15 (m, 1H).

Tosylate **110 (-)** was converted to sulfone **111 (-)** according to the procedure in Step 2 (above). ^{1}H-NMR ($CDCl_3$ 400 MHz) δ 7.79 (m, 4H), 7.08 (m, 1H), 6.43 (m, 1H), 5.18 (d, 1H), 4.58 (d, 1H), 3.00 (m, 2H), 2.98 (s, 3H), 2.52 (d, 1H), 2.43 (d, 1H), 1.78 (m, 6H), 1.45 (s, 1H), 1.40 (m, 1H), 1.05 (m, 2H). MS: Calcd. for $C_{24}H_{26}F_5O_5S_2$ (MH^+), m/z = 553.11; found 553.3. Retention time: 4.62 min.

The following examples illustrate the processes of this invention.

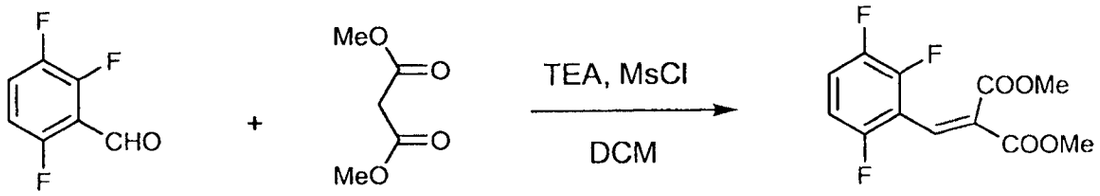
Process Example 1



To a solution of 4-nitrobenzaldehyde (3.02g, 20mmol) and dimethylmalonate (2.77g, 21mmol) in anhydrous dichloromethane (30ml) under N_2 at 5°C in ice and water bath, was added triethylamine (4.86g, 48mmol) over 5min. The reaction was stirred for 20 min. Methanesulfonyl chloride (2.75g, 24mmol) was added over 4 hrs at 5°C. The reaction was stirred for 30 min. Water (20ml) was added, separated the layers. Aqueous layer was extracted with dichloromethane (20ml). The Combined dichloromethane layer was washed with water and dried over anhydrous sodium sulfate. It was concentrated to solid (5.7g) and identified as 2-(4-nitrobenzylidene)-malonic acid dimethyl ester. ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 2H), 7.80 (s, 1H), 7.58 (d, 2H), 3.88 (s, 3H), 3.84 (s, 3H). Mass: [M+1] 266.

Process Example 2

2-(2,3,5-triflorobenzylidene)-malonic acid dimethyl ester

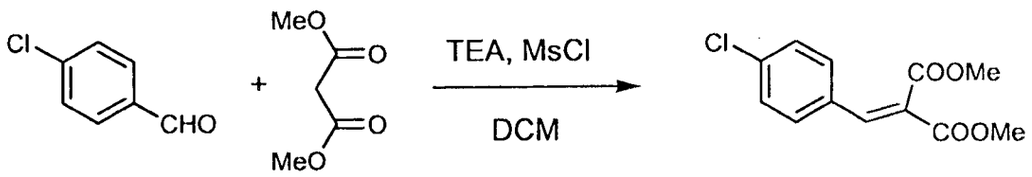


To a solution of 2,3,5-triflorobenzaldehyde (1.6g, 10mmol) and dimethylmalonate (1.2 ml, 10.5mmol) in anhydrous dichloromethane (20ml) under N_2 at room temperature in a water bath, was added triethylamine (2.1 ml, 15.4mmol).

Methanesulfonyl chloride (1.0 ml, 12.8mmol) was added at room temperature. The reaction was stirred for 1hr. Additional triethylamine (2.1 ml, 15.4mmol) was added. After the mixture was stirred for 3hr at room temperature, additional methanesulfonyl chloride (0.5 ml, 6.4mmol) and triethylamine (1.5 ml, 10mmol) were added. The mixture was stirred for 1hr. Water (50ml) and ethyl acetate (50 ml) were added, separated the layers. Aqueous layer was extracted with ethyl acetate (50ml). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. It was concentrated to oil (3.5g) and identified as 2-(2,3,5-triflorobenzylidene)-malonic acid dimethyl ester. ^{1}H NMR ($CDCl_3$): δ 7.20 (m, 1H), 6.85 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H). Mass: [M+1] 243.

Process Example 3

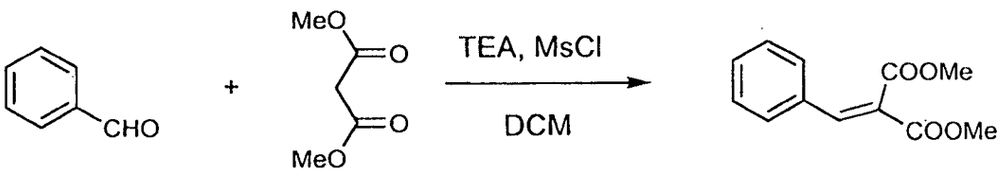
2-(4-chlorobenzylidene)-malonic acid dimethyl ester



Following a process similar to that of Process Example 1, 4-chlorobenzaldehyde reacts with dimethylmalonate under triethylamine and methanesulfonyl chloride in anhydrous dichloromethane to yield 2-(4-chlorobenzylidene)-malonic acid dimethyl ester.

Process Example 4

2-(benzylidene)-malonic acid dimethyl ester



Following a process similar to that of Process Example 1, Benzaldehyde reacts with dimethylmalonate under triethylamine and methanesulfonyl chloride in anhydrous dichloromethane to yield 2-(benzylidene)-malonic acid dimethyl ester.

Assay

The pharmacological properties of the compounds of this invention may be evaluated by a number of pharmacological assays. Gamma secretase activity can be determined by the assay described below.

Gamma-secretase activity was determined as described by Zhang et al. (Biochemistry, 40 (16), 5049 -5055, 2001), which is herein incorporated by reference. Activity is expressed either as a percent inhibition or as the concentration of compound producing 50% inhibition of enzyme activity.

Reagents.

Antibodies W02, G2-10, and G2-11 were obtained from Dr. Konrad Beyreuther (University of Heidelberg, Heidelberg, Germany). W02 recognizes residues 5-8 of Aβ peptide, while G2-10 and G2-11 recognize the specific C-terminal structure of Aβ 40 and Aβ 42, respectively. Biotin-4G8 was purchased from Senetec (St. Louis, MO). All tissue culture reagents used in this work were from Life Technologies, Inc., unless otherwise specified. Pepstatin A was purchased from Roche Molecular Biochemicals; DFK167 was from Enzyme Systems Products (Livermore, CA).

cDNA Constructs, Tissue Culture, and Cell Line Construction.

The construct SPC99-lon, which contains the first 18 residues and the C-terminal 99 amino acids of APP carrying the London mutation, has been described (Zhang, L., Song, L., and Parker, E. (1999) J. Biol. Chem. 274, 8966-8972). Upon insertion into the membrane, the 17 amino acid signal peptide is processed, leaving an additional leucine at the N-terminus of Aβ. SPC99-lon was cloned into the pcDNA4/TO vector (Invitrogen) and transfected into 293 cells stably transfected with pcDNA6/TR, which is provided in the T-REx system (Invitrogen). The transfected cells were selected in Dulbecco's modified Eagle's media (DMEM) supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 g/mL streptomycin, 250 g/mL zeocin, and 5 g/mL blasticidin (Invitrogen). Colonies were screened for Aβ production by inducing C99 expression with 0.1 g/mL tetracycline for 16-20 h and analyzing conditioned media with a sandwich immunoassay (see below). One of the clones, designated as pTRE.15, was used in these studies.

Membrane Preparation.

C99 expression in cells was induced with 0.1 g/mL tetracycline for 20 h. The cells were pretreated with 1 M phorbol 12-myristate 13-acetate (PMA) and 1 M brefeldin A (BFA) for 5-6 h at 37 C before harvesting. The cells were washed 3 times with cold phosphate-buffered saline (PBS) and harvested in buffer A containing 20 mM Hepes (pH 7.5), 250 mM sucrose, 50 mM KCl, 2 mM EDTA, 2 mM EGTA, and Complete protease inhibitor tablets (Roche Molecular Biochemicals). The cell pellets were flash-frozen in liquid nitrogen and stored at -70°C before use.

To make membranes, the cells were resuspended in buffer A and lysed in a nitrogen bomb at 600 psi. The cell lysate was centrifuged at 1500 g for 10 min to remove nuclei and large cell debris. The supernatant was centrifuged at 100000g for 1 h. The membrane pellet was resuspended in buffer A plus 0.5 M NaCl, and the membranes were collected by centrifugation at 200000 g for 1 h. The salt-washed membrane pellet was washed again in buffer A and centrifuged at 100000g for 1 h. The final membrane pellet was resuspended in a small volume of buffer A using a Teflon-glass homogenizer. The protein concentration was determined, and membrane aliquots were flash-frozen in liquid nitrogen and stored at -70°C.

γ-Secretase Reaction and Aβ Analysis.

To measure γ-secretase activity, membranes were incubated at 37°C for 1 h in 50 μL of buffer containing 20 mM Hepes (pH 7.0) and 2 mM EDTA. At the end of the incubation, Aβ 40 and Aβ 42 were measured using an electrochemiluminescence (ECL)-based immunoassay. Aβ 40 was identified with antibody pairs TAG-G2-10 and biotin-W02, while Aβ 42 was identified with TAG-G2-11 and biotin-4G8. The ECL signal was measured using an ECL-M8 instrument (IGEN International, Inc.) according to the manufacturer's instructions. The data presented were the means of the duplicate or triplicate measurements in each experiment. The characteristics of γ-secretase activity described were confirmed using more than five independent membrane preparations.

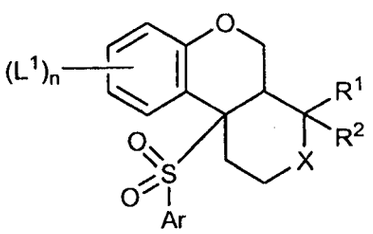
Compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-),

86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-) had a $A\beta_{40}$ IC_{50} in the range of about 6 μM to about 1 nM.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

X is selected from the group consisting of N and CH_2;

R^1 is selected from the group consisting of: (1) -alkylene-$S(O)_2$-(C_1-C_6)alkyl, (2) -alkylene-$S(O)_2$-(C_1-C_6)haloalkyl; (3) -alkylene-$S(O)_2$-R^6, (4) -alkylene-$S(O)_2$-R^8, (5) -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl, (6) –alkylene-(tetrahydrothiophene 1,1-dioxide), (7) -alkenyl-$S(O)_2$-(C_1-C_6)alkyl, and (8) –cycloalkyl-$S(O)_2$-(C_1-C_6)alkyl;

wherein said -alkylene-$S(O)_2$-substituted(C_1-C_6)alkyl R^1 group is substituted with one or more substituents independently selected from the group consisting of: -OH, halo, -CN, $–CF_3$, -O-(C_1-C_6)alkyl, and -O-(halo(C_1-C_6)alkyl);

R^2 is selected from the group consisting of: H and alkyl;

R^6 is selected from the group consisting of: (1) unsubstituted (C_6-C_{14})aryl, (2) (C_6-C_{14})aryl substituted with one or more L^{1A} groups, (3) unsubstituted (C_5-C_{14})heteroaryl, (4) (C_5-C_{14})heteroaryl substituted with one or more L^{1A} groups, (5) unsubstituted (C_5-C_{14})heteroarylalkyl-, and (5) (C_5-C_{14})heteroarylalkyl- substituted with one or more L^{1A} groups;

R^8 is selected from the group consisting of unsubstituted cycloalkyl and cycloalkyl substituted with one or more L^3 groups (wherein examples of said cycloalkyl groups (unsubstituted or substituted) include C_3 –C_{10} cycloalkyl rings);

each L^3 is independently selected from the group consisting of: (1) -CN, (2) =O, (3) -CH_2OH, (4) amino, (5) halo, (6) -CH_2NH_2, (7) -CH_2NHalkyl, (8) -C(O)OH, (9) -alkylene-C(O)NH(C_1 to C_6)alkyl, (10) -alkylene-C(O)N((C_1 to C_6)alkyl)$_2$ wherein each alkyl is independently selected, (11) -alkylene-C(O)NH(C_1 to C_6)haloalkyl, and (12) -alkylene-C(O)N((C_1 to C_6)haloalkyl)$_2$ wherein each alkyl is independently selected);

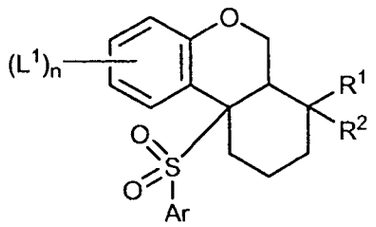
Ar is selected from the group consisting of: (1) unsubstituted aryl, (2) aryl substituted with one or more L^{1A} groups, (3) unsubstituted heteroaryl, and (4) substituted heteroaryl substituted with one or more L^{1A} groups;

each L^1 is independently selected from the group consisting of: halogen, alkyl (e.g., C_1-C_6 alkyl), -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, alkoxyalkoxy-, and $-S(O)_2$(C_1-C_6)alkyl;

each L^{1A} is independently selected from the group consisting of: halogen, alkyl, -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, alkoxyalkoxy-, and $-S(O)_2$(C_1-C_6)alkyl; and

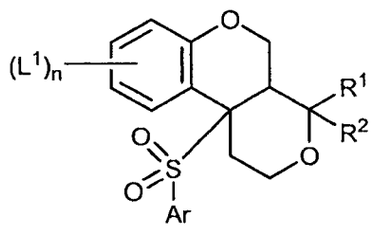
n is 0, 1, 2 or 3.

2. The compound of Claim 1 haaving the formula:



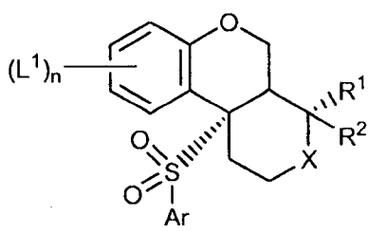
(I.A1)

3. The compound of Claim 1 having the formula:



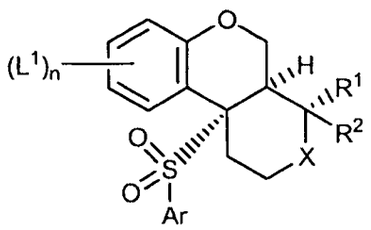
(I.A2)

4. The compound of Claim 1 having the formula:



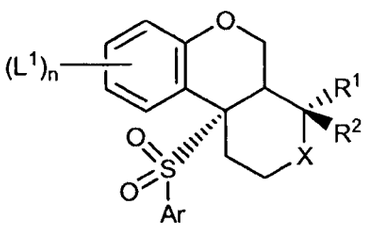
(Ii)

5. The compound of Claim 1 having the formula:



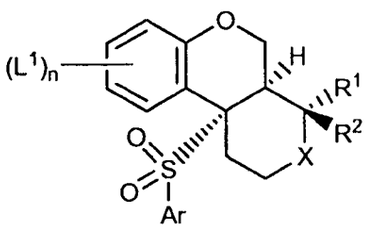
(Iii)

6. The compound of Claim 1 having the formula:



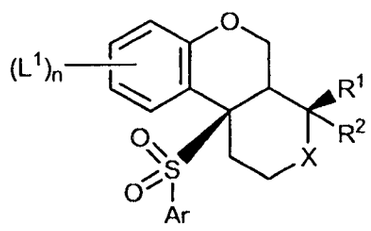
(Iiii)

7. The compound of Claim 1 having the formula:



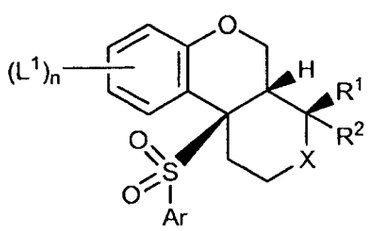
(Iiv)

8. The compound of Claim 1 having the formula:



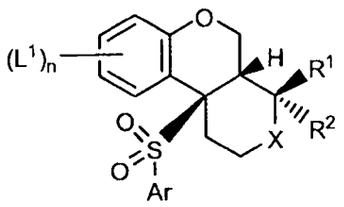
(Iv)

9. The compound of Claim 1 having the formula:



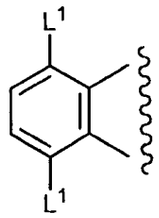
(Ivi)

10. The compound of Claim 1 having the formula:



(Ivii)

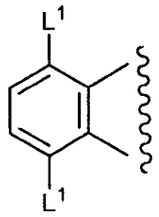
11. The compound of Claim 1 selected from the group consisting of the compounds of formulas (Ii) to (Ivii) wherein n is 2, each L^1 is the same or different halo, and said L^1 groups are bound to the phenyl moiety as shown in formula (IIA):



(IIA)

12. The compound of Claim 11 wherein each L^1 is F.

13. The compound of Claim 1 wherein said compound is selected from the group consisting of the compounds of formulas (Ii) to (Ivii) wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA)



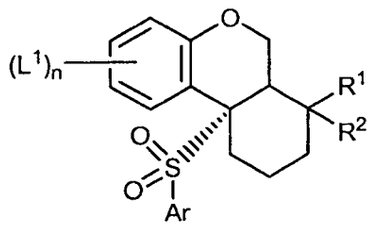
(IIA)

and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl, -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, and alkoxyalkoxy-.

14. The compound of Claim 13 wherein each L^1 is the same or different halo.

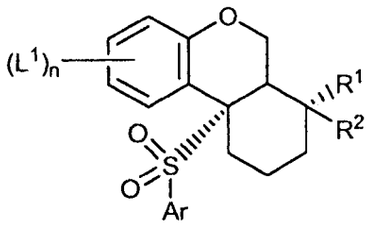
15. The compound of Claim 14 wherein said L^1 groups are F.

16. The compound of Claim 1 having the formula:



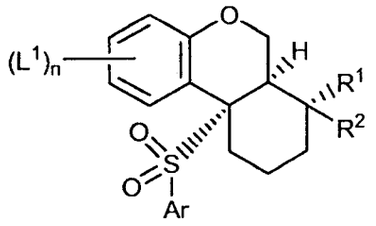
(I.A1a)

17. The compound of Claim 1 having the formula:



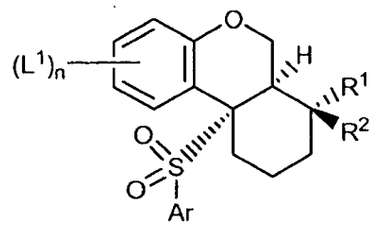
(I.A1b)

18. The compound of Claim 1 having the formula:



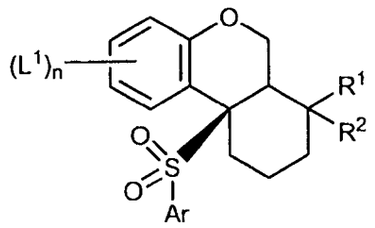
(I.A1c)

19. The compound of Claim 1 having the formula:



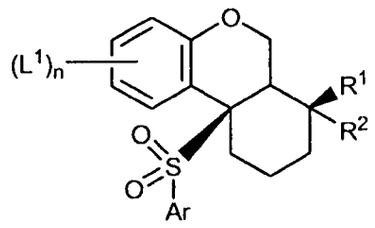
(I.A1d)

20. The compound of Claim 1 having the formula:



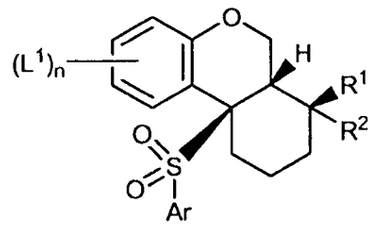
(I.A1e)

21. The compound of Claim 1 having the formula:



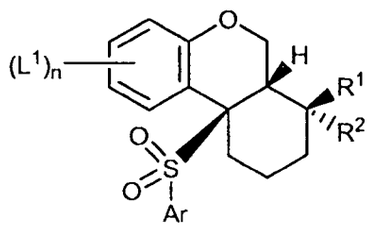
(I.A1f)

22. The compound of Claim 1 having the formula:



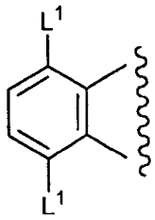
(I.A1g)

23. The compound of Claim 1 having the formula:



(I.A1h)

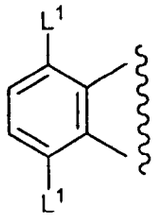
24. The compound of Claim 1 selected from the group consisting of the compounds of formulas (I.A1a) to (I.A1h) wherein n is 2, each L^1 is the same or different halo, and said L^1 groups are bound to the phenyl moiety as shown in formula (IIA):



(IIA)

25. The compound of Claim 24 wherein each L^1 is F.

26. The compound of Claim 1 wherein said compound is selected from the group consisting of the compounds of formulas (I.A1a) to (I.A1h) wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA)



(IIA)

and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl, -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, and alkoxyalkoxy-.

27. The compound of Claim 26 wherein each L^1 is the same or different halo.

28. The compound of Claim 27 wherein said L^1 groups are F.

29. The compound of Claim 28 wherein Ar is p-Cl-phenyl-.

30. The compound of Claim 28 wherein Ar is p-CN-phenyl-.

31. The compound of Claim 28 wherein Ar is p-CF_3-phenyl.

32. The compound of Claim 28 wherein Ar is p-$CH_3CH_2SO_2$phenyl.

33. The compound of Claim 28 wherein Ar is p-Br-phenyl.

34. The compound of Claim 28 wherein Ar is m,p-di-F-phenyl.

35. The compound of Claim 28 wherein Ar is m,p-di-CN-phenyl.

36. The compound of Claim 28 wherein Ar is p-CH_3O-phenyl.

37. The compound of Claim 28 wherein Ar is p-CF_3CH_2Ophenyl.

38. The compound of Claim 24 wherein R^2 is H.

39. The compound of Claim 24 wherein R^2 is alkyl.

40. The compound of Claim 24 wherein R^2 is methyl.

41. The compound of Claim 25 wherein R^2 is H.

42. The compound of Claim 25 wherein R^2 is alkyl.

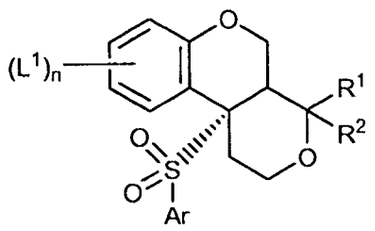
43. The compound of Claim 25 wherein R^2 is methyl.

44. The compound of Claim 28 wherein R^2 is H.

45. The compound of Claim 28 wherein R^2 is alkyl.

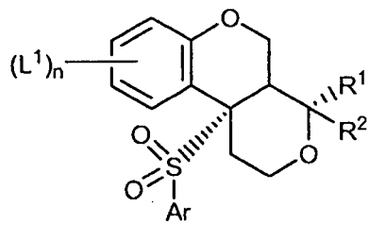
46. The compound of Claim 28 wherein R^2 is methyl.

47. The compound of Claim 1 having the formula:



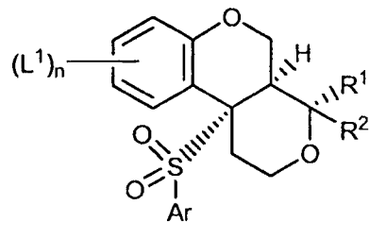
(I.A2a)

48. The compound of Claim 1 having the formula:



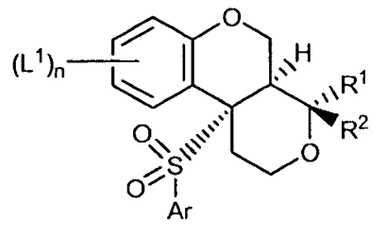
(I.A2b)

49. The compound of Claim 1 having the formula:



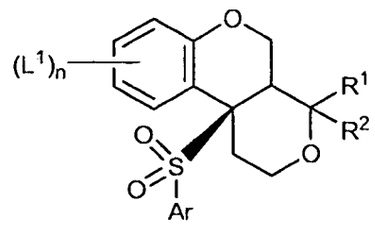
(I.A2c)

50. The compound of Claim 1 having the formula:



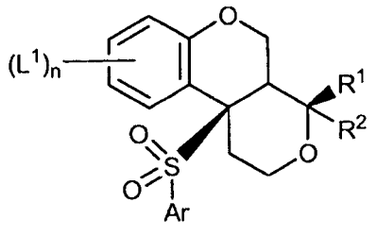
(I.A2d)

51. The compound of Claim 1 having the formula:



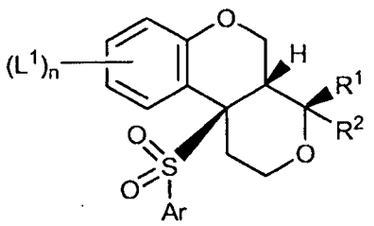
(I.A2e)

52. The compound of Claim 1 having the formula:



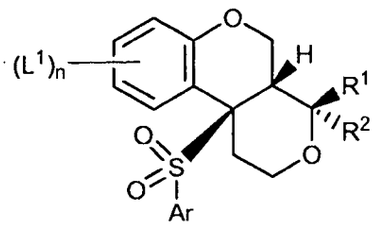
(I.A2f)

53. The compound of Claim 1 having the formula:



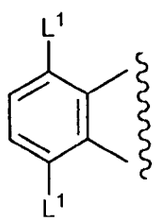
(I.A2g)

54. The compound of Claim 1 having the formula:



(I.A2h)

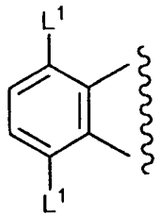
55. The compound of Claim 1 selected from the group consisting of the compounds of formulas (I.A2a) to (I.A2h) wherein n is 2, each L^1 is the same or different halo, and said L^1 groups are bound to the phenyl moiety as shown in formula (IIA):



(IIA)

56. The compound of Claim 55 wherein each L^1 is F.

57. The compound of Claim 1 wherein said compound is selected from the group consisting of the compounds of formulas (I.A2a) to (I.A2h) wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA)



(IIA)

,

and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl, -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, and alkoxyalkoxy-.

58. The compound of Claim 57 wherein each L^1 is the same or different halo.

59. The compound of Claim 58 wherein said L^1 groups are F.

60. The compound of Claim 59 wherein Ar is p-Cl-phenyl-.

61. The compound of Claim 59 wherein Ar is p-CN-phenyl-.

62. The compound of Claim 59 wherein Ar is p-CF_3-phenyl.

63. The compound of Claim 59 wherein Ar is p-$CH_3CH_2SO_2$phenyl.

64. The compound of Claim 59 wherein Ar is p-Br-phenyl.

65. The compound of Claim 59 wherein Ar is m,p-di-F-phenyl.

66. The compound of Claim 59 wherein Ar is m,p-di-CN-phenyl.

67. The compound of Claim 59 wherein Ar is p-CH_3O-phenyl.

68. The compound of Claim 59 wherein Ar is p-CF_3CH_2Ophenyl.

69. The compound of Claim 55 wherein R^2 is H.

70. The compound of Claim 55 wherein R^2 is alkyl.

71. The compound of Claim 55 wherein R^2 is methyl.

72. The compound of Claim 56 wherein R^2 is H.

73. The compound of Claim 56 wherein R^2 is alkyl.

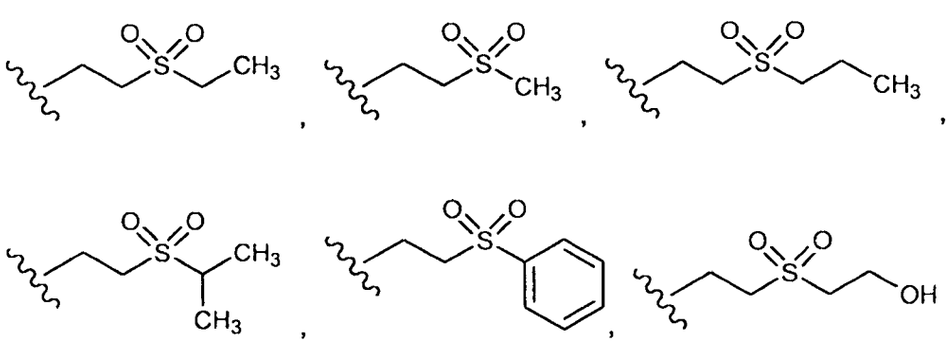
74. The compound of Claim 56 wherein R^2 is methyl.

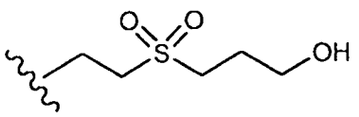
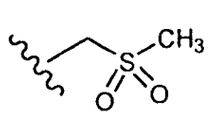
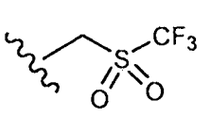
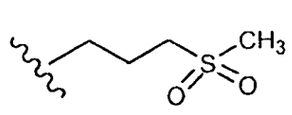
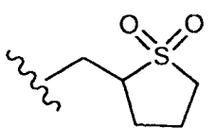
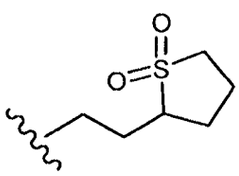
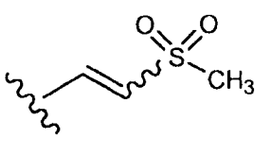
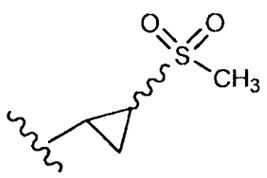
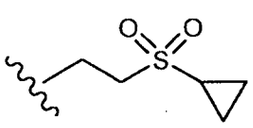
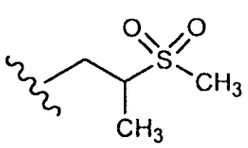
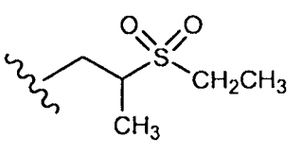
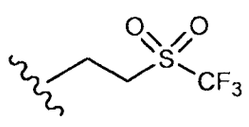
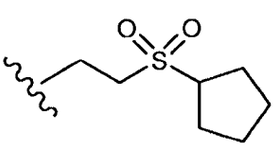
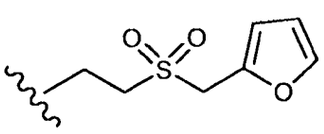
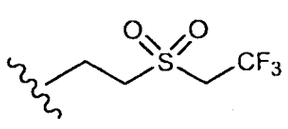
75. The compound of Claim 59 wherein R^2 is H.

76. The compound of Claim 59 wherein R^2 is alkyl.

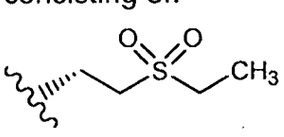
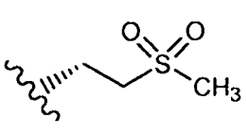
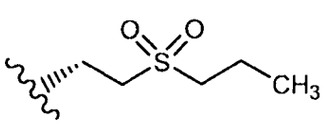
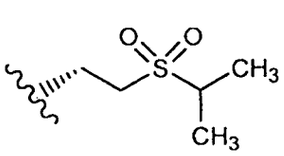
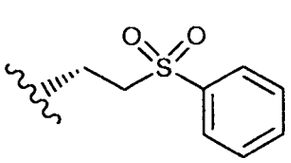
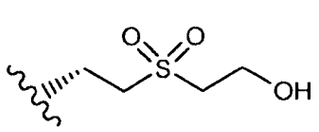
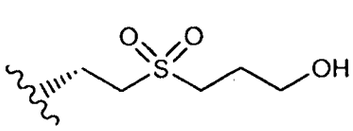
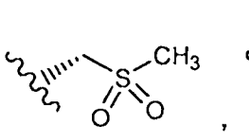
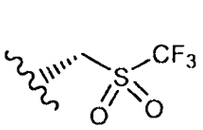
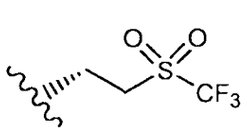
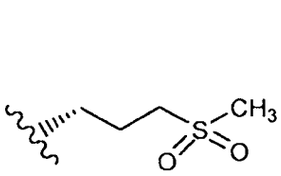
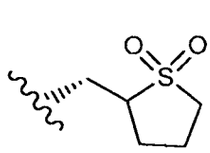
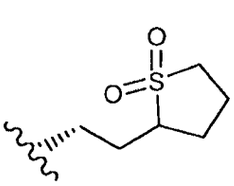
77. The compound of Claim 59 wherein R^2 is methyl.

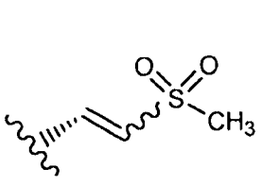
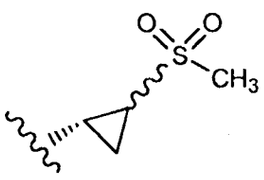
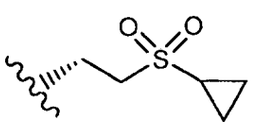
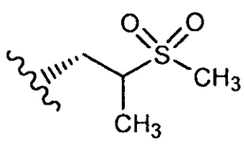
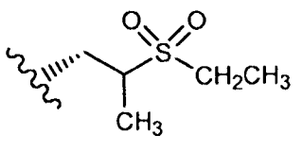
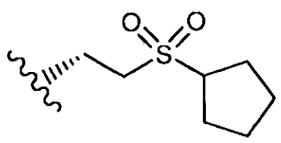
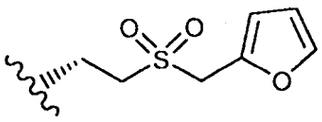
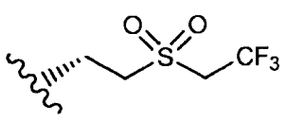
78. The compound of Claim 1 wherein R^1 is selected from the group consisting of:




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and

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79. The compound of Claim 1 wherein R^1 is selected from the group consisting of:

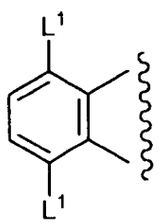

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and .

80. The compound of Claim 79 wherein the compound of formula (I) is a compound selected from the group consisting of the compounds of formulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), or (I.A1d).

81. The compound of Claim 80 wherein wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA)


(IIA)

,

and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl, -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, and alkoxyalkoxy-.

82. The compound of Claim 81 wherein each L^1 is the same or different halo.

83. The compound of Claim 82 wherein said L^1 groups are F.

84. The compound of Claim 83 wherein R^2 is H.

85. The compound of Claim 83 wherein R^2 is alkyl.

86. The compound of Claim 83 wherein R^2 is methyl.

87. The compound of Claim 84 wherein Ar is p-Cl-phenyl-.

88. The compound of Claim 84 wherein Ar is p-CN-phenyl-.

89. The compound of Claim 84 wherein Ar is p-CF_3-phenyl.

90. The compound of Claim 84 wherein Ar is p-$CH_3CH_2SO_2$phenyl.

91. The compound of Claim 84 wherein Ar is p-Br-phenyl.

92. The compound of Claim 84 wherein Ar is m,p-di-F-phenyl.

93. The compound of Claim 84 wherein Ar is m,p-di-CN-phenyl.

94. The compound of Claim 84 wherein Ar is p-CH_3O-phenyl.

95. The compound of Claim 84 wherein Ar is p-CF_3CH_2Ophenyl.

96. The compound of Claim 86 wherein Ar is p-Cl-phenyl-.

97. The compound of Claim 86 wherein Ar is p-CN-phenyl-.

98. The compound of Claim 86 wherein Ar is p-CF_3-phenyl.

99. The compound of Claim 86 wherein Ar is p-$S(O)_2CH_2CH_3$.

100. The compound of Claim 86 wherein Ar is p-Br-phenyl.

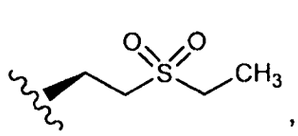
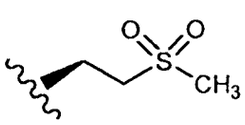
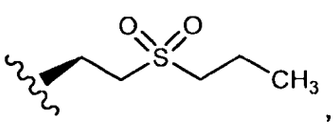
101. The compound of Claim 86 wherein Ar is m,p-di-F-phenyl.

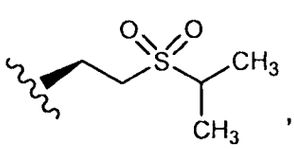
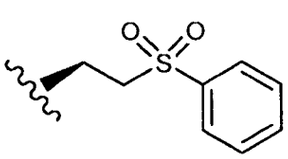
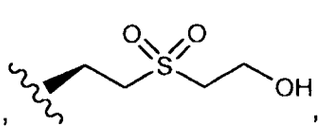
102. The compound of Claim 86 wherein Ar is m,p-di-CN-phenyl.

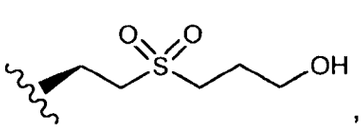
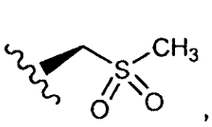
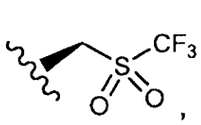
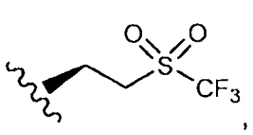
103. The compound of Claim 86 wherein Ar is p-CH_3O-phenyl.

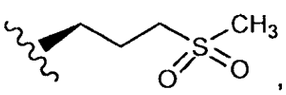
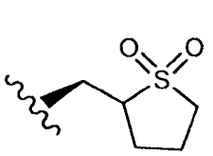
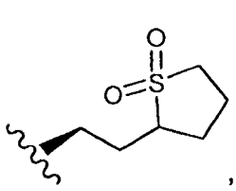
104. The compound of Claim 86 wherein Ar is p-CF_3CH_2Ophenyl.

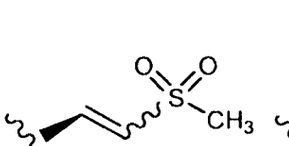
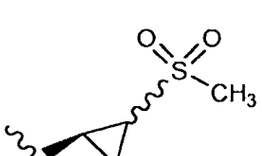
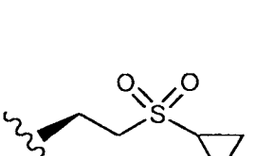
105. The compound of Claim 1 wherein R^1 is selected from the group consisting of:

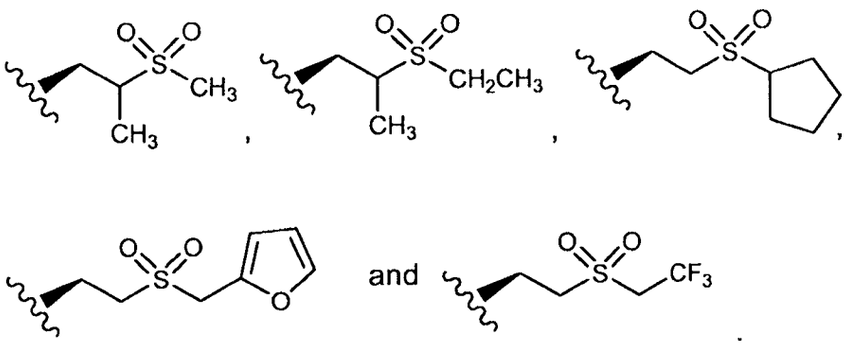

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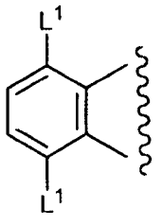

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106. The compound of Claim 105 wherein the compound of formula (I) is selected from the group consisting of the compounds of formulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), and (I.A2h).

107. The compound of Claim 106 wherein wherein n is 2, and the L^1 groups are bound to the phenyl moiety as shown in (IIA)



(IIA)

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and Ar is selected from the group consisting of p-Cl-phenyl-, p-CN-phenyl-, p-CF_3-phenyl, p-$CH_3CH_2SO_2$phenyl, p-Br-phenyl, m,p-di-F-phenyl, m,p-di-CN-phenyl, p-CH_3O-phenyl, p-CF_3CH_2Ophenyl, pyridyl, and pyridyl substituted with 1 or 2 substituents independently selected from the group consisting of: halogen, alkyl, -CN, $-CF_3$, -O-(C_1-C_6)alkyl, -O-(halo(C_1-C_6)alkyl), -C(O)-O-(C_1-C_6)alkyl, -alkylene-OH, halo(C_1-C_6)alkyl, hydroxyalkoxy-, and alkoxyalkoxy-.

108. The compound of Claim 107 wherein each L^1 is the same or different halo.

109. The compound of Claim 108 wherein said L^1 groups are F.

110. The compound of Claim 109 wherein R^2 is H.

111. The compound of Claim 109 wherein R^2 is alkyl.

112. The compound of Claim 109 wherein R^2 is methyl.

113. The compound of Claim 110 wherein Ar is p-Cl-phenyl-.

114. The compound of Claim 110 wherein Ar is p-CN-phenyl-.

115. The compound of Claim 110 wherein Ar is p-CF_3-phenyl.

116. The compound of Claim 110 wherein Ar is p-$CH_3CH_2SO_2$phenyl.

117. The compound of Claim 110 wherein Ar is p-Br-phenyl.

118. The compound of Claim 110 wherein Ar is m,p-di-F-phenyl.

119. The compound of Claim 110 wherein Ar is m,p-di-CN-phenyl.

120. The compound of Claim 110 wherein Ar is p-CH_3O-phenyl.

121. The compound of Claim 110 wherein Ar is p-CF_3CH_2Ophenyl.

122. The compound of Claim 112 wherein Ar is p-Cl-phenyl-.

123. The compound of Claim 112 wherein Ar is p-CN-phenyl-.

124. The compound of Claim 112 wherein Ar is p-CF_3-phenyl.

125. The compound of Claim 112 wherein Ar is p-$CH_3CH_2SO_2$phenyl.

126. The compound of Claim 112 wherein Ar is p-Br-phenyl.

127. The compound of Claim 112 wherein Ar is m,p-di-F-phenyl.

128. The compound of Claim 112 wherein Ar is m,p-di-CN-phenyl.

129. The compound of Claim 112 wherein Ar is p-CH_3O-phenyl.

130. The compound of Claim 112 wherein Ar is p-CF_3CH_2Ophenyl.

131. The compound of Claim 1 selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

132. The compound of Claim 1 selected from a solvate of a compound selected from the group consisting of 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

133. The compound of Claim 1 wherein said compound is compound 12.

134. The compound of Claim 1 wherein said compound is compound 13.

135. The compound of Claim 1 wherein said compound is compound 22A.

136. The compound of Claim 1 wherein said compound is compound 22B.

137. The compound of Claim 1 wherein said compound is compound 22B-RAC.

138. The compound of Claim 1 wherein said compound is compound 22C.

139. The compound of Claim 1 wherein said compound is compound 22D.

140. The compound of Claim 1 wherein said compound is compound 22E.

141. The compound of Claim 1 wherein said compound is compound 22F.

142. The compound of Claim 1 wherein said compound is compound 22G.

143. The compound of Claim 1 wherein said compound is compound 22H.

144. The compound of Claim 1 wherein said compound is compound 22I.

145. The compound of Claim 1 wherein said compound is compound 22J.

146. The compound of Claim 1 wherein said compound is compound 22K.

147. The compound of Claim 1 wherein said compound is compound 22L.

148. The compound of Claim 1 wherein said compound is compound 22M.

149. The compound of Claim 1 wherein said compound is compound 22N.

150. The compound of Claim 1 wherein said compound is compound 26A.

151. The compound of Claim 1 wherein said compound is compound 26B.

152. The compound of Claim 1 wherein said compound is compound 27.

153. The compound of Claim 1 wherein said compound is compound 28.

154. The compound of Claim 1 wherein said compound is compound 31.

155. The compound of Claim 1 wherein said compound is compound 33(-).

156. The compound of Claim 1 wherein said compound is compound 36.

157. The compound of Claim 1 wherein said compound is compound 37.

158. The compound of Claim 1 wherein said compound is compound 39.

159. The compound of Claim 1 wherein said compound is compound 44A.

160. The compound of Claim 1 wherein said compound is compound 44B.

161. The compound of Claim 1 wherein said compound is compound 55.

162. The compound of Claim 1 wherein said compound is compound 56.

163. The compound of Claim 1 wherein said compound is compound 57.

164. The compound of Claim 1 wherein said compound is compound 60.

165. The compound of Claim 1 wherein said compound is compound 70A.

166. The compound of Claim 1 wherein said compound is compound 71A(-).

167. The compound of Claim 1 wherein said compound is compound 75A-rac.

168. The compound of Claim 1 wherein said compound is compound 75B(-).

169. The compound of Claim 1 wherein said compound is compound 76A(-).

170. The compound of Claim 1 wherein said compound is compound 76A(+).

171. The compound of Claim 1 wherein said compound is compound 76B(-).

172. The compound of Claim 1 wherein said compound is compound 78A(-).

173. The compound of Claim 1 wherein said compound is compound 79A(-).

174. The compound of Claim 1 wherein said compound is compound 80A(+).

175. The compound of Claim 1 wherein said compound is compound 81A-rac.

176. The compound of Claim 1 wherein said compound is compound 81A(-).

177. The compound of Claim 1 wherein said compound is compound 81A(+).

178. The compound of Claim 1 wherein said compound is compound 81B(-).

179. The compound of Claim 1 wherein said compound is compound 82A.

180. The compound of Claim 1 wherein said compound is compound 83A.

181. The compound of Claim 1 wherein said compound is compound 84A.

182. The compound of Claim 1 wherein said compound is compound 85A.

183. The compound of Claim 1 wherein said compound is compound 85B(-).

184. The compound of Claim 1 wherein said compound is compound 86A.

185. The compound of Claim 1 wherein said compound is compound 87B.

186. The compound of Claim 1 wherein said compound is compound 95B-rac.

187. The compound of Claim 1 wherein said compound is compound 95B(-).

188. The compound of Claim 1 wherein said compound is compound 95B(+).

189. The compound of Claim 1 wherein said compound is compound 106(-).

190. The compound of Claim 1 wherein said compound is compound 107(-).

191. The compound of Claim 1 wherein said compound is compound 108(-).

192. The compound of Claim 1 wherein said compound is compound 111(-).

193. A pharmaceutical composition comprising an effective amount of at least one compound of Claim 1 and at least one pharmaceutically acceptable carrier.

194. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

195. The pharmaceutical composition of Claim 194 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

196. The pharmaceutical composition of Claim 194 wherein said compound is a solvate of a compound selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

197. A method of inhibiting gamma-secretase in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1.

198. A method of inhibiting gamma-secretase in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

199. A method of treating one or more neurodegenerative diseases in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1.

200. A method of treating one or more neurodegenerative diseases in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

201. A method of inhibiting the deposition of beta amyloid protein in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1.

202. A method of inhibiting the deposition of beta amyloid protein in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-),

79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

203. A method of treating Alzheimer's disease in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1.

204. A method of treating Alzheimer's disease in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+), 76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

205. A method of inhibiting gamma secretase in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: (a) drugs for the treatment of Alzheimer's disease, (b) drugs for inhibiting the deposition of amyloid protein in, on or around neurological tissue, (c) drugs for treating neurodegenerative diseases, and (d) drugs for inhibiting gamma-secretase.

206. A method of inhibiting gamma secretase in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists;

inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors.

207. A method of inhibiting gamma secretase in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more BACE inhibitors.

208. The method of Claim 205 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

209. The method of Claim 206 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

210. The method of Claim 207 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

211. A method of treating one or more neurodegenerative diseases in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: (a) drugs for the treatment of Alzheimer's disease, (b) drugs for inhibiting the deposition of amyloid protein in, on or around neurological tissue, (c)

drugs for treating neurodegenerative diseases, and (d) drugs for inhibiting gamma-secretase.

212. A method of treating one or more neurodegenerative diseases in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors.

213. A method of treating one or more neurodegenerative diseases in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more BACE inhibitors.

214. The method of Claim 211 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

215. The method of Claim 212 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

216. The method of Claim 213 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

217. A method of inhibiting the deposition of amyloid protein in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: (a) drugs for the treatment of Alzheimer's disease, (b) drugs for inhibiting the deposition of amyloid protein in, on or around neurological tissue, (c) drugs for treating neurodegenerative diseases, and (d) drugs for inhibiting gamma-secretase.

218. A method of inhibiting the deposition of amyloid protein in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors.

219. A method of inhibiting the deposition of amyloid protein in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more BACE inhibitors.

220. The method of Claim 217 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

221. The method of Claim 218 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

222. The method of Claim 219 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

223. A method of treating Alzheimer's disease in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: (a) drugs for the treatment of Alzheimer's disease, (b) drugs for inhibiting the deposition of amyloid protein in, on or around neurological tissue, (c) drugs for treating neurodegenerative diseases, and (d) drugs for inhibiting gamma-secretase.

224. A method of treating Alzheimer's disease in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more other drugs selected from the group consisting of: BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-

inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors.

225. A method of treating Alzheimer's disease in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of one or more compounds of Claim 1, and a therapeutically effective amount of one or more BACE inhibitors.

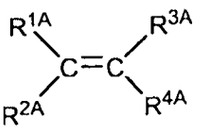
226. The method of Claim 223 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 22B-RAC, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

227. The method of Claim 224 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

228. The method of Claim 225 wherein said compound is selected from the group consisting of compounds 12, 13, 22A to 22N, 26A, 26B, 27, 28, 31, 33(-), 36, 37, 39, 44A, 44B, 55 to 57, 60, 70A, 71A(-), 75A-rac, 75B(-), 76A(-), 76A(+),76B(-), 78A(-), 79A(-), 80A(+), 81A-rac, 81A(-), 81A(+), 81B(-), 82A, 83A, 84A, 85A, 85B(-), 86A, 87B, 95B-rac, 95B(-), 95B(+), 106(-), 107(-), 108(-), and 111(-).

229. The compound of Claim 1 in purified form.

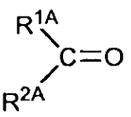
230. A process for preparing a compound of the formula:



said process comprising reacting:

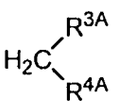
(1) a mixture comprising:

(a) a compound of the formula:



, and

(b) a compound of the formula:

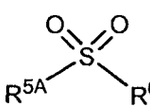


, and

(c) a suitable organic solvent; with

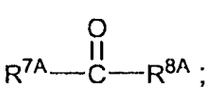
(2) either:

(a) a basic amine, and a compound of the formula



, or

(b) a basic amine, and a compound of the formula



;

wherein:

R^{1A} and R^{2A} are each independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroalkyl, aryl, heteroaryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl; wherein said substituted groups are substituted with one or more substituents each independently selected from the group consisting of: $-NO_2$, -NO, $-SO_2R^{7B}$, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2OR^{7B}$, -CN, -COOH, halo, $-CF_3$, -Oaryl, -Oheteroaryl, $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, -CHO, $-OR^{7B}$, $-COR^{7B}$, -SH, $-SR^{7B}$, -OH, aryl, and heteroaryl;

R^{3A} and R^{4A} are each independently selected from the group consisting of: $-NO_2$, -NO, $-SO_2R^{7B}$, $-SO_2$-aryl, $-SO_2$-heteroaryl, $-SO_2OR^{7B}$, -CN, -COOH, halo, $-CF_3$, -Oaryl, -Oheteroaryl, $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, -CHO, $-OR^{7B}$, $-COR^{7B}$, -SH, $-SR^{7B}$, -OH, aryl, and heteroaryl;

R^{5A} is selected from the group consisting of: H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroalkyl, aryl, heteroaryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl; and wherein:

said substituted alkyl groups are substituted with one or more substituents each independently selected from the group consisting of: halo, $-NO_2$, -CN, and $-OR^{12A}$; and

said substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl groups are substituted with one or more substituents each independently selected from the group consisting of: halo, $-NO_2$, -CN, and $-OR^{12A}$, alkyl and halo substituted alkyl (e.g., F substituted alkyl, such as, for example, $-CF_3$);

R^{6A} is selected from the group consisting of: halo, and $-OSO_2R^{5A}$;

R^{7A} is selected from the group consisting of: unsubstituted aryl, aryl substituted with at least one electron withdrawing group, heteroaryl, and heteroaryl substituted with at least one electron withdrawing group;

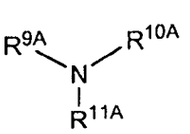
Each R^{7B} is independently selected from the group consisting of: alkyl, cycloalkyl and heteroalkyl;

R^{8A} is selected from the group consisting of: halo, and $-OC(O)R^{7A}$;

R^{12A} is alkyl; and

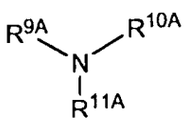
R^{13A} is selected from the the group consisting of: alkyl, alkoxyalkyl, hydroxyalkyl, alkanoyl, aryl, heteroaryl, aroyl, and carbamoyl, and preferably alkyl.

231. The process of Claim 230 wherein said basic amine is a compound of the formula:



wherein each R^{9A}, R^{10A}, and R^{11A} is independently selected from the group consisting of: alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroalkyl, aryl, heteroaryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted heteroalkyl, substituted aryl, and substituted heteroaryl; wherein said substituted groups are substituted with one or more substituents each independently selected from the group consisting of: halo, alkyl and alkoxy.

232. The process of Claim 230 wherein said basic amine is a compound of the formula:



wherein R^{9A}, R^{10A}, and R^{11A} are alkyl groups, wherein each alkyl group is independently selected.

233. The process of Claim 232 wherein said basic amine is triethylamine.

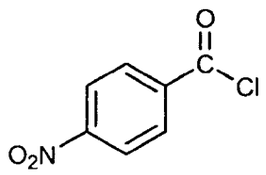
234. The process of Claim 233 wherein said basic amine is diisopropyl ethyl amine.

235. The process of Claim 230 wherein said organic solvent is selected from the group consisting of: (1) haloalkanes, (2) arylhalides, (3) DMSO, (4) DMF, (5) THF, (6) ethers, and (7) mixtures thereof.

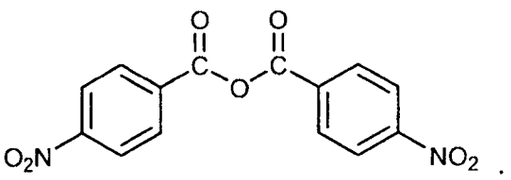
236. The process of Claim 230 wherein said solvent is selected from the group consisting of: anhydrous dichloromethane, anhydrous dichloroethane, anhydrous chlorobenzene, anhydrous DMSO, anhydrous DMF, anhydrous THF, and anhydrous diethylether.

237. The process of Claim 236 wherein said organic solvent is anhydrous dichloromethane.

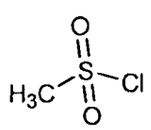
238. The process of Claim 230 wherein said compound $R^{7A}C(O)R^{8A}$ is selected from the group consisting of:

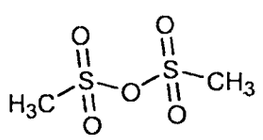


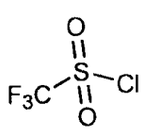
and

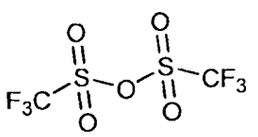


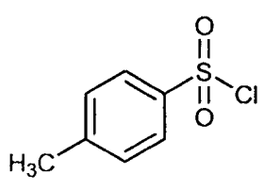
239. The process of Claim 230 wherein said compound $R^{5A}S(O)_2R^{6A}$ is selected from the group consisting of:

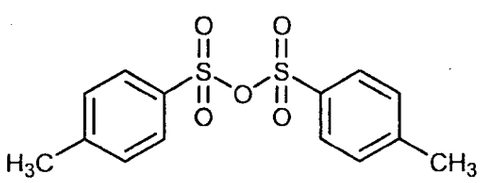


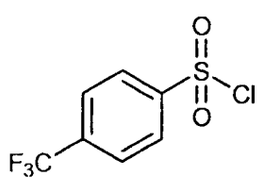




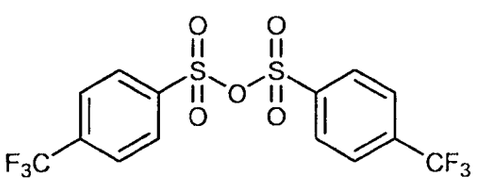




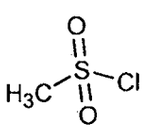




and



240. The process of Claim 239 wherein the compound is:



241. The process of Claim 230 wherein the process is carried out at a temperature within the range of about -40°C to about 40°C.

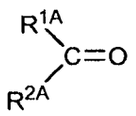
242. The process of Claim 230 wherein the process is carried out at a temperature within the range of about 0°C to about 30°C.

243. The process of Claim 230 wherein the process is carried out at a temperature within the range of about 0°C to about 10°C.

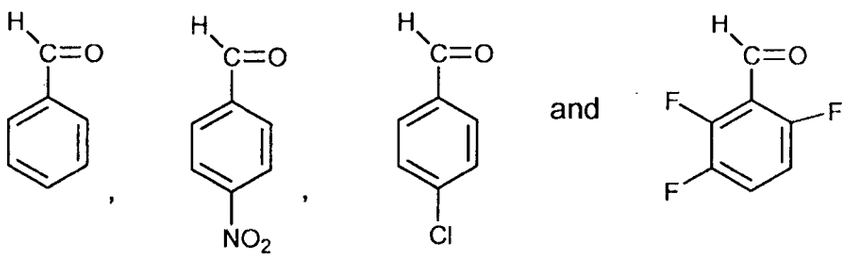
244. The process of Claim 230 wherein the mixture of (1)(a) and (1)(b) is reacted with (2)(a).

245. The process of Claim 230 wherein the mixture of (1)(a) and (1)(b) is reacted with (2)(b).

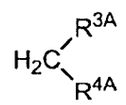
246. The process of Claim 230 wherein the compound



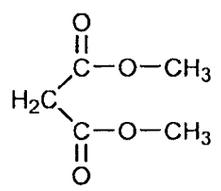
is selected from the group consisting of:



247. The process of Claim 230 wherein the compound



is:



248. The process of Claim 230 wherein the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{3A}CH_2R^{4A}$ is about 1:0.8 to about 1:1.2.

249. The process of Claim 230 wherein the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{5A}S(O)_2R^{6A}$ is about 1:1 to about 1:4.

250. The process of Claim 230 wherein the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{7A}C(O)R^{8A}$ is about 1:1 to about 1:4.

251. The process of Claim 230 wherein the molar ratio of $R^{5A}S(O)_2R^{6A}$ to the basic amine is about 1:2 to about 1:3.

252. The process of Claim 230 wherein the molar ratio of $R^{7A}C(O)R^{8A}$ to the basic amine is about 1:2 to about 1:3.

253. The process of Claim 230 wherein the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{3A}CH_2R^{4A}$ is about 1:1.

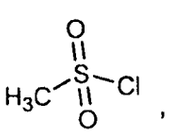
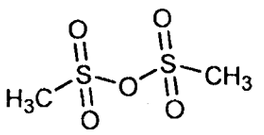
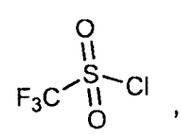
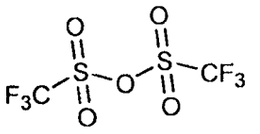
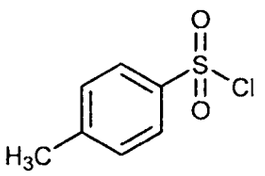
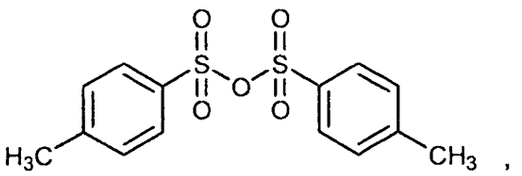
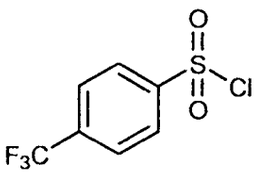
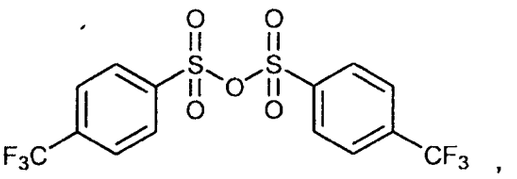
254. The process of Claim 230 wherein the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{5A}S(O)_2R^{6A}$ is about 1:1.

255. The process of Claim 230 wherein the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{7A}C(O)R^{8A}$ is about 1:1.

256. The process of Claim 230 wherein the molar ratio of $R^{5A}S(O)_2R^{6A}$ to the basic amine is about 1:2.

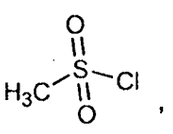
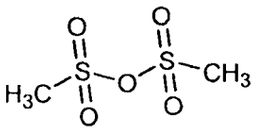
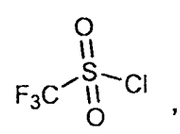
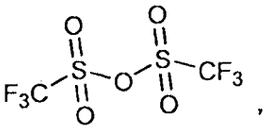
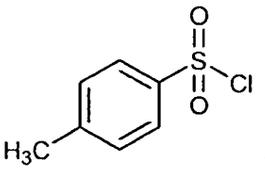
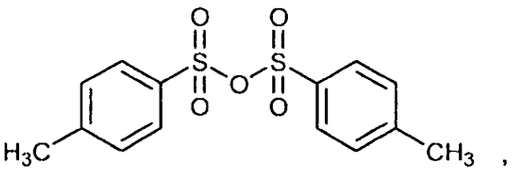
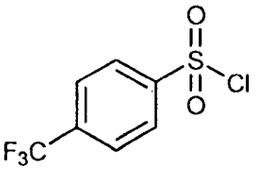
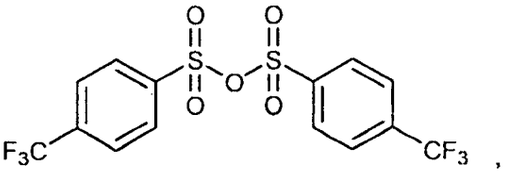
257. The process of Claim 230 wherein the molar ratio of $R^{7A}C(O)R^{8A}$ to the basic amine is about 1:2.

258. The process of Claim 230 wherein the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 30°C, the basic amine is a trialkylamine, the organic solvent is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consiting of:








and


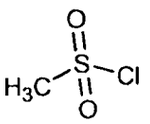
one of R^{1A} and R^{2A} is selected from the group consisting of: aryl and substituted aryl, and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same -C(O)OR^{12A} moiety, and R^{12A} is a C_1 to C_4 alkyl.

259. The process of Claim 230 wherein the mixture of (1)(a) and (1)(b) is reacted with (2)(a), the reaction is carried out at a temperature within the range of about 0°C to about 10°C, the basic amine is a trialkylamine, the organic solvent is anhydrous dichloromethane, the $R^{5A}S(O)_2R^{6A}$ moiety is selected from the group consiting of:








and


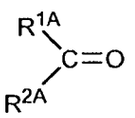
one of R^{1A} and R^{2A} is selected from the group consisting of: aryl and substituted aryl, and the other one of R^{1A} and R^{2A} is H, and R^{3A} and R^{4A} are the same $-C(O)OR^{12A}$ moiety, and R^{12A} is a C_1 to C_4 alkyl.

260. The process of Claim 230 wherein the $R^{5A}S(O)_2R^{6A}$ moiety is

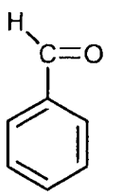
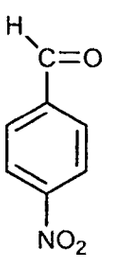
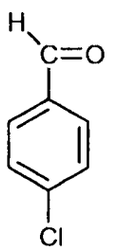
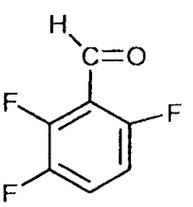


261. The process of Claim 260 wherein the basic amine is triethylamine.

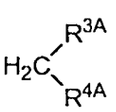
262. The process of Claim 261 wherein the moiety



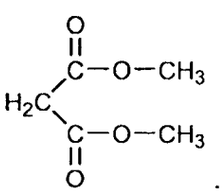
is selected from the group consisting of:


,

,

and

, and

the moiety



is



263. The process of Claim 262 wherein:

the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{3A}CH_2R^{4A}$ is about 1:0.8 to about 1:1.2,

the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{5A}S(O)_2R^{6A}$ is about 1:1 to about 1:4, and

the molar ratio of $R^{5A}S(O)_2R^{6A}$ to the basic amine is about 1:2 to about 1:3,

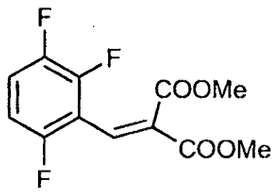
264. The process of Claim 263 wherein:

the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{3A}CH_2R^{4A}$ is 1:1,

the molar ratio of $R^{1A}C(O)R^{2A}$ to $R^{5A}S(O)_2R^{6A}$ is 1:1, and

the molar ratio of $R^{5A}S(O)_2R^{6A}$ to the basic amine is about 1:2.

265. A process for preparing a compound of the formula:



said process comprising reacting:

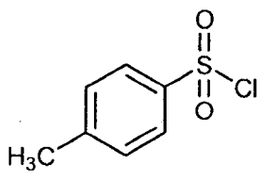
(1) a mixture comprising:

(a) 2,3,5-triflorobenzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) anhydrous dichloromethane; with

(2)



;

wherein:

said process is carried out at a temperature within the range of about -40°C to about 40°C;

the molar ratio of 2,3,5-triflorobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2, and preferably 1:1;

the molar ratio of 2,3,5-triflorobenzaldehyde to mesyl chloride is about 1:1 to about 1:4, and preferably 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3, and preferably about 1:2.

266. The process of Claim 265 wherein:

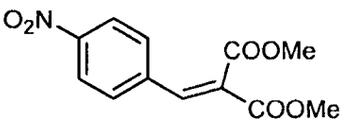
said process is carried out at a temperature within the range of about 0°C to about 10°C;

the molar ratio of 2,3,5-triflorobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:1;

the molar ratio of 2,3,5-triflorobenzaldehyde to mesyl chloride is about 1 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2.

267. A processes for preparing a compound of the formula:



said process comprising reacting:

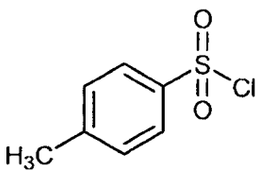
(1) a mixture comprising:

(a) 4-nitrobenzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) anhydrous dichloromethane; with

(2)



;

wherein:

said process is carried out at a temperature within the range of about -40°C to about 40°C;

the molar ratio of 4-nitrobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2;

the molar ratio of 4-nitrobenzaldehyde to mesyl chloride is about 1:1 to about 1:4; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3.

268. The process of Claim 267 wherein:

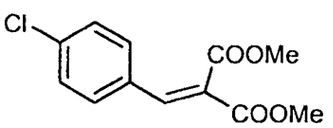
said process is carried out at a temperature within the range of about 0°C to about 10°C;

the molar ratio of 4-nitrobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:1;

the molar ratio of 4-nitrobenzaldehyde to mesyl chloride is about 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2.

269. A process for preparing a compound of the formula:



said process comprising reacting:

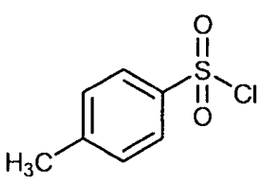
(1) a mixture comprising:

(a) 4-chlorobenzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) dichloromethane (preferably anhydrous); with

(2)



;

wherein:

said process is carried out at a temperature within the range of about -40°C to about 40°C;

the molar ratio of 4-chlorobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2;

the molar ratio of 4-chlorobenzaldehyde to mesyl chloride is about 1:1 to about 1:4; and

the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3.

270. The process of Claim 269 wherein :

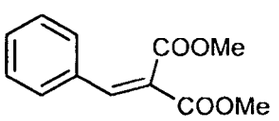
said process is carried out at a temperature within the range of about 0°C to about 10°C;

the molar ratio of 4-chlorobenzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:1;

the molar ratio of 4-chlorobenzaldehyde to mesyl chloride is about 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2.

271. A process for preparing a compound of the formula:



said process comprising reacting:

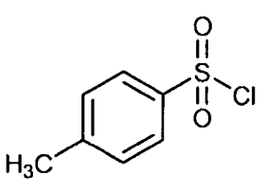
(1) a mixture comprising:

(a) benzaldehyde, and

(b) $CH_2(C(O)OCH_3)_2$; and

(c) dichloromethane (preferably anhydrous); with

(2)



;

wherein:

said process is carried out at a temperature within the range of about -40°C to about 40°C; the molar ratio of benzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:0.8 to about 1:1.2; the molar ratio of benzaldehyde to mesyl chloride is about 1:1 to about 1:4; and the molar ratio of mesyl chloride to TEA is about 1:2 to about 1:3.

272. The process of Claim 271 wherein:

said process is carried out at a temperature within the range of about 0°C to about 10°C;

the molar ratio of benzaldehyde to $CH_2(C(O)OCH_3)_2$ is about 1:1;

the molar ratio of benzaldehyde to mesyl chloride is about 1:1; and

the molar ratio of mesyl chloride to TEA is about 1:2.

INHIBIDORES TETRAHIDROPIRANOCROMENO DE GAMMA SECRETASA

REFERENCIA A SOLICITUD RELACIONADA

Esta solicitud reivindica el beneficio de la solicitud provisional U.S. No. 60/948033 presentada el 5 de julio de 2007.

ANTECEDENTES

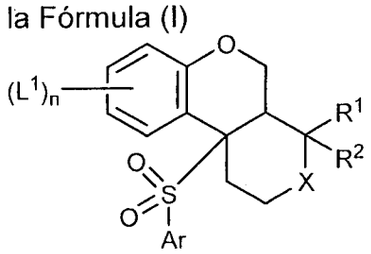
WO 00/50391, publicado el 13 de agosto de 2000, describe compuestos que tienen un resto sulfonamida que son útiles para el tratamiento y prevención de la enfermedad de Alzheimer y otras enfermedades relacionadas con el depósito de proteína amiloide.

McCombie et al., Tetrahedron Letters, Vol. 34, No. 50, pp. 8033–8036 (1993) describe métodos de preparación de cromanos y tiocromanos. Sin embargo, los cromanos y tiocromanos descriptos en la presente son diferentes de los compuestos de la presente invención.

En vista del presente interés en el tratamiento o prevención de enfermedades neurodegenerativas, tales como enfermedad de Alzheimer, una contribución bienvenida al arte sería los compuestos para usar en dicho tratamiento o prevención. Esta invención proporciona dicha contribución.

BREVE SÍNTESIS DE LA INVENCIÓN

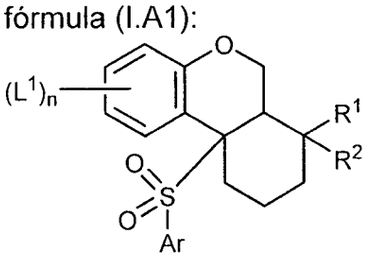
Esta invención proporciona compuestos que son inhibidores (por ej., antagonistas) de gamma–secretasa (también denominado "γ–secretasa") y tener la Fórmula (I)



(I)

o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico, en donde X, L^1, R^1, R^2 y Ar son como se definen a continuación.

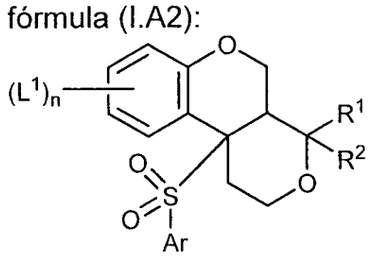
Esta invención también proporciona los compuestos de fórmula (I) que tiene la fórmula (I.A1):



(I.A1)

o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico, en donde L^1, R^1, R^2 y Ar son como se definen a continuación.

Esta invención también proporciona los compuestos de fórmula (I) que tiene la fórmula (I.A2):



(I.A2)

o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico, en donde L^1, R^1, R^2 y Ar son como se definen a continuación.

Esta invención también proporciona los compuestos de la fórmula (I) en forma pura y aislada.

Esta invención también proporciona los compuestos de la fórmula (I) en forma pura.

Esta invención también proporciona los compuestos de la fórmula (I) en forma y aislada.

Esta invención también proporciona los compuestos de la fórmula (I.A1) en forma pura y aislada.

Esta invención también proporciona los compuestos de la fórmula (I.A1) en forma pura.

Esta invención también proporciona los compuestos de la fórmula (I.A1) en forma aislada.

Esta invención también proporciona los compuestos de la fórmula (I.A2) en forma pura y aislada.

Esta invención también proporciona los compuestos de la fórmula (I.A2) en forma pura.

Esta invención también proporciona los compuestos de la fórmula (I.A2) en forma y aislada.

Esta invención también proporciona los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–) dichos compuestos se identifican a continuación.

Esta invención también proporciona los compuestos de 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–) en forma pura.

Esta invención también proporciona los compuestos de 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–) en forma y aislada.

Esta invención también proporciona una sal aceptable para uso farmacéutico de un compuesto de fórmula (I).

Esta invención también proporciona un solvato de un compuesto de fórmula (I).

Esta invención también proporciona una sal aceptable para uso farmacéutico de un compuesto de fórmula (I.A1).

Esta invención también proporciona un solvato de un compuesto de fórmula (I.A1).

Esta invención también proporciona una sal aceptable para uso farmacéutico de un compuesto de fórmula (I.A2).

Esta invención también proporciona un solvato de un compuesto de fórmula (I.A2).

Esta invención también proporciona a un solvato de un compuesto seleccionado del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona una éster aceptable para uso farmacéutico de un compuesto de fórmula (I).

Esta invención también proporciona una éster aceptable para uso farmacéutico de un compuesto de fórmula (I.A1).

Esta invención también proporciona una éster aceptable para uso farmacéutico de un compuesto de fórmula (I.A2).

Esta invención también proporciona una composición farmaceutical que comprende una cantidad efectiva de uno o más compuestos de Fórmula (I) y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más compuestos de Fórmula (I.A1) y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más compuestos de Fórmula (I.A2) y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula (I) y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula (I.A1) y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula (I.A2) y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una o más sales aceptables para uso farmacéutico de los compuestos de fórmula (I), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una o más sales aceptables para uso farmacéutico de los compuestos de fórmula (I.A1), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una o más sales aceptables para uso farmacéutico de los compuestos de fórmula (I.A2), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una sal aceptable para uso farmacéutico de un compuesto de fórmula (I), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una sal aceptable para uso farmacéutico de un compuesto de fórmula (I.A1), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una sal aceptable para uso farmacéutico de

un compuesto de fórmula (I.A2), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más solvatos de los compuestos de fórmula (I), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más solvatos de los compuestos de fórmula (I.A1), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más solvatos de los compuestos de fórmula (I.A2), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un solvato de un compuesto de fórmula (I), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un solvato de un compuesto de fórmula (I.A1), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un solvato de un compuesto de fórmula (I.A2), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más ésteres aceptables para uso farmacéutico de los compuestos de fórmula (I), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más ésteres aceptables para uso farmacéutico de los compuestos de fórmula (I.A1), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más ésteres aceptables para uso farmacéutico de los compuestos de fórmula (I.A2), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una éster aceptable para uso farmacéutico de un compuesto de fórmula (I), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una éster aceptable para uso farmacéutico de un compuesto de fórmula (I.A1), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de una éster aceptable para uso farmacéutico de un compuesto de fórmula (I.A2), y al menos un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A,

83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)), y una cantidad efectiva de uno o más (por ej., uno) componentes activos para uso farmacéutico diferentes (por ej.,) drogas, y un vehículo aceptable para uso farmacéutico. Los ejemplos de los componentes activos para uso farmacéutico diferentes incluyen, pero sin limitación drogas seleccionadas del grupo que consiste en: (a) drogas útiles para el tratamiento de la enfermedad de Alzheimer, (b) drogas útiles para inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro), (c) drogas útiles para tratar enfermedades neurodegenerativas, y (d) drogas útiles para inhibir la gamma-secretasa.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más (por ej., uno) componentes activos farmacéuticos terapéuticamente efectivos diferentes (por ej., drogas), y un vehículo aceptable para uso farmacéutico. Los ejemplos de las otras drogas incluyen, pero sin limitación drogas seleccionadas del grupo que consiste en: (a) drogas útiles para el tratamiento de enfermedad de Alzheimer, (b) drogas útiles para inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el

cerebro), (c) drogas útiles para tratar enfermedades neurodegenerativas, y (d) drogas útiles para inhibir la gamma-secretasa.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)), y una cantidad efectiva de uno o más inhibidores de BACE, y un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más inhibidores de BACE y un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más inhibidores de colinesterasa (por ej., inhibidores de acetil y/o butirilcolinesterasa), y un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmulas (I.A1), o compuestos de fórmula

(I.A2)), y una cantidad efectiva de uno o más antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), y un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), y un vehículo aceptable para uso farmacéutico.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para inhibir la gamma-secretasa que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona un método de tratar una o más enfermedades neurodegenerativas que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar una o más enfermedades neurodegenerativas que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar una o más enfermedades neurodegenerativas que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar una o más enfermedades neurodegenerativas que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar una o más enfermedades neurodegenerativas que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar una o más enfermedades neurodegenerativas que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método para tratar una o más enfermedades neurodegenerativas que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+),106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido

neurológico (por ej., el cerebro) que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en

los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A1) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A2) a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Esta invención también proporciona terapias de combinación para (1) inhibir la gamma-secretasa, o (2) tratar una o más enfermedades neurodegenerativas, o (3)inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro), o (4) tratar enfermedad de Alzheimer. Las terapias de combinación se refieren a métodos que comprenden la administración de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)) y la administración de uno o más (por ej., uno) componentes activos farmacéuticos diferentes (por ej., drogas). Los compuestos de fórmula (I) y las otras drogas se pueden administrar separadamente (es decir, cada una en su propia forma de dosis separada), o los compuestos de fórmula (I) se pueden combinar con las otras drogas en la misma forma de dosis.

En consecuencia, esta invención también proporciona cualquiera de los métodos de tratamiento, o métodos de inhibición, descriptos en la presente memoria, en donde el compuesto de fórmula (I) (por ej., el compuesto de fórmula (I.A1), o el compuesto de fórmula (I.A2)) se usa en combinación con una cantidad efectiva de uno o más componentes activos para uso farmacéutico diferentes seleccionado del grupo que consiste en: inhibidores de BACE (inhibidores de beta secretasa), antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), inhibidores de colinesterasa (por ej., inhibidores de acetil y/o butirilcolinesterasa);

inhibidores de gamma secretasa; moduladores de gamma secretasa; inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa; inhibidores de PDE–10 e inhibidores de absorción de colesterol (por ej., ezetimibe).

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I), en combinación con una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metilo]–1H–inden–1–ona, es decir, clorhidrato de donepeziloo, disponible con la marca Aricept ® de clorhidrato de donepeziloo), a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A1), en combinación con una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metilo]–1H–inden–1–ona, es decir, clorhidrato de donepeziloo, disponible con la marca Aricept ® de clorhidrato de donepeziloo), a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir,

terapéuticamente efectiva) de uno o más compuestos de fórmula (I.A2), en combinación con una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metilo]–1H–inden–1–ona, es decir, clorhidrato de donepeziloo, disponible con la marca Aricept ® de clorhidrato de donepeziloo), a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I), en combinación con una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metilo]–1H–inden–1–ona, es decir, clorhidrato de donepeziloo, disponible con la marca Aricept ® de clorhidrato de donepeziloo), a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A1), en combinación con una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metilo]–1H–inden–1–ona, es decir, clorhidrato de donepeziloo, disponible con la marca Aricept ® de clorhidrato de donepeziloo), a un paciente que necesita tratamiento.

Esta invención también proporciona un método de tratar enfermedad de Alzheimer que comprende administrar una cantidad efectiva (es decir, terapéuticamente efectiva) de un compuesto de fórmula (I.A2), en combinación con una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metilo]–1H–inden–1–

ona, es decir, clorhidrato de donepeziloo, disponible con la marca Aricept ® de clorhidrato de donepeziloo), a un paciente que necesita tratamiento.

La frase "cualquiera de los métodos anteriores" que se usa a continuación significa que la siguiente descripción se aplica a cada método descripto anteriormente igualmente que si cada método anterior se describiera en forma separada con el alcance que se describe más adelante.

Esta invención también proporciona cualquiera de los métodos anteriores en donde se usa una sal aceptable para uso farmacéutico de un compuesto de fórmula (I) en vez del compuesto de fórmula (I).

Esta invención también proporciona cualquiera de los métodos anteriores en donde una sal aceptable para uso farmacéutico de un compuesto de fórmula (I.A1) se usa en vez del compuesto de fórmula (I.A1).

Esta invención también proporciona cualquiera de los métodos anteriores en donde una sal aceptable para uso farmacéutico de un compuesto de fórmula (I.A2) se usa en vez del compuesto de fórmula (I.A2).

Esta invención también proporciona cualquiera de los métodos anteriores en donde una éster aceptable para uso farmacéutico de un compuesto de fórmula (I) se usa en vez del compuesto de fórmula (I).

Esta invención también proporciona cualquiera de los métodos anteriores en donde una éster aceptable para uso farmacéutico de un compuesto de fórmula (I.A1) se usa en vez del compuesto de fórmula (I.A1).

Esta invención también proporciona cualquiera de los métodos anteriores en donde una éster aceptable para uso farmacéutico de un compuesto de fórmula (I.A2) se usa en vez del compuesto de fórmula (I.A2).

Esta invención también proporciona cualquiera de los métodos anteriores en donde un solvato de un compuesto de fórmula (I) se usa en vez del compuesto de fórmula (I).

Esta invención también proporciona cualquiera de los métodos anteriores en donde un solvato de un compuesto de fórmula (I.A1) se usa en vez del compuesto de fórmula (I.A1).

Esta invención también proporciona cualquiera de los métodos anteriores en donde un solvato de un compuesto de fórmula (I.A2) se usa en vez del compuesto de fórmula (I.A2).

Esta invención también proporciona un kit que comprende, en recipientes separados, en un envase único, composiciones farmacéuticas para usar en combinación, en donde un recipiente comprende una cantidad efectiva de un compuesto de fórmula (I) (por ej., un compuesto de fórmula (I.A1), o un compuesto de fórmula (I.A2)) en un vehículo aceptable para uso farmacéutico, y otro recipiente (es decir, un segundo recipiente) comprende una cantidad efectiva de otro componente farmacéuticamente activo (como se describió anteriormente), las cantidades combinadas del compuesto de fórmula (I) y el otro componente farmacéuticamente activo que es efectivo para: (a) tratar enfermedad de Alzheimer, o (b) inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro), o (c) tratar enfermedades neurodegenerativas, o (d) inhibir gamma–secretasa.

Esta invención también proporciona un proceso para preparación de alquenos (es decir, diéster de alquenos), dicho proceso que comprende hacer reaccionar:

(1) una mezcla de

(a) un aldehído o una cetona y

(b) un alquilo sustituido con dos grupos atrayentes de electrones (es decir, un resto (EWG)–CH_2–(EWG)), tales como, por ejemplo, un diéster de un ácido dicarboxílico, (EWG representa un grupo atrayente de electrones), y

(2) alguno de:

(a) un haluro de sulfonilo (por ej., un cloruro de sulfonilo) y una amina básica (por ej., una amina terciaria básica), o,

(b) un anhídrido de sulfonilo y una amina básica (por ej., una amina terciaria básica), o

(c) un aril–C(O)–haluro y una amina básica (por ej., una amina terciaria básica), o

(d) un aril–C(O)–O–C(O)–arilo y una amina básica (por ej., una amina terciaria básica), o

(e) un heteroaril–C(O)–haluro y una amina básica (por ej., una amina terciaria básica), o

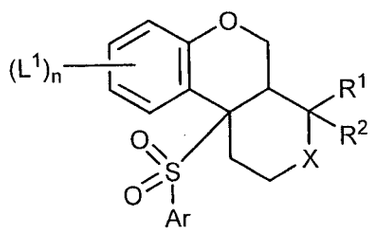
(f) un heteroaril–C(O)–O–C(O)–heteroarilo y una amina básica (por ej., una amina terciaria básica).

El proceso (reacción) se realiza en un solvente orgánico adecuado (es decir, un solvente orgánico en donde los restos (1) y (2) están en solución en una concentración adecuada, es decir, solvente orgánico en donde los restos (1) y (2) están en una mezcla). El solvente orgánico con preferencia es anhidro. El proceso (reacción) se realiza a una temperatura adecuada (es decir, una temperatura que permite que reacción proceda en una velocidad razonable para producir el producto final deseado sin producir subproductos de reacción no deseables). La reacción se puede realizar y con preferencia, en una atmósfera inerte (por ej., N_2). El producto deseado se puede separar y aislar por técnicas bien conocidas en el arte (por ej., extracción con un solvente orgánico y concentración del solvente orgánico).

Este proceso produce el producto final deseado en una reacción.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Esta invención proporciona nuevos compuestos, útiles como inhibidores de gamma secretasa, de la fórmula:



(I)

o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico, en donde:

X se selecciona del grupo que consiste en N y CH_2;

R^1 se selecciona del grupo que consiste en: (1) –alquilen–$S(O)_2$–alquilo(C_1–C_6), (2) –alquilen–$S(O)_2$–haloalquilo(C_1–C_6); (3) –alquilen–$S(O)_2$–R^6, (4) –alquilen–$S(O)_2$–R^8, (5) –alquilen–$S(O)_2$–alquilo(C_1–C_6) sustituido, (6) –alquilen–(1,1–dióxido de tetrahidrotiofeno), (7) –alquenil–$S(O)_2$–alquilo(C_1–C_6), y (8) –cicloalquilo–$S(O)_2$–alquilo(C_1–C_6);

en donde dicho grupo R^1 –alquilen–$S(O)_2$–alquilo(C_1–C_6) sustituido está sustituido con uno o más sustituyentes seleccionados de modo independiente del grupo que consiste en: –OH, halo, –CN, $–CF_3$, –O–alquilo(C_1–C_6) (por ej., $–OCH_3$), y –O–(haloalquilo(C_1–C_6)) (por ej., $–OCF_3$), y con preferencia –OH, y con más preferencia un –OH, y en donde un ejemplo de dicho grupo R^1 –alquilen–$S(O)_2$–alquilo(C_1–C_6) sustituido es –alquilen–$S(O)_2$–hidroxialquilo (C_1–C_6);

R^2 se selecciona del grupo que consiste en: H y alquilo (por ej., alquilo C_1–C_6 o alquilo (C_1–C_2)), y en un ejemplo R^2 es H, y en otro ejemplo R^2 es metilo;

R^6 se selecciona del grupo que consiste en: (1) arilo (C_6–C_{14}) no sustituido, (2) arilo (C_6–C_{14}) sustituido con uno o más grupos L^{1A}, (3) heteroarilo (C_5–C_{14}) no sustituido, (4) heteroarilo (C_5–C_{14}) sustituido con uno o más grupos L^{1A}, (5) heteroarilalquilo (C_5–C_{14})no sustituido, y (5) heteroarilalquilo (C_5–C_{14}) sustituido con uno o más grupos L^{1A};

R^8 se selecciona del grupo que consiste en cicloalquilo no sustituido y cicloalquilo sustituido con uno o más grupos L^3 (en donde los ejemplos de dichos grupos cicloalquilo (no sustituido o sustituido) incluyen los anillos cicloalquilo C_3–C_{10});

cada L^3 se selecciona de modo independiente del grupo que consiste en: (1) –CN, (2) =O, (3) $–CH_2OH$, (4) amino (es decir, $–NH_2$), (5) halo (por ej., Cl, F, y Br), (6) $–CH_2NH_2$, (7) $–CH_2NH$alquilo (tales como, por ejemplo, $–CH_2NH$alquilo(C_1–C_6)), (8) –C(O)OH,

(9) –alquilen–C(O)NHalquilo (C_1 a C_6), (10) –alquilen–C(O)N(alquilo (C_1 a C_6))$_2$ en donde cada alquilo se selecciona de modo independiente, (11) –alquilen–C(O)NHhaloalquilo (C_1 a C_6), y (12) –alquilen–C(O)N(haloalquilo (C_1 a C_6))$_2$ en donde cada alquilo se selecciona de modo independiente);

Ar se selecciona del grupo que consiste en: (1) arilo no sustituido (por ej., fenilo no sustituido), (2) arilo (por ej., fenilo) sustituido con uno o más grupos L^{1A}, (3) heteroarilo no sustituido (por ej., piridilo), y (4) heteroarilo sustituido (por ej., piridilo sustituido) sustituido con uno o más grupos L^{1A};

cada L^1 se selecciona de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $–CF_3$, –O–alquilo(C_1–C_6) (por ej., $–OCH_3$), –O–(haloalquilo(C_1–C_6)) (por ej., $–OCF_3$ y $–OCH_2CF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $–C(O)OCH_3$), –alquilen–OH (por ej., $–CH_2OH$), haloalquilo(C_1–C_6) (por ej., $–CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O–$), alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O–$), y –S(O)$_2$alquilo(C_1–C_6) (por ej., $–S(O)_2CH_2CH_3$);

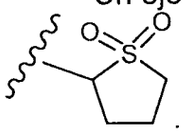
cada L^{1A} se selecciona de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $–CF_3$, –O–alquilo(C_1–C_6) (por ej., $–OCH_3$), –O–(haloalquilo(C_1–C_6)) (por ej., $–OCF_3$ y $–OCH_2CF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $–C(O)OCH_3$), –alquilen–OH (por ej., $–CH_2OH$),

haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–), y –$S(O)_2$alquilo(C_1–C_6) (por ej., –$S(O)_2CH_2CH_3$); y

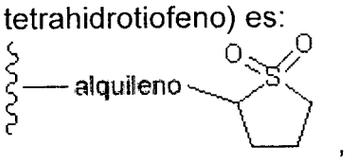
n es 0, 1, 2 o 3.

En los compuestos de esta invención, el resto –$S(O)_2$– de los sustituyentes R^1 se puede unir a cualquier carbono de la cadena alquileno. En general el resto –$S(O)_2$– de los sustituyentes R^1 se une al carbono terminal de la cadena alquileno.

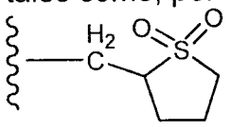
Un ejemplo de un resto 1,1–dióxido de tetrahidrotiofeno es:



En consecuencia, y ejemplo del resto R^1 –alquilen–(1,1–dióxido de tetrahidrotiofeno) es:



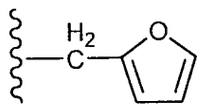
tales como, por ejemplo,



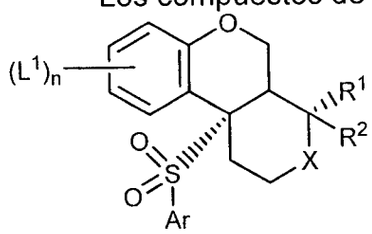
Un ejemplo del resto R^1 –alquenil–$S(O)_2$–alquilo(C_1–C_6) es –alquenil (C_2 a C_6)–$S(O)_2$–alquilo(C_1–C_6), tales como, por ejemplo, –alquenil (C_2 a C_3)–$S(O)_2$–alquilo(C_1–C_6), tales como, por ejemplo, –CH=CH–$S(O)_2$–alquilo(C_1–C_6).

Un ejemplo del resto R^1 –cicloalquilo–$S(O)_2$–alquilo(C_1–C_6)es –cicloalquil (C_3 a C_6)-$S(O)_2$–alquilo(C_1–C_6), tales como por ejemplo, –cicloalquil (C_3 a C_5)–$S(O)_2$–alquilo(C_1–C_6), tales como, por ejemplo, –ciclopropil–$S(O)_2$–alquilo(C_1–C_6).

Un ejemplo del resto heteroarilalquilo del sustituyente R^6 heteroarilalquilo (C_5–C_{14}) no sustituido o el heteroarilalquilo (C_5–C_{14}) sustituido es furanil–alquilo–, tales como, por ejemplo, furanil–CH_2–, tales como, por ejemplo,

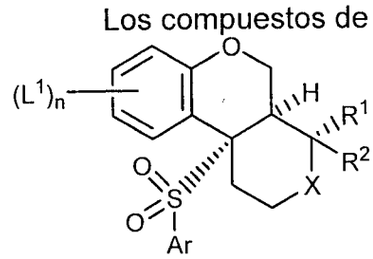


Los compuestos de fórmula (I) incluyen compuestos de fórmula (Ii):



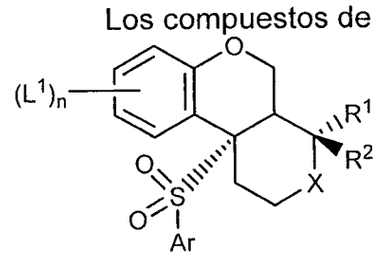
(Ii)

Los compuestos de fórmula (I) incluyen compuestos de fórmula (Iii):



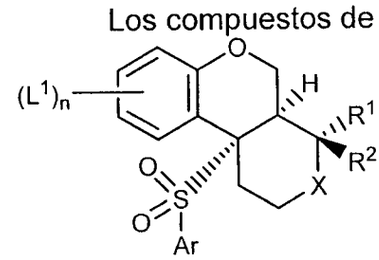
(Iii)

Los compuestos de fórmula (I) incluyen compuestos de fórmula (Iiii):



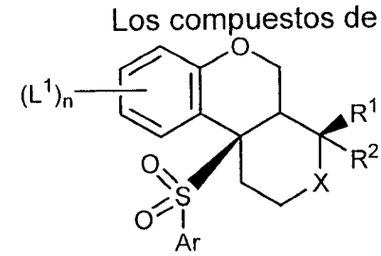
(Iiii)

Los compuestos de fórmula (I) incluyen compuestos de fórmula (Iiv):



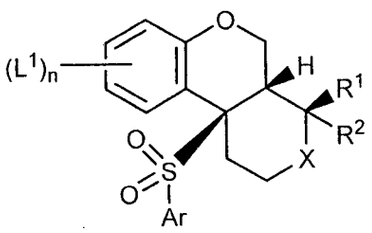
(Iiv)

Los compuestos de fórmula (I) incluyen compuestos de fórmula (Iv):



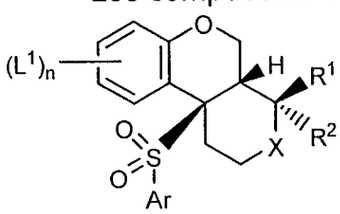
(Iv)

Los compuestos de fórmula (I) incluyen compuestos de fórmula (Ivi):



(Ivi)

Los compuestos de fórmula (I) incluyen compuestos de fórmula (Ivii):



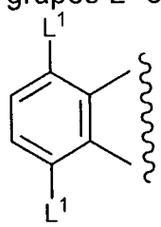
(Ivii)

La frase "cualquiera de los compuestos" que se usa a continuación para los compuestos de las fórmulas (Ii) a (Ivii), (I.A1a) a (I.A1h), y (I.A2a) a (I.A2h), a menos que se indique de otro modo, significa que dicha descripciones aplica a cada compuesto mencionado en la descripción igualmente como si cada compuesto mencionado se describiera por separado. En consecuencia, por ejemplo, la siguiente descripción de los "compuestos de fórmula (I) también incluye cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) en donde n es 2" describe una realización referida a un compuesto de fórmula (Ii) en donde n es 2. También se considera que describe una realización referida a un compuesto de fórmula (Iii) en donde n es 2. También se considera que describe una realización referida a un compuesto de fórmula (Iiii) en donde n es 2. También se considera que describe una realización referida a un compuesto de fórmula (Iiv) en donde n es 2. También se considera que describe una realización referida a un compuesto de fórmula (Iv) en donde n es 2. También se considera que describe una realización referida a un compuesto de fórmula (Ivi) en donde n es 2. También se considera que describe una realización referida a un compuesto de fórmula (Ivii) en donde n es 2.

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Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2.

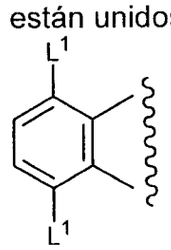
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1) o (I.A2) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo as como se muestra en (IIA):



(IIA)

(en donde la línea ondulada ∿∿∿ representa el resto de la fórmula).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA):



(IIA)

(en donde la línea ondulada ∿∿∿ representa el resto de la fórmula).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y cada L^1 es el mismo o diferente halo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y cada L^1 es F.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivi) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–

$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH),

haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en: piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por

ej., $-C(O)OCH_3$), –alquilen–OH (por ej., $-CH_2OH$), haloalquilo(C_1–C_6) (por ej., $-CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$-).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $-CF_3$, –O–alquilo(C_1–C_6) (por ej., $-OCH_3$), –O–(haloalquilo(C_1–C_6)) (por ej., $-OCF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $-C(O)OCH_3$), –alquilen–OH (por ej., $-CH_2OH$), haloalquilo(C_1–C_6) (por ej., $-CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, $-CF_3$ y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en: piridilo, y piridilo

sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, $–CF_3$ y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $–CF_3$, –O–alquilo(C_1–C_6) (por ej., $–OCH_3$), –O–(haloalquilo(C_1–C_6)) (por ej., $–OCF_3$ y $–OCH_2CF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $–C(O)OCH_3$), –alquilen–OH ($–CH_2OH$), haloalquilo(C_1–C_6) (por ej., $–CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $–CF_3$, –O–alquilo(C_1–C_6) (por ej., $–OCH_3$), –O–(haloalquilo(C_1–C_6)) (por ej., $–OCF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $–C(O)OCH_3$), –alquilen–OH (por ej., $–CH_2OH$), haloalquilo(C_1–C_6) (por ej., $–CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

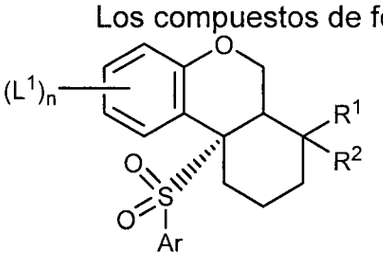
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo,

piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, $–CF_3$ y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en: piridilo, y piridilo sustituido con substituent seleccionado del grupo que consiste en: –Cl, $–CF_3$ y –CN.

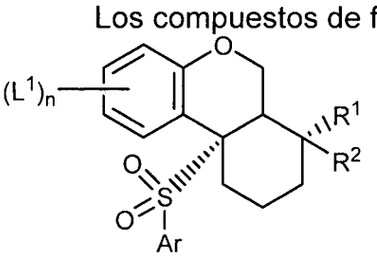
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1a):



(I.A1a)

en donde todos los sustituyentes son como se definen para la fórmula (I).

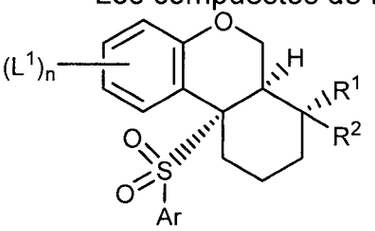
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1b):



(I.A1b)

en donde todos los sustituyentes son como se definen para la fórmula (I).

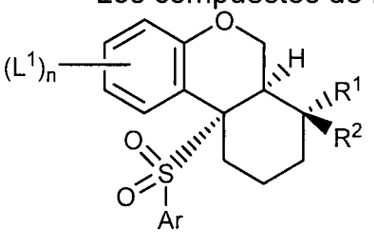
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1c):



(I.A1c)

en donde todos los sustituyentes son como se definen para la fórmula (I).

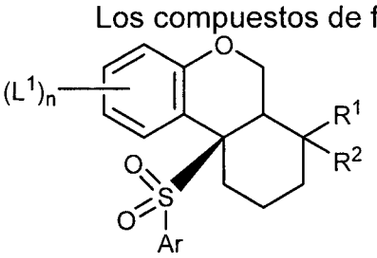
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1d):



(I.A1d)

en donde todos los sustituyentes son como se definen para la fórmula (I).

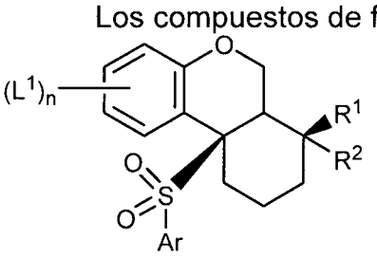
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1e):



(I.A1e)

en donde todos los sustituyentes son como se definen para la fórmula (I).

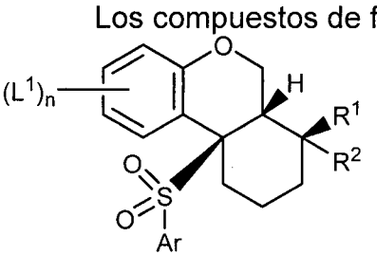
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1f):



(I.A1f)

en donde todos los sustituyentes son como se definen para la fórmula (I).

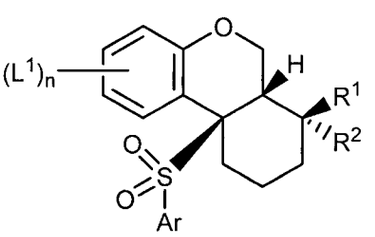
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1g):



(I.A1g)

en donde todos los sustituyentes son como se definen para la fórmula (I).

Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A1h):



(I.A1h)

en donde todos los sustituyentes son como se definen para la fórmula (I).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y cada L^1 es el mismo o diferente halo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y cada L^1 es F.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –$C(O)OCH_3$), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3),

–C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi–

(por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en: piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en:–Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenil, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y

$-OCH_2CF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $-C(O)OCH_3$), –alquilen–OH (por ej., $-CH_2OH$), haloalquilo(C_1–C_6) (por ej., $-CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $-CF_3$, –O–alquilo(C_1–C_6) (por ej., $-OCH_3$), –O–(haloalquilo(C_1–C_6)) (por ej., $-OCF_3$), –C(O)–O–alquilo(C_1–C_6) (por ej., $-C(O)OCH_3$), –alquilen–OH (por ej., $-CH_2OH$), haloalquilo(C_1–C_6) (por ej., $-CF_3$), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

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Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los

grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en: piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en:–Cl, –CF_3 y –CN.

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–OCF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH),
haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en: piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en:–Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–Cl–fenilo–.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CN–fenilo–.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–$CH_3CH_2SO_2$fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–Br–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es m,p–di–F–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es m,p–di–CN–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CH_3O–fenilo.

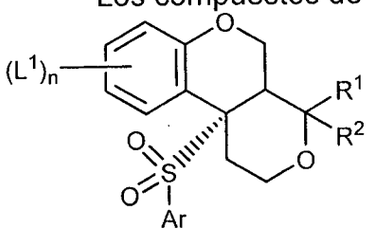
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CF_3CH_2Ofenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) descriptos anteriormente en donde R^2 es H.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) descriptos anteriormente en donde R^2 es alquilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h) descriptos anteriormente en donde R^2 es metilo.

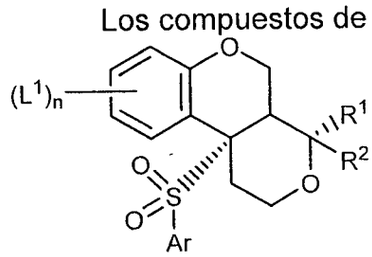
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2a):



(I.A2a)

en donde todos los sustituyentes son como se definen para la fórmula (I).

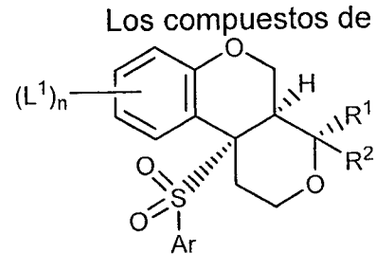
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2b):



(I.A2b)

en donde todos los sustituyentes son como se definen para la fórmula (I).

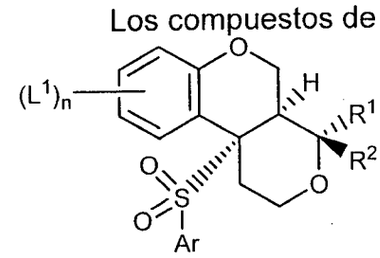
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2c):



(I.A2c)

en donde todos los sustituyentes son como se definen para la fórmula (I).

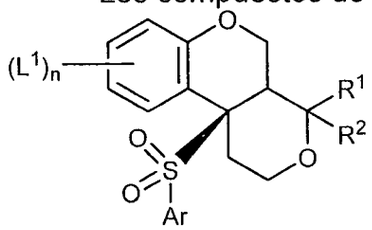
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2d):



(I.A2d)

en donde todos los sustituyentes son como se definen para la fórmula (I).

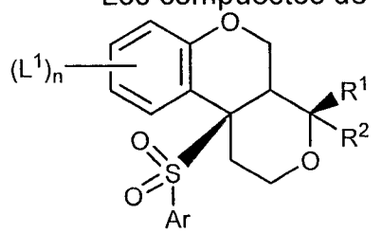
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2e):



(I.A2e)

en donde todos los sustituyentes son como se definen para la fórmula (I).

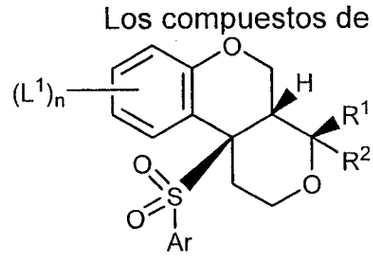
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2f):



(I.A2f)

en donde todos los sustituyentes son como se definen para la fórmula (I).

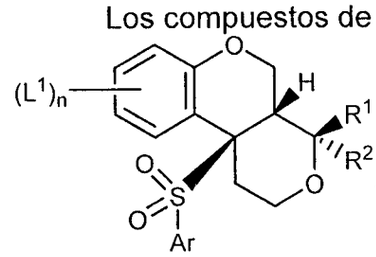
Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2g):



(I.A2g)

en donde todos los sustituyentes son como se definen para la fórmula (I).

Los compuestos de fórmula (I) incluyen compuestos de fórmula (I.A2h):



(I.A2h)

en donde todos los sustituyentes son como se definen para la fórmula (I).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y cada L^1 es el mismo o diferente halo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y cada L^1 es F.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los

grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA) y Ar se selecciona del grupo que consiste en: piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en:–Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenil, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –C(O)OCH_3), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –$C(O)OCH_3$),
–alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es el mismo o diferente halo, y Ar se selecciona del grupo que consiste en: piridilo, y

piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en:–Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenil, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3 y –OCH_2CF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –$C(O)OCH_3$), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, –CF_3, –O–alquilo(C_1–C_6) (por ej., –OCH_3), –O–(haloalquilo(C_1–C_6)) (por ej., –OCF_3), –C(O)–O–alquilo(C_1–C_6) (por ej., –$C(O)OCH_3$), –alquilen–OH (por ej., –CH_2OH), haloalquilo(C_1–C_6) (por ej., –CF_3), hidroxialcoxi– (por ej., $HOCH_2CH_2O$–), y alcoxialcoxi– (por ej., $CH_3OCH_2CH_2O$–).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los

grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, piridilo, y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en: –Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, y p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar se selecciona del grupo que consiste en: piridilo y piridilo sustituido con 1 sustituyente seleccionado del grupo que consiste en:–Cl, –CF_3 y –CN.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–Cl–fenilo–.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CN–fenilo–.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CF_3–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los

grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–$CH_3CH_2SO_2$fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–Br–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es m,p–di–F–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es m,p–di–CN–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CH_3O–fenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) anteriores en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA), cada L^1 es F, y Ar es p–CF_3CH_2Ofenilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) descriptos anteriormente en donde R^2 es H.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) descriptos anteriormente en donde R^2 es alquilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h) descriptos anteriormente en donde R^2 es metilo.

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente en donde R^1 es –alquilen–(1,1–dióxido de tetrahidrotiofeno).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente R^1 es –alquenil–$S(O)_2$–alquilo(C_1–C_6).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente en donde R^1 es –cicloalquil–$S(O)_2$–alquilo(C_1–C_6).

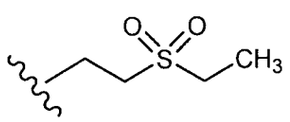
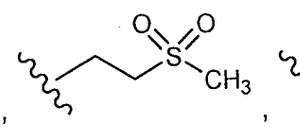
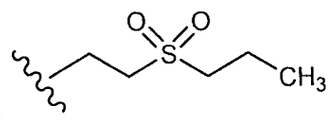
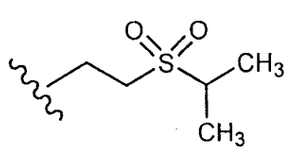
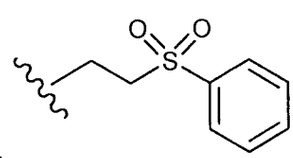
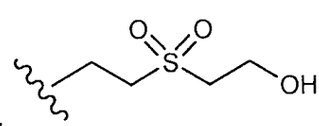
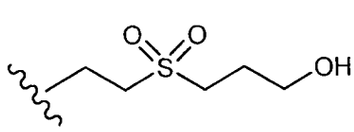
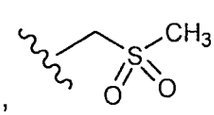
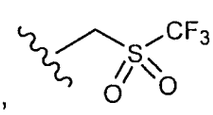
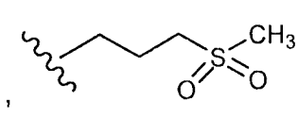
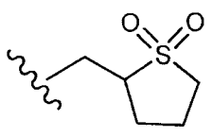
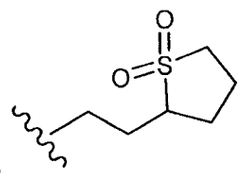
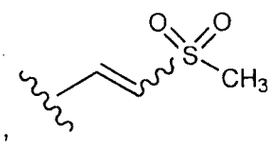
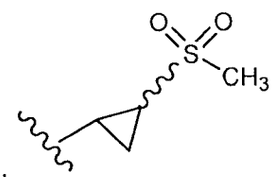
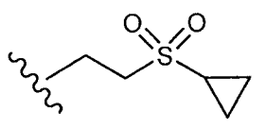
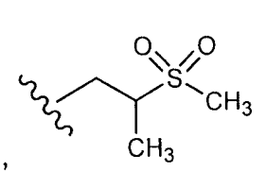
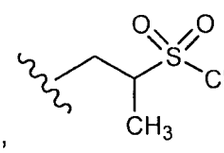
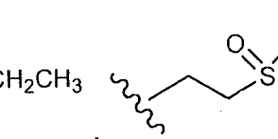
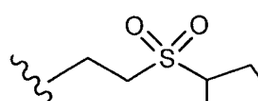
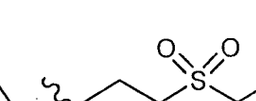
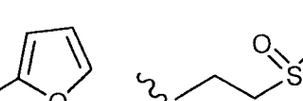
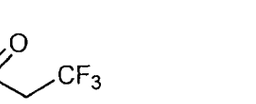
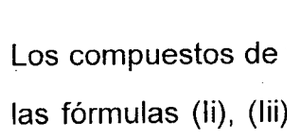
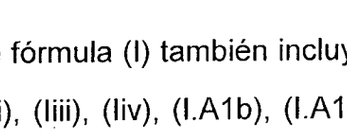
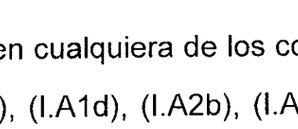
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente en donde R^1 es un grupo – alquilen–$S(O)_2$–alquilo(C_1–C_6).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo(C_1–C_6).

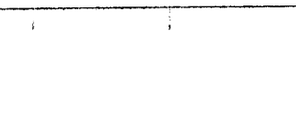
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo (C_1–C_3) group.

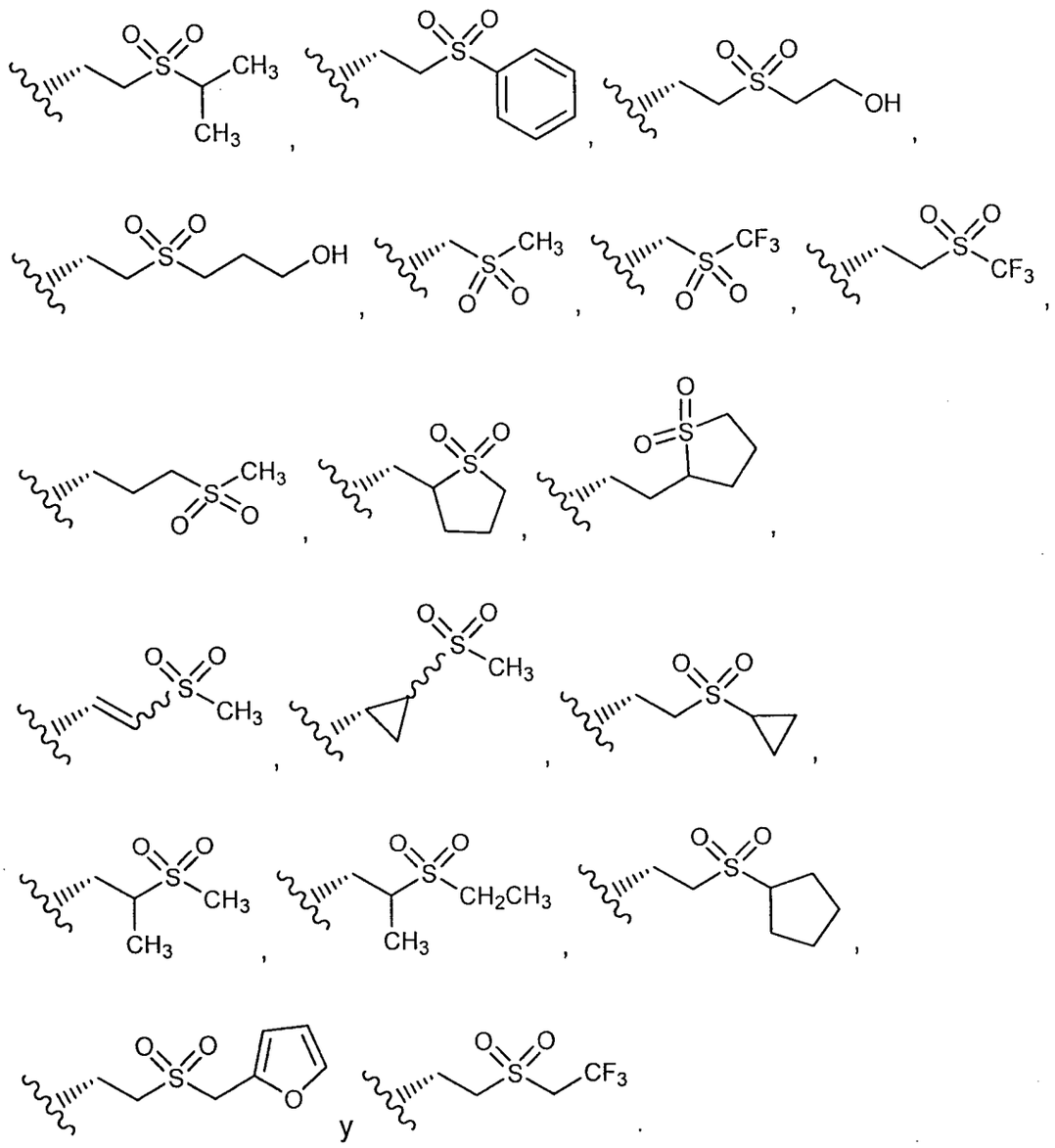
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) descriptos anteriormente en donde R^1 es un grupo –(C_2) alquilen–$S(O)_2$–alquilo(C_1–C_6).

Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (I.A1), (I.A2), (I.A1a), (I.A1e), (I.A2a) o (I.A2e) en donde R^1 se selecciona del grupo que consiste en:

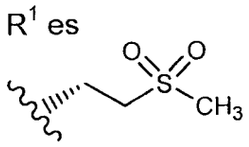
























y


Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d) en donde R^1 se selecciona del grupo que consiste en:

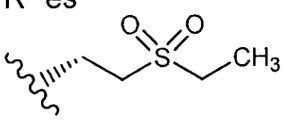




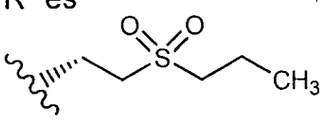
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



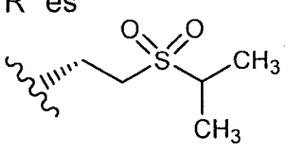
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



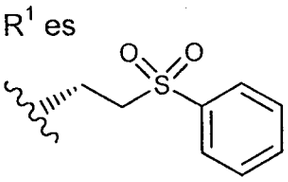
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



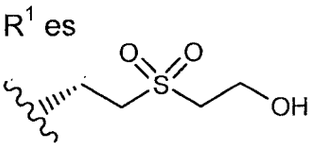
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



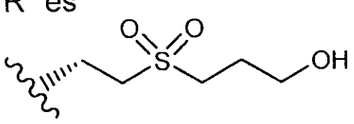
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



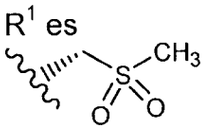
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



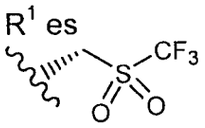
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



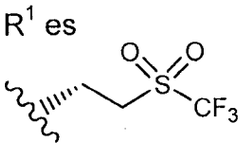
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



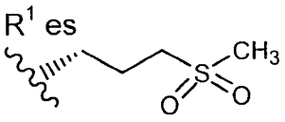
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



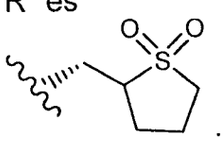
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



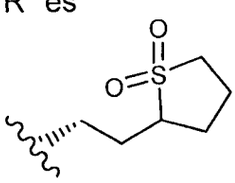
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



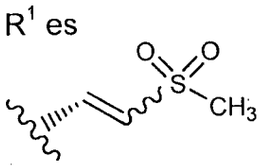
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



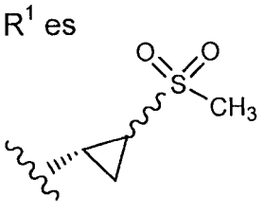
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



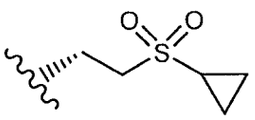
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



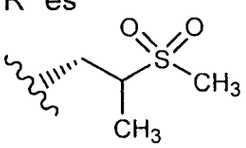
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



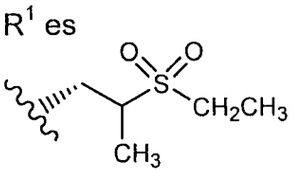
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



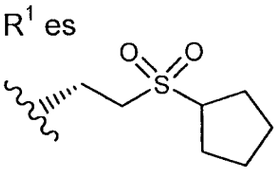
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



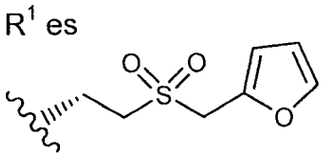
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



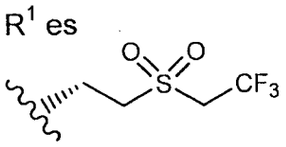
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



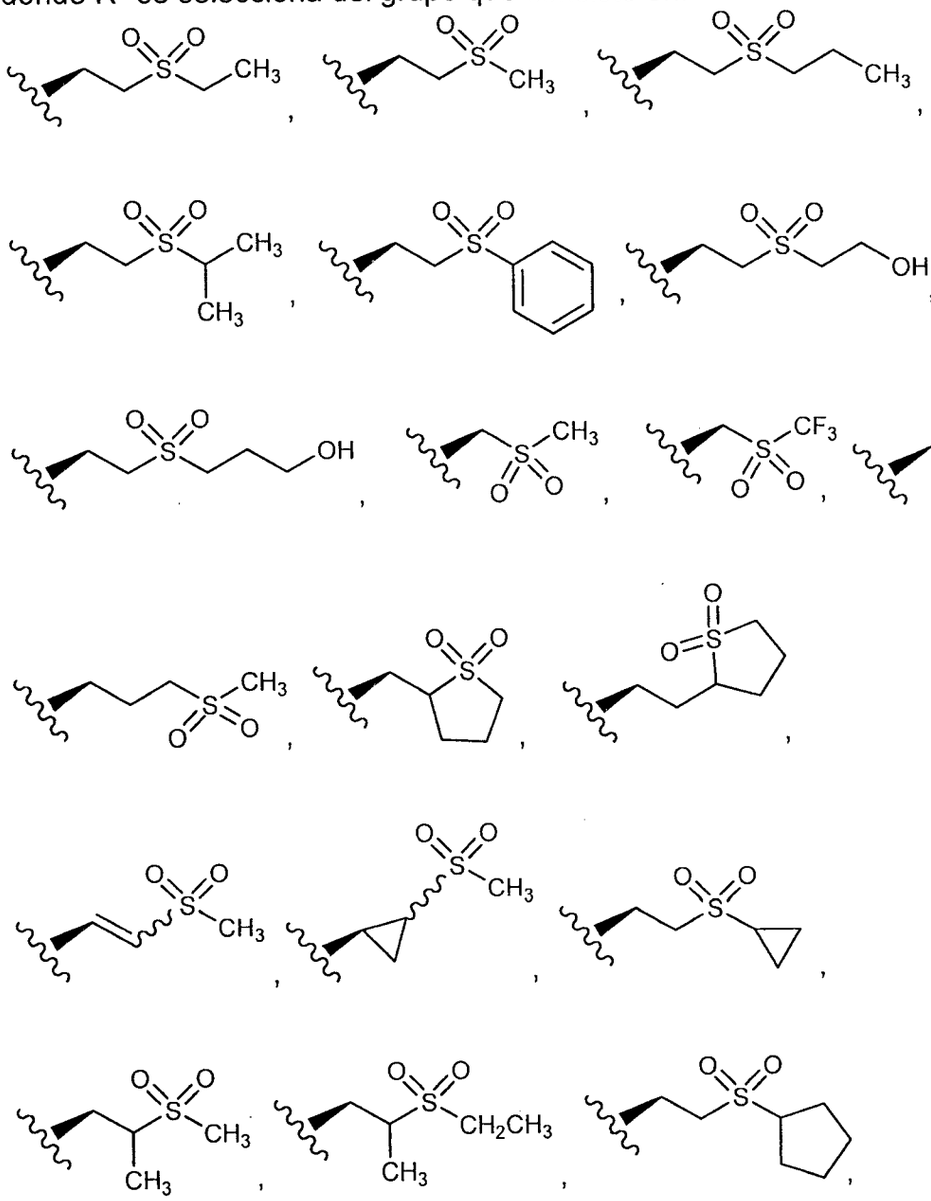
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

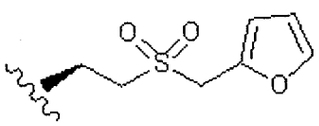
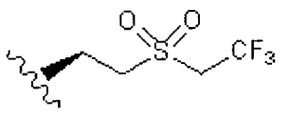


Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

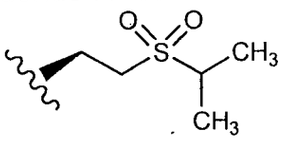


Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 se selecciona del grupo que consiste en:

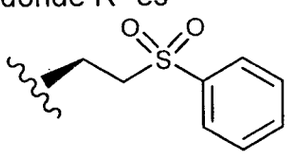



y


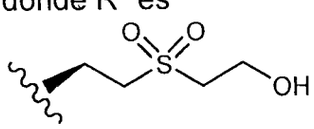
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



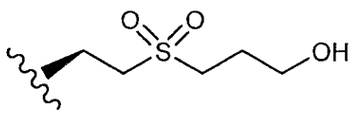
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



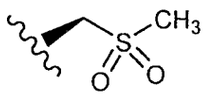
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



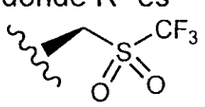
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



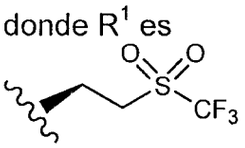
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



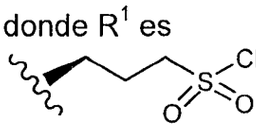
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



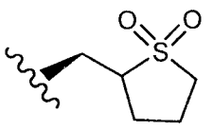
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



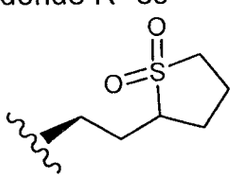
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



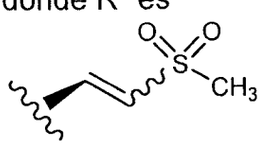
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



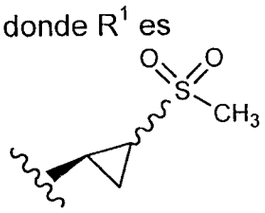
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



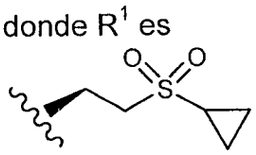
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

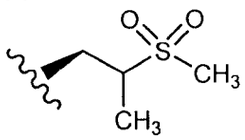


Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

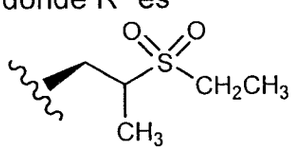


Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

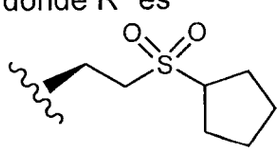
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



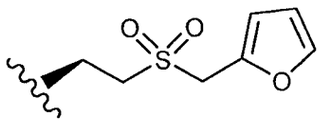
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



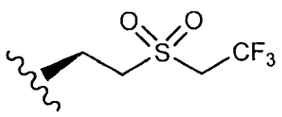
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



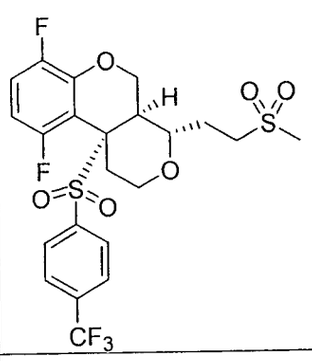
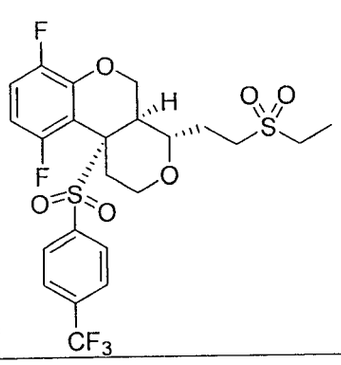
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

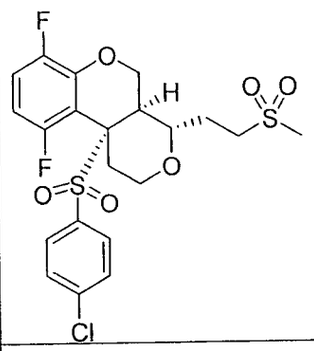
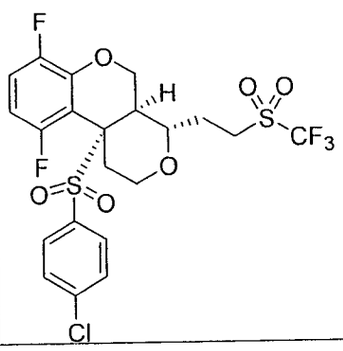
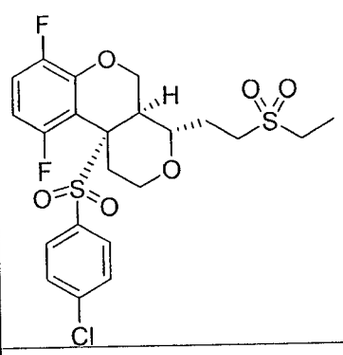
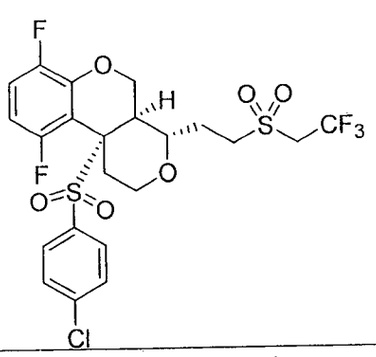


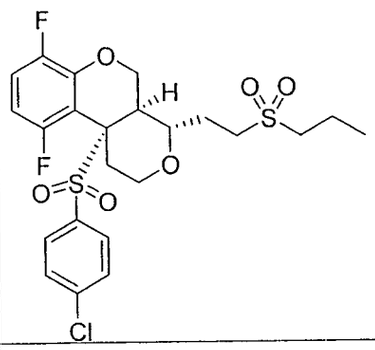
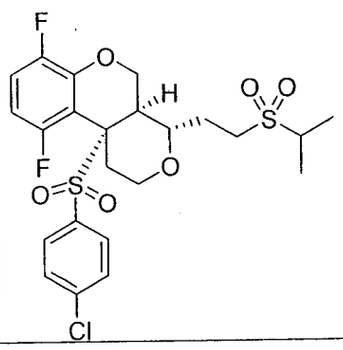
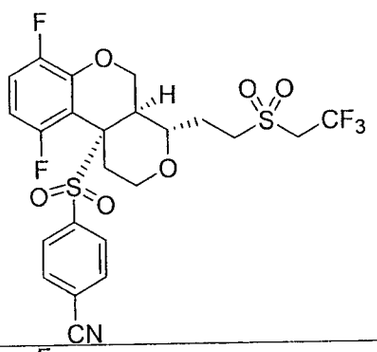
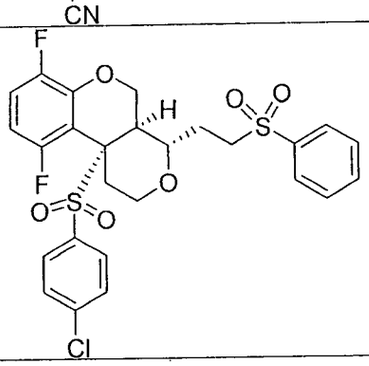
Los compuestos de fórmula (I) también incluyen cualquiera de los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

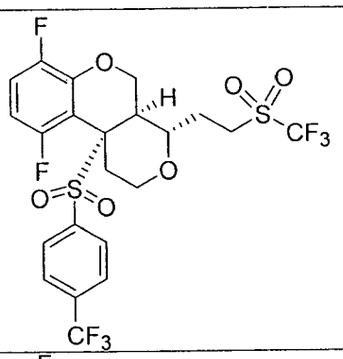
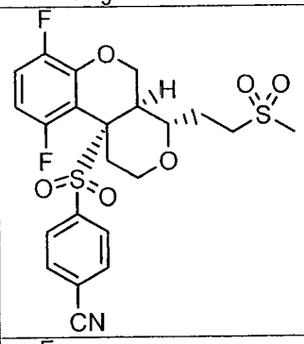
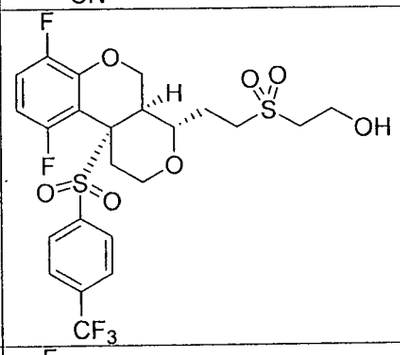
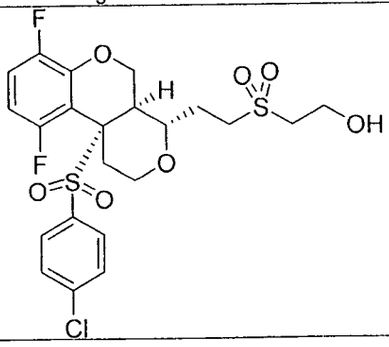


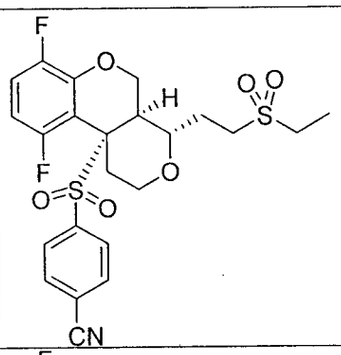
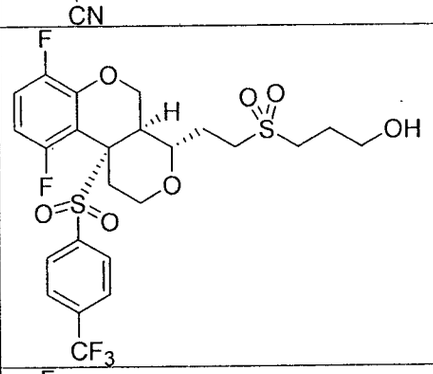
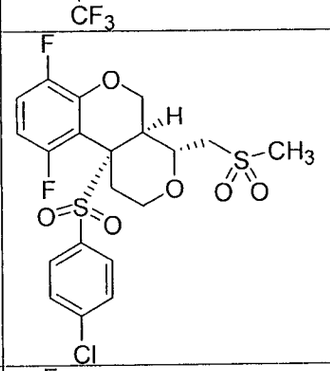
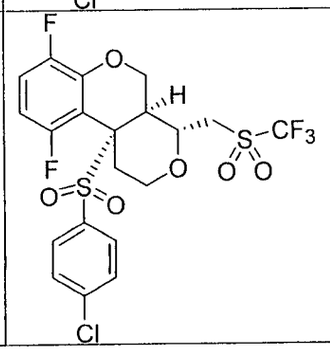
LOs compuestos representativos de fórmula (I) incluyen, pero sin limitación:

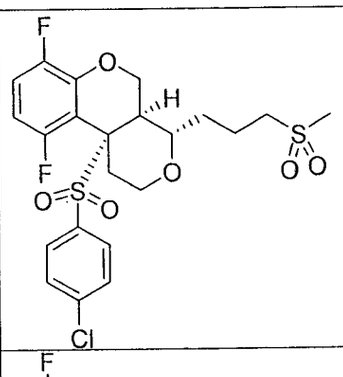
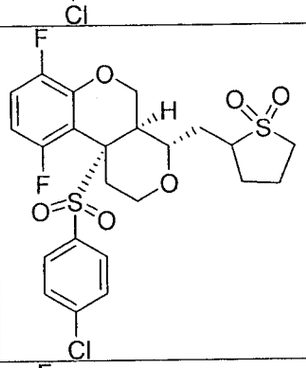
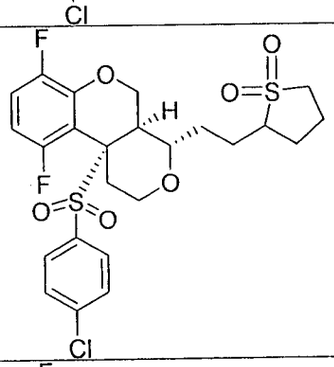
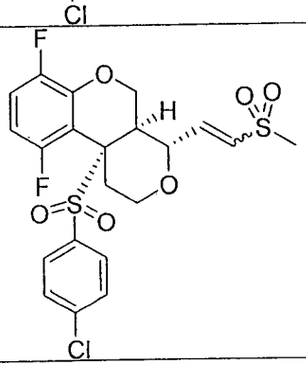
Compuesto No.	ESTRUCTURA
12	
13	

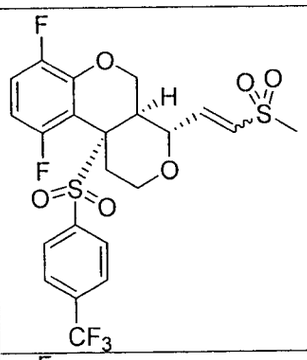
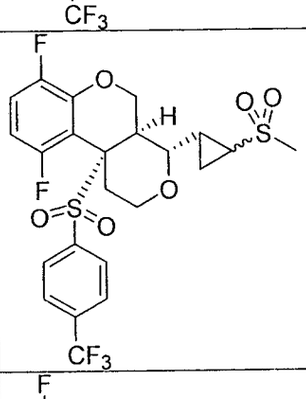
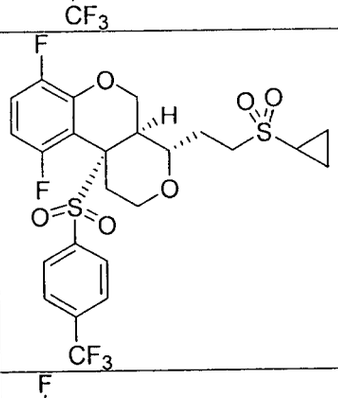
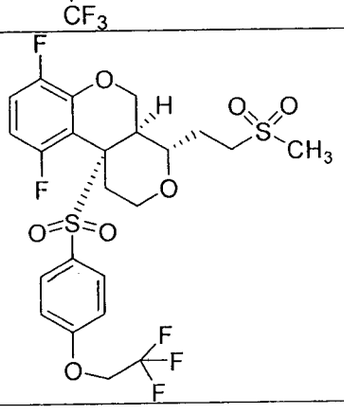
Compuesto No.	ESTRUCTURA
22A	
22B	
22C	
22D	

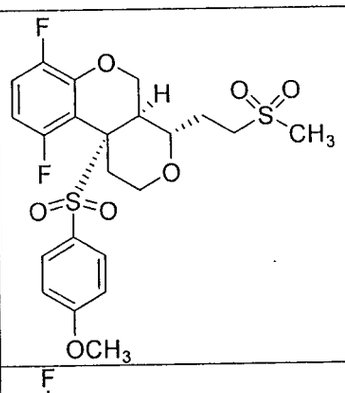
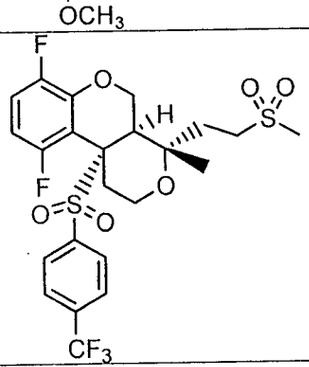
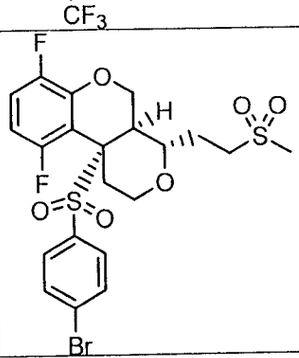
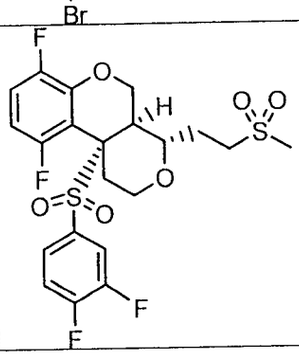
Compuesto No.	ESTRUCTURA
22E	
22F	
22G	
22H	

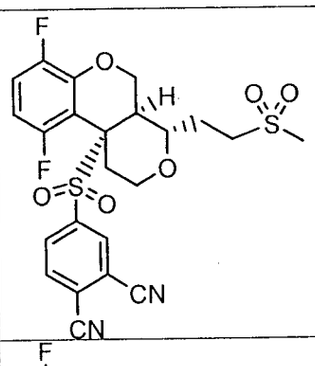
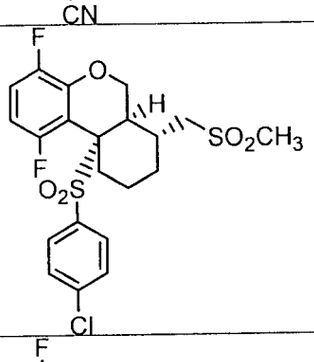
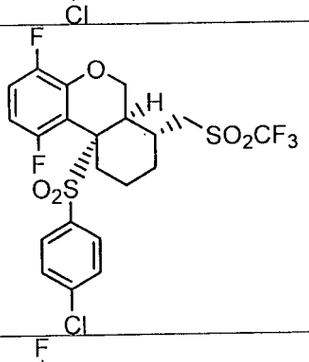
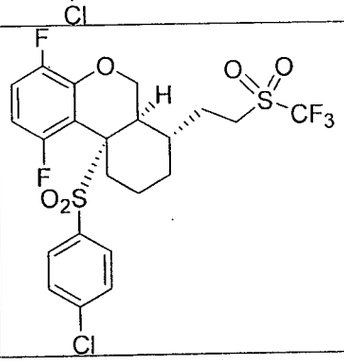
Compuesto No.	ESTRUCTURA
22I	
22J	
22K	
22L	

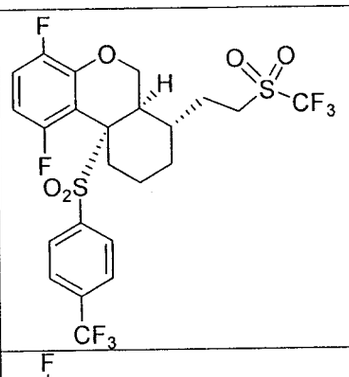
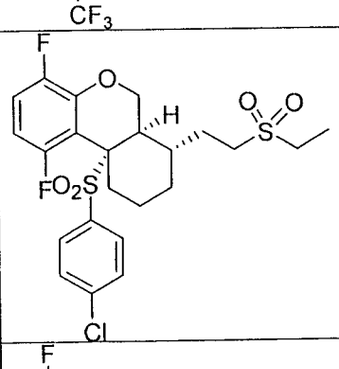
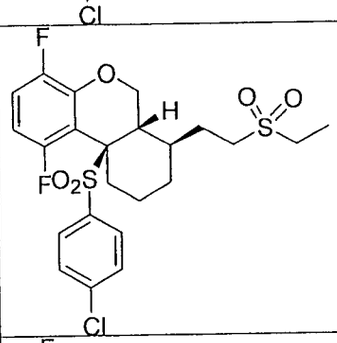
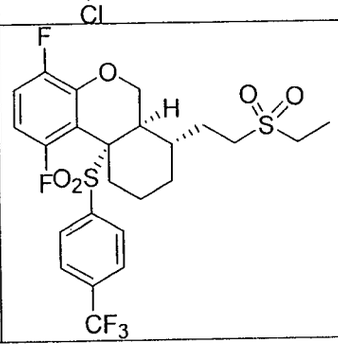
Compuesto No.	ESTRUCTURA
22M	
22N	
26A	
26B	

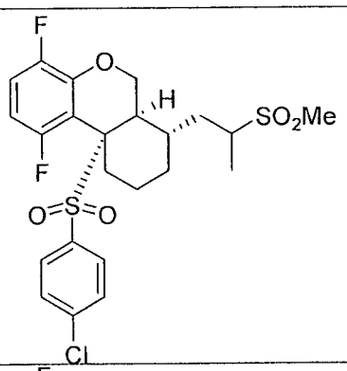
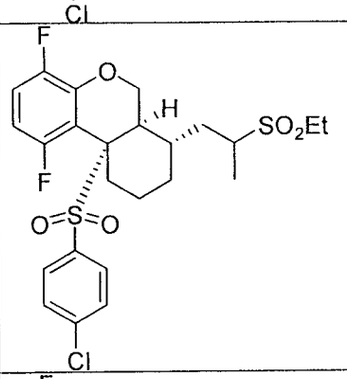
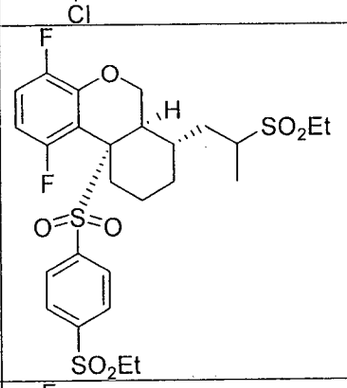
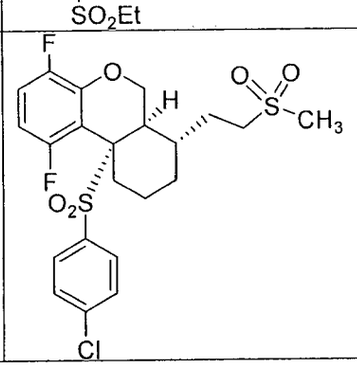
Compuesto No.	ESTRUCTURA
27	
28	
31	
33 (–)	

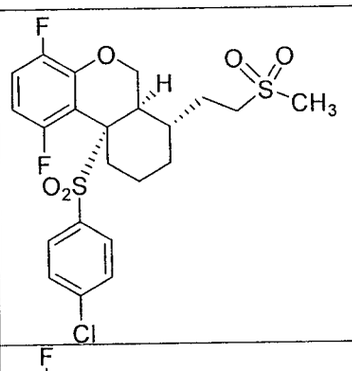
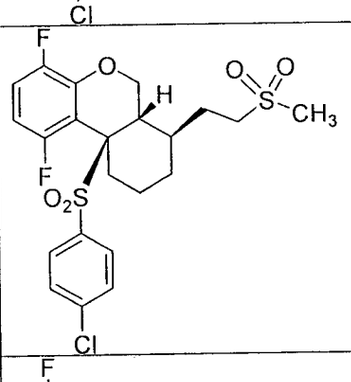
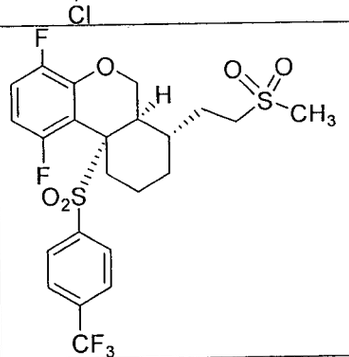
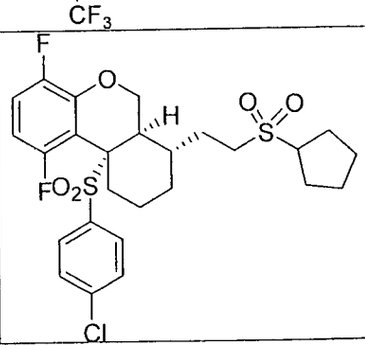
Compuesto No.	ESTRUCTURA
36	
37	
39	
44A	

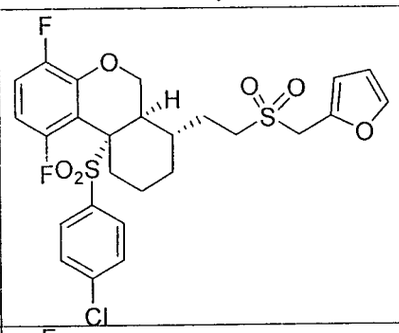
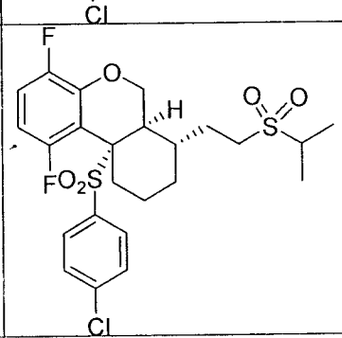
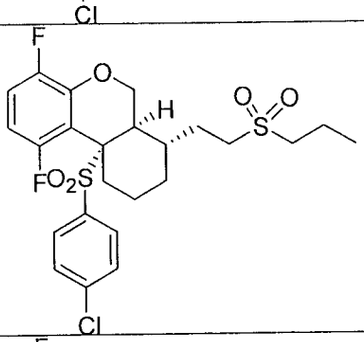
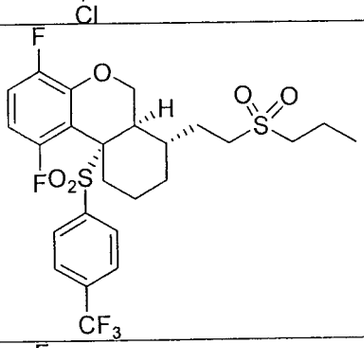
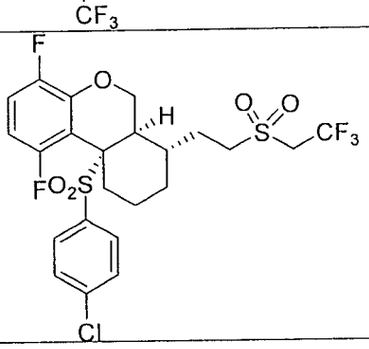
Compuesto No.	ESTRUCTURA
44B	
55	
56	
57	

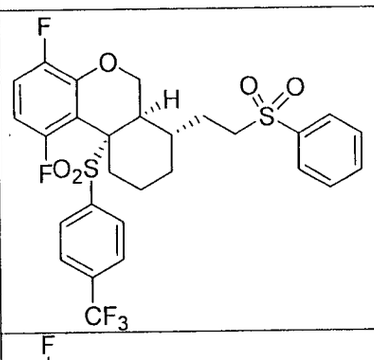
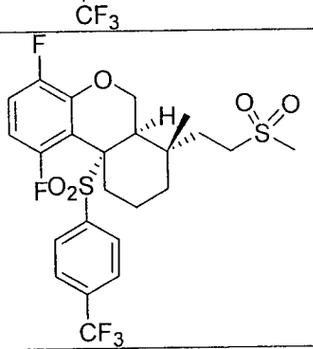
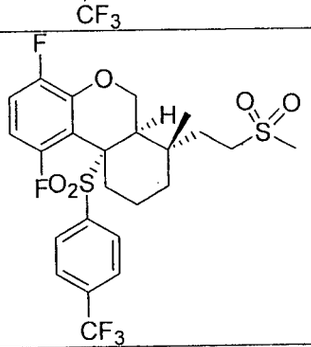
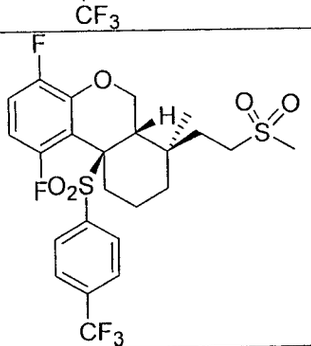
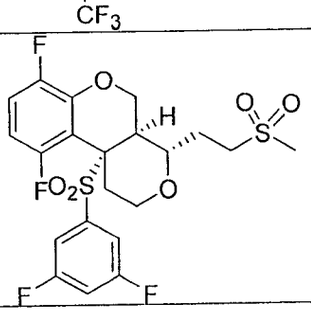
Compuesto No.	ESTRUCTURA
60	
70A	
71A (–)	
75A–rac	

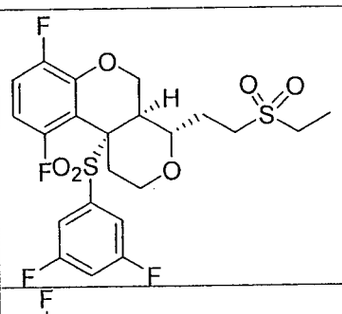
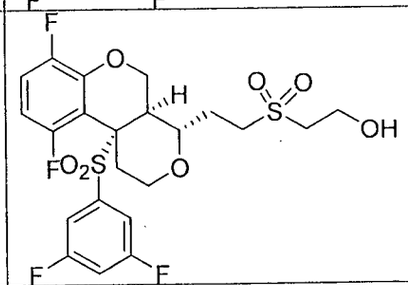
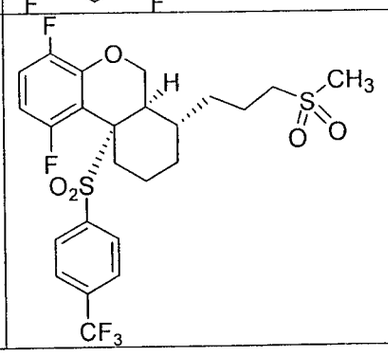
Compuesto No.	ESTRUCTURA
75B (–)	
76A (–)	
76A (+)	
76B (–)	

Compuesto No.	ESTRUCTURA
78A (–)	
79A (–)	
80A (–)	
81A–rac	

Compuesto No.	ESTRUCTURA
81A (–)	
81A (+)	
81B (–)	
82A	

Compuesto No.	ESTRUCTURA
83A	
84A	
85A	
85B (–)	
86A	

Compuesto No.	ESTRUCTURA
87B	
95B–rac	
95B (–)	
95B (+)	
106 (–)	

Compuesto No.	ESTRUCTURA
107 (–)	
108 (–)	
111 (–)	

Una forma de realización de la presente invención se refiere a compuestos de fórmula (I), o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico.

Otra realización de esta invención se refiere a compuestos de fórmula (I).

Otra realización de esta invención se refiere a sales aceptables para uso farmacéutico de los compuestos de fórmula (I).

Otra realización de esta invención se refiere a solvatos de los compuestos de fórmula (I).

Otra realización de esta invención se refiere a ésteres aceptables para uso farmacéutico de los compuestos de fórmula (I).

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Otra realización de la presente invención se refiere a cualquiera de los compuestos de las fórmulas (Ii) a (Ivii), o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico.

Otra realización de esta invención se refiere a cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a sales aceptables para uso farmacéutico de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a solvatos de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a ésteres aceptables para uso farmacéutico de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de la presente invención se refiere a cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h), o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico.

Otra realización de esta invención se refiere a cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a sales aceptables para uso farmacéutico de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a solvatos de cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a ésteres aceptables para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de la presente invención se refiere a cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h), o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico.

Otra realización de esta invención se refiere a cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a sales aceptables para uso farmacéutico de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a solvatos de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a ésteres aceptables para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa una sal aceptable para uso farmacéutico de cualquiera de (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un éster aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa sal aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un éster

aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención se usa una sal aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un éster aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto usado se selecciona del grupo que consiste en los compuestos: 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto usado se selecciona del grupo que consiste en: los solvatos de los compuestos 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–),

80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 12.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 12.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 13.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 13.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22B–RAC.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22B–RAC.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22C.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22C.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22D.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22D.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22E.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22E.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22F.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22F.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22G.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22G.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22H.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22H.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22I.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22I.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22J.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22J.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22K.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22K.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22L.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22L.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22M.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22M.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 22N.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 22N.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 26A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 26A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 26B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 26B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 27.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 27.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 28.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 28.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 31.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 31.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 33(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 33(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 36.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 36.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 37.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 37.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 39.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 39.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 44A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 44A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 44B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 44B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 55.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 55.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 56.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 56.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 57.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 57.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 60.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 60.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 70A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 70A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 71A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 71A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 75A–rac.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 75A–rac.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 75B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 75B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 76A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 76A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 76A(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 76A(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 76B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 76B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 78A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 78A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 79A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 79A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 80A(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 80A(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 81A–rac.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 81A–rac.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 81A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 81A(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 81A(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 81A(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 81B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 81B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 82A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 82A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 83A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 83A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 84A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 84A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 85A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 85A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 85B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 85B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 86A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 86A.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 87B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 87B.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 95B–rac.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 95B–rac.

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 95B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 95B(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 95B(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 95B(+).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 106(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 106(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 107(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 107(–).

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Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 108(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 108(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde el compuesto de fórmula (I) es el compuesto 111(–).

Otra realización de esta invención se refiere a cualquiera de los métodos de tratamiento descriptos en la Síntesis de la invención en donde se usa un solvato de un compuesto de fórmula (I), y el solvato es un solvato del compuesto 111(–).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un compuesto de cualquiera de las fórmulas (Ii) a (Ivii). .

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa una sal aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un solvato de cualquiera de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un éster aceptable para uso farmacéutico de los compuestos de las fórmulas (Ii) a (Ivii).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un compuesto de cualquiera de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa una sal aceptable para

uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un solvato de cualquiera de los compuestos de las fórmulas (I.A1a) a (I.A1h).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un éster aceptable para uso farmacéutico de los compuestos de las fórmulas (I.A1a).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un compuesto de cualquiera de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa una sal aceptable para uso farmacéutico de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un solvato de cualquiera de los compuestos de las fórmulas (I.A2a) a (I.A2h).

Otra realización de esta invención se refiere a cualquiera de las composiciones farmacéuticas descriptas anteriormente en donde se usa un éster aceptable para uso farmacéutico de los compuestos de las fórmulas (I.A2a) a (I.A2h)d.

Otra realización de esta invención se refiere a un compuesto 12.

Otra realización de esta invención se refiere a un compuesto 12 en forma pura.

Otra realización de esta invención se refiere a un compuesto 12 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 12.

Otra realización de esta invención se refiere a un compuesto 13.

Otra realización de esta invención se refiere a un compuesto 13 en forma pura.

Otra realización de esta invención se refiere a un solvato del compuesto 22D.

Otra realización de esta invención se refiere a un compuesto 22E.

Otra realización de esta invención se refiere a un compuesto 22E en forma pura.

Otra realización de esta invención se refiere a un compuesto 22E en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22E.

Otra realización de esta invención se refiere a un compuesto 22F.

Otra realización de esta invención se refiere a un compuesto 22F en forma pura.

Otra realización de esta invención se refiere a un compuesto 22F en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22F.

Otra realización de esta invención se refiere a un compuesto 22G.

Otra realización de esta invención se refiere a un compuesto 22G en forma pura.

Otra realización de esta invención se refiere a un compuesto 22G en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22G.

Otra realización de esta invención se refiere a un compuesto 22H.

Otra realización de esta invención se refiere a un compuesto 22H en forma pura.

Otra realización de esta invención se refiere a un compuesto 22H en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22H.

Otra realización de esta invención se refiere a un compuesto 22I.

Otra realización de esta invención se refiere a un compuesto 22I en forma pura.

Otra realización de esta invención se refiere a un compuesto 22I en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22I.

Otra realización de esta invención se refiere a un compuesto 22J.

Otra realización de esta invención se refiere a un compuesto 22J en forma pura.

Otra realización de esta invención se refiere a un compuesto 13 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 13.

Otra realización de esta invención se refiere a un compuesto 22A.

Otra realización de esta invención se refiere a un compuesto 22A en forma pura.

Otra realización de esta invención se refiere a un compuesto 22A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22A.

Otra realización de esta invención se refiere a un compuesto 22B.

Otra realización de esta invención se refiere a un compuesto 22B en forma pura.

Otra realización de esta invención se refiere a un compuesto 22B en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22B.

Otra realización de esta invención se refiere a un compuesto 22B–RAC.

Otra realización de esta invención se refiere a un compuesto 22B–RAC en forma pura.

Otra realización de esta invención se refiere a un compuesto 22B–RAC en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22B–RAC.

Otra realización de esta invención se refiere a un compuesto 22C.

Otra realización de esta invención se refiere a un compuesto 22C en forma pura.

Otra realización de esta invención se refiere a un compuesto 22C en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22C.

Otra realización de esta invención se refiere a un compuesto 22D.

Otra realización de esta invención se refiere a un compuesto 22D en forma pura.

Otra realización de esta invención se refiere a un compuesto 22D en forma y aislada.

Otra realización de esta invención se refiere a un compuesto 22J en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22J.

Otra realización de esta invención se refiere a un compuesto 22K.

Otra realización de esta invención se refiere a un compuesto 22K en forma pura.

Otra realización de esta invención se refiere a un compuesto 22K en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22K.

Otra realización de esta invención se refiere a un compuesto 22L.

Otra realización de esta invención se refiere a un compuesto 22L en forma pura.

Otra realización de esta invención se refiere a un compuesto 22L en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22L.

Otra realización de esta invención se refiere a un compuesto 22M.

Otra realización de esta invención se refiere a un compuesto 22M en forma pura.

Otra realización de esta invención se refiere a un compuesto 22M en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22M.

Otra realización de esta invención se refiere a un compuesto 22N.

Otra realización de esta invención se refiere a un compuesto 22N en forma pura.

Otra realización de esta invención se refiere a un compuesto 22N en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 22N.

Otra realización de esta invención se refiere a un compuesto 26A.

Otra realización de esta invención se refiere a un compuesto 26A en forma pura.

Otra realización de esta invención se refiere a un compuesto 26A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 26A.

Otra realización de esta invención se refiere a un compuesto 26B.

Otra realización de esta invención se refiere a un compuesto 26B en forma pura.

Otra realización de esta invención se refiere a un compuesto 26B en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 26B.

Otra realización de esta invención se refiere a un compuesto 27.

Otra realización de esta invención se refiere a un compuesto 27en forma pura.

Otra realización de esta invención se refiere a un compuesto 27en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 27.

Otra realización de esta invención se refiere a un compuesto 28.

Otra realización de esta invención se refiere a un compuesto 28 en forma pura.

Otra realización de esta invención se refiere a un compuesto 28 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 28.

Otra realización de esta invención se refiere a un compuesto 31.

Otra realización de esta invención se refiere a un compuesto 31 en forma pura.

Otra realización de esta invención se refiere a un compuesto 31 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 31.

Otra realización de esta invención se refiere a un compuesto 33(–).

Otra realización de esta invención se refiere a un compuesto 33(–) en forma pura.

Otra realización de esta invención se refiere a un compuesto 33(–) en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 33(–).

Otra realización de esta invención se refiere a un compuesto 36.

Otra realización de esta invención se refiere a un compuesto 36 en forma pura.

Otra realización de esta invención se refiere a un compuesto 36 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 36.

Otra realización de esta invención se refiere a un compuesto 37.

Otra realización de esta invención se refiere a un compuesto 37 en forma pura.

Otra realización de esta invención se refiere a un compuesto 37 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 37.

Otra realización de esta invención se refiere a un compuesto 39.

Otra realización de esta invención se refiere a un compuesto 39 en forma pura.

Otra realización de esta invención se refiere a un compuesto 39 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 39.

Otra realización de esta invención se refiere a un compuesto 44A.

Otra realización de esta invención se refiere a un compuesto 44A en forma pura.

Otra realización de esta invención se refiere a un compuesto 44A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 44A.

Otra realización de esta invención se refiere a un compuesto 44B.

Otra realización de esta invención se refiere a un compuesto 44B en forma pura.

Otra realización de esta invención se refiere a un compuesto 44B en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 44B.

Otra realización de esta invención se refiere a un compuesto 55.

Otra realización de esta invención se refiere a un compuesto 55 en forma pura.

Otra realización de esta invención se refiere a un compuesto 55 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 55.

Otra realización de esta invención se refiere a un compuesto 56.

Otra realización de esta invención se refiere a un compuesto 56 en forma pura.

Otra realización de esta invención se refiere a un compuesto 56 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 56.

Otra realización de esta invención se refiere a un compuesto 57.

Otra realización de esta invención se refiere a un compuesto 57 en forma pura.

Otra realización de esta invención se refiere a un compuesto 57 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 57.

Otra realización de esta invención se refiere a un compuesto 60.

Otra realización de esta invención se refiere a un compuesto 60 en forma pura.

Otra realización de esta invención se refiere a un compuesto 60 en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 60.

Otra realización de esta invención se refiere a un compuesto 70A.

Otra realización de esta invención se refiere a un compuesto 70A en forma pura.

Otra realización de esta invención se refiere a un compuesto 70A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 70A.

Otra realización de esta invención se refiere a un compuesto 71A(–).

Otra realización de esta invención se refiere a un compuesto 71A(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 71A(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 71A(–).

Otra realización de esta invención se refiere a un compuesto 75A–rac.

Otra realización de esta invención se refiere a un compuesto 75A–rac en forma pura.

Otra realización de esta invención se refiere a un compuesto 75A–rac en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 75A–rac.

Otra realización de esta invención se refiere a un compuesto 75B(–).

Otra realización de esta invención se refiere a un compuesto 75B(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 75B(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 75B(–).

Otra realización de esta invención se refiere a un compuesto 76A(–).

Otra realización de esta invención se refiere a un compuesto 76A(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 76A(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 76A(–).

Otra realización de esta invención se refiere a un compuesto 76A(+).

Otra realización de esta invención se refiere a un compuesto 76A(+)en forma pura.

Otra realización de esta invención se refiere a un compuesto 76A(+)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 76A(+).

Otra realización de esta invención se refiere a un compuesto 76B(–).

Otra realización de esta invención se refiere a un compuesto 76B(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 76B(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 76B(–).

Otra realización de esta invención se refiere a un compuesto 78A(–).

Otra realización de esta invención se refiere a un compuesto 78A(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 78A(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 78A(–).

Otra realización de esta invención se refiere a un compuesto 79A(–).

Otra realización de esta invención se refiere a un compuesto 79A(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 79A(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 79A(–).

Otra realización de esta invención se refiere a un compuesto 80A(+).

Otra realización de esta invención se refiere a un compuesto 80A(+)en forma pura.

Otra realización de esta invención se refiere a un compuesto 80A(+)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 80A(+).

Otra realización de esta invención se refiere a un compuesto 81A–rac.

Otra realización de esta invención se refiere a un compuesto 81A–rac en forma pura.

Otra realización de esta invención se refiere a un compuesto 81A–rac en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 81A–rac.

Otra realización de esta invención se refiere a un compuesto 81A(–).

Otra realización de esta invención se refiere a un compuesto 81A(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 81A(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 81A(–).

Otra realización de esta invención se refiere a un compuesto 81A(+).

Otra realización de esta invención se refiere a un compuesto 81A(+)en forma pura.

Otra realización de esta invención se refiere a un compuesto 81A(+)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 81A(+).

Otra realización de esta invención se refiere a un compuesto 81B(–).

Otra realización de esta invención se refiere a un compuesto 81B(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 81B(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 81B(–).

Otra realización de esta invención se refiere a un compuesto 82A.

Otra realización de esta invención se refiere a un compuesto 82A en forma pura.

Otra realización de esta invención se refiere a un compuesto 82A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 82A.

Otra realización de esta invención se refiere a un compuesto 83A.

Otra realización de esta invención se refiere a un compuesto 83A en forma pura.

Otra realización de esta invención se refiere a un compuesto 83A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 83A.

Otra realización de esta invención se refiere a un compuesto 84A.

Otra realización de esta invención se refiere a un compuesto 84A en forma pura.

Otra realización de esta invención se refiere a un compuesto 84A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 84A.

Otra realización de esta invención se refiere a un compuesto 85A.

Otra realización de esta invención se refiere a un compuesto 85A en forma pura.

Otra realización de esta invención se refiere a un compuesto 85A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 85A.

Otra realización de esta invención se refiere a un compuesto 85B(–).

Otra realización de esta invención se refiere a un compuesto 85B(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 85B(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 85B(–).

Otra realización de esta invención se refiere a un compuesto 86A.

Otra realización de esta invención se refiere a un compuesto 86A en forma pura.

Otra realización de esta invención se refiere a un compuesto 86A en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 86A.

Otra realización de esta invención se refiere a un compuesto 87B.

Otra realización de esta invención se refiere a un compuesto 87B en forma pura.

Otra realización de esta invención se refiere a un compuesto 87B en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 87B.

Otra realización de esta invención se refiere a un compuesto 95B–rac.

Otra realización de esta invención se refiere a un compuesto 95B–rac en forma pura.

Otra realización de esta invención se refiere a un compuesto 95B–rac en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 95B–rac.

Otra realización de esta invención se refiere a un compuesto 95B(–).

Otra realización de esta invención se refiere a un compuesto 95B(–)en forma pura.

Otra realización de esta invención se refiere a un compuesto 95B(–)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 95B(–).

Otra realización de esta invención se refiere a un compuesto 95B(+).

Otra realización de esta invención se refiere a un compuesto 95B(+)en forma pura.

Otra realización de esta invención se refiere a un compuesto 95B(+)en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 95B(+).

Otra realización de esta invención se refiere a un compuesto 106(–).

Otra realización de esta invención se refiere a un compuesto 106(–) en forma pura.

Otra realización de esta invención se refiere a un compuesto 106(–) en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 106(–).

Otra realización de esta invención se refiere a un compuesto 107(–).

Otra realización de esta invención se refiere a un compuesto 107(–) en forma pura.

Otra realización de esta invención se refiere a un compuesto 107(–) en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 107(–).

Otra realización de esta invención se refiere a un compuesto 108(–).

Otra realización de esta invención se refiere a un compuesto 108(–) en forma pura.

Otra realización de esta invención se refiere a un compuesto 108(–) en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 108(–).

Otra realización de esta invención se refiere a un compuesto 111(–).

Otra realización de esta invención se refiere a un compuesto 111(–) en forma pura.

Otra realización de esta invención se refiere a un compuesto 111(–) en forma y aislada.

Otra realización de esta invención se refiere a un solvato del compuesto 111(–).

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más compuestos seleccionados del grupo que consiste en: 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un compuesto seleccionado del grupo que consiste en: 12, 13, 22A a 22N, 22B–rac, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 12, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 13, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22B–RAC, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22C, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22D, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22E, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22F, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22G, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22H, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22I, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22J, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22K, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22L, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22M, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 22N, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 26A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 26B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 27, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 28, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 31, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 33(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 36, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 37, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 39, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 44A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 44B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 55, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 56, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 57, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 60, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 70A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 7IA(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 75A–rac, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 75B (–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 76A (–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 76A(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 76B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 78A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 79A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 80A(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 81A–rac, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 81A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 81A(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 81B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 82A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 83A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 84A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 85A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 85B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 86A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 87B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 95B–rac, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 95B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 95B(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 106(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 107(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 108(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva del compuesto 111(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más solvatos seleccionados del grupo que consiste en: los solvatos de los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un sovato seleccionado del grupo que consiste en: los solvatos de los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–) y 111(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 12, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 13, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22B–RAC, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22C, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22D, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22E, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22F, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22G, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22H, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22I, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22J, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22K, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22L, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22M, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 22N, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 26A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 26B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 27, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 28, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 31, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 33(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 36, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 37, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 39, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 44A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 44B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 55, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 56, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 57, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 60, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 70A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 71A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 75A–rac, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 75B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 76A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 76A(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 76B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 78A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 79A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 80A(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 81A–rac, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 81A(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 81A(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 81B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 82A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 83A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 84A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 85A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 85B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 86A, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 87B, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 95B–rac, y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 95B(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 95B(+), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 106(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 107(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 108(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de un solvato del compuesto 111(–), y al menos un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)), y una cantidad efectiva de uno o más (por ej., uno) componentes activos para uso farmacéutico diferentes (por ej.,) drogas, y un vehículo aceptable para uso farmacéutico. Los ejemplos de los componentes activos para uso farmacéutico diferentes incluyen, pero sin limitación drogas seleccionadas del grupo que consiste en: (a) drogas útiles para el tratamiento de enfermedad de Alzheimer, (b) drogas útiles para inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro), (c) drogas útiles para tratar enfermedades neurodegenerativas, y (d) drogas útiles para inhibir la gamma-secretasa.

Otra realización de esta invención también proporciona una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60,

70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más (por ej., uno) componentes activos farmacéuticos terapéuticamente efectivos diferentes (por ej., drogas), y un vehículo aceptable para uso farmacéutico. Los ejemplos de las otras drogas incluyen, pero sin limitación drogas seleccionadas del grupo que consiste en: (a) drogas útiles para el tratamiento de enfermedad de Alzheimer, (b) drogas útiles para inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro), (c) drogas útiles para tratar enfermedades neurodegenerativas, y (d) drogas útiles para inhibir la gamma-secretasa.

Los componentes activos para uso farmacéutico diferentes (por ej., drogas), usados en las composiciones farmacéuticas con los compuestos de fórmula (I), además de los que se usan en los métodos de tratamiento con los compuestos de fórmula (I) (es decir, las terapias de combinación descriptas en la presente memoria) incluyen, pero sin limitación: inhibidores de BACE (inhibidores de beta secretasa), antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), inhibidores de colinesterasa (por ej., inhibidores de acetil y/o butirilcolinesterasa); inhibidores de gamma secretasa; moduladores de gamma secretasa, inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de alfa

secretasa, inhibidores de PDE–10, e inhibidores de absorción de colesterol (por ej., ezetimibe).

En consecuencia, otra realización de esta invención se refiere a composiciones farmacéuticas que comprenden una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)), y una cantidad efectiva de uno o más (por ej., uno) componentes activos para uso farmacéutico diferentes (por ej., drogas), y un vehículo aceptable para uso farmacéutico, en donde dicho componentes activos para uso farmacéutico diferentes are seleccionado del grupo que consiste en: : inhibidores de BACE (inhibidores de beta secretasa), antagonistas muscarínicos (por ej., m_1 o m_2 antagonists), inhibidores de colinesterasa (por ej., inhibidores de acetil y/o butirilcolinesterasa); inhibidores de gamma secretasa; moduladores de gamma secretasa, inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa, inhibidores de PDE–10 e inhibidores de absorción de colesterol (por ej., ezetimibe).

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)), y una cantidad efectiva de uno o más inhibidores de BACE, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más inhibidores de BACE, y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más inhibidores de colinesterasa (por ej., inhibidores de acetil y/o butirilcolinesterasa), y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmulas (I.A1), o compuestos de fórmula (I.A2)), y una cantidad efectiva de uno o más antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a una composición farmacéutica que comprende una cantidad efectiva de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60,

70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–), y una cantidad efectiva de uno o más antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), y un vehículo aceptable para uso farmacéutico.

Otra realización de esta invención se refiere a un método para inhibir la gamma-secretasa que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Otra realización de esta invención se refiere a un método para tratar una o más enfermedades neurodegenerativas que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+),106(–), 107(–), 108(–), y 111(–).

Otra realización de esta invención se refiere a un método de inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro) que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A,

26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Otra realización de esta invención se refiere a un método de tratar enfermedad de Alzheimer que comprende administrar a un paciente que necesita tratamiento una cantidad efectiva (es decir, terapéuticamente efectiva) de uno o más (por ej., uno) compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

Otras realizaciones de esta invención se refieren a terapias de combinación para (1) inhibir la gamma-secretasa, o (2) tratar una o más enfermedades neurodegenerativas, o (3)inhibir el depósito de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor del tejido neurológico (por ej., el cerebro), o (4) tratar la enfermedad de Alzheimer. Las terapias de combinación se refieren a métodos que comprenden la administración de uno o más (por ej., uno) compuestos de fórmula (I) (por ej., compuestos de fórmula (I.A1), o compuestos de fórmula (I.A2)) y la administración de uno o más (por ej., uno) componentes activos farmacéuticos diferentes (por ej., drogas). Los compuestos de fórmula (I) y las otras drogas se pueden administrar en forma separada (es decir, cada una en su propia forma de dosis separada), o los compuestos de fórmula (I) se pueden combinar con las otras drogas en la misma forma de dosis.

En consecuencia, otras realizaciones de esta invención se refieren a cualquiera de los métodos de tratamiento, o métodos de inhibición, descriptos en la presente memoria, en donde el compuesto de fórmula (I) (por ej., el compuesto

de fórmula (I.A1), o el compuesto de fórmula (I.A2)) se usa en combinación con una cantidad efectiva de uno o más componentes activos para uso farmacéutico diferentes seleccionado del grupo que consiste en: inhibidores de BACE (inhibidores de beta secretasa), antagonistas muscarínicos (por ej., antagonistas de m_1 o m_2), inhibidores de colinesterasa (por ej., inhibidores de acetil y/o butirilcolinesterasa); inhibidores de gamma secretasa; moduladores de gamma secretasa; inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa; inhibidores de PDE–10 e inhibidores de absorción de colesterol (por ej., ezetimibe).

Los ejemplos de inhibidores de colinesterasa son tacrina, donepezilo, rivastigmina, galantamina, piridostigmina y neostigmina, los preferidos son tacrina, donepezilo, rivastigmina y galantamina.

Los ejemplos de antagonistas de m_1 son conocidos en el arte. Los ejemplos de antagonists de m_2 también son conocidos en el arte; en particular, los antagonistas de m_2 se describen en las patentes estadounidenses 5.883.096; 6.037.352; 5.889.006; 6.043.255; 5.952.349; 5.935.958; 6.066.636; 5.977.138; 6.294.554; 6.043.255; y 6.458.812; y en WO 03/031412, las cuales están incorporadas en la presente memoria como referencia.

Los ejemplos de inhibidores de BACE incluyen los descriptos en: US2005/0119227 publicado 06/02/2005 (ver también WO2005/016876 publicado 02/24/2005), US2005/0043290 publicado 02/24/2005 (ver también WO2005/014540 publicado 02/17/2005), WO2005/058311 publicado 06/30/2005

(ver también US2007/0072852 publicado 03/29/2007), US2006/0111370 publicado 05/25/2006 (ver también WO2006/065277 publicado 06/22/2006), Solicitud Estadounidense Serie No. 11/710582 presentada 02/23/2007, US2006/0040994 publicado 02/23/2006 (ver también WO2006/014762 publicado 02/09/2006), WO2006/014944 publicado 02/09/2006 (ver también US2006/0040948 publicado 02/23/2006), WO2006/138266 publicado 12/28/2006 (ver también US2007/0010667 publicado 01/11/2007), WO2006/138265 publicado 12/28/2006, WO2006/138230 publicado 12/28/2006, WO2006/138195 publicado 12/28/2006 (ver también US2006/0281729 publicado 12/14/2006), WO2006/138264 publicado 12/28/2006 (ver también US2007/0060575 publicado 03/15/2007), WO2006/138192 publicado 12/28/2006 (ver también US2006/0281730 publicado 12/14/2006), WO2006/138217 publicado 12/28/2006 (ver también US2006/0287294 publicado 12/21/2006), US2007/0099898 publicado 05/03/200 (ver también WO2007/050721 publicado 05/03/2007), WO2007/053506 publicado 05/10/2007 (ver también US2007/099875 publicado 05/03/2007), Solicitud Estadounidense Serie No. 11/759336 presentada 06/07/2007, Solicitud Estadounidense Serie No. 60/874362 presentada 12/12/2006, y Solicitud Estadounidense Serie No. 60/874419 presentada 12/12/2006, cuyas descripciones están incorporadas en la presente memoria como referencia.

Otras realizaciones de esta invención se describen a continuación. Estas realizaciones se han numerado para facilitar la referencia. Cuando una Realización se refiere a "cualquiera de" esta realización describe una realización separada para cada grupo o realización enumerada. Por ejemplo, Realización No. 1 significa que describe: (1) una realización referida a compuestos de fórmula (I) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido), (2) una realización referida a cualquiera de los compuestos (il) a (lvii) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido), (3) una realización referida a compuestos

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de fórmula (I.A1) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido), (4) una realización referida a cualquiera de los compuestos (I.A1a) a (I.A1h) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido), (5) una realización referida a compuestos de fórmula (I.A2) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido), y (6) una realización referida a cualquiera de los compuestos (I.A2a) a (I.A2h) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido).

La realización No. 1 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde Ar es arilo no sustituido (por ej., fenilo no sustituido).

La realización No. 2 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde Ar es arilo sustituido (por ej., fenilo sustituido). Los ejemplos de fenilos sustituidos incluyen, por ejemplo, (1) fenilo sustituido con halo (tal como, por ejemplo fenilo sustituido con cloro, tal como, por ejemplo, p–Cl–fenilo–), (2) fenilo sustituido con haloalquilo (tal como, por ejemplo, fenilo sustituido con $–CF_3$, tales como, por ejemplo, p–CF_3–fenilo–), y (3) fenilo sustituido con ciano (tal como, por ejemplo, p–CN–fenilo–).

La realización No. 3 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde Ar es heteroarilo no sustituido (por ej., piridilo no sustituido).

La realización No. 4 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde Ar es heteroarilo sustituido (por ej., piridilo sustituido). Los ejemplos de piridilos sustituidos incluyen, por ejemplo, (1) piridilo sustituido con halo (tal como, por ejemplo piridilo sustituido con cloro), (2) piridilo sustituido con haloalquilo (tal como, por ejemplo, piridilo sustituido con $–CF_3$), y (3) piridilo sustituido con ciano.

La realización No. 5 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde cada L^1 es el mismo o diferente halo.

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La realización No. 6 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde n es 2 y cada L^1 es el mismo o diferente halo.

La realización No. 7 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde n es 2 y cada L^1 es el mismo halo.

La realización No. 8 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h) en donde n es 2 y cada L^1 es F.

La realización No. 9 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde cada L^1 es el mismo o diferente halo, y Ar es arilo no sustituido (por ej., fenilo no sustituido).

La realización No. 10 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo o diferente halo, y Ar es arilo no sustituido (por ej., fenilo no sustituido).

La realización No. 11 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo halo, y Ar es arilo no sustituido (por ej., fenilo no sustituido).

La realización No. 12 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es F, y Ar es arilo no sustituido (por ej., fenilo no sustituido).

La realización No. 13 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde cada L^1 es el mismo o diferente halo, y Ar es arilo sustituido (por ej., fenilo sustituido). Los ejemplos de fenilos sustituidos incluyen, por ejemplo, (1) fenilo sustituido con halo (tal como, por ejemplo fenilo sustituido con cloro, tales como, por ejemplo, p–Cl–fenilo–), (2) fenilo sustituido con haloalquilo (tal como, por ejemplo, fenilo

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sustituido con $-CF_3$, tales como, por ejemplo, p–CF_3–fenilo–), y (3) fenilo sustituido con ciano (tal como, por ejemplo, p–CN–fenilo–).

La realización No. 14 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo o diferente halo, y Ar es arilo sustituido (por ej., fenilo sustituido). Los ejemplos de fenilos sustituidos incluyen, por ejemplo, (1) fenilo sustituido con halo (tal como, por ejemplo fenilo sustituido con cloro, tal como, por ejemplo, p–Cl–fenilo–), (2) fenilo sustituido con haloalquilo (tal como, por ejemplo, fenilo sustituido con $-CF_3$, tal como, por ejemplo, p–CF_3–fenilo–), y (3) fenilo sustituido con ciano (tal como, por ejemplo, p–CN–fenilo–).

La realización No. 15 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo halo, y Ar es arilo sustituido (por ej., fenilo sustituido). Los ejemplos de fenilos sustituidos incluyen, por ejemplo, (1) fenilo sustituido con halo (tal como, por ejemplo fenilo sustituido con cloro, tal como, por ejemplo, p–Cl–fenilo–), (2) fenilo sustituido con haloalquilo (tal como, por ejemplo, fenilo sustituido con $-CF_3$, tal como, por ejemplo, p–CF_3–fenilo–), y (3) fenilo sustituido con ciano (tales como, por ejemplo, p–CN–fenilo–).

La realización No. 16 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es F, y Ar es arilo sustituido (por ej., fenilo sustituido). Los ejemplos de fenilos sustituidos incluyen, por ejemplo, (1) fenilo sustituido con halo (tal como, por ejemplo fenilo sustituido con cloro, tal como, por ejemplo, p–Cl–fenilo–), (2) fenilo sustituido con haloalquilo (tal como, por ejemplo, fenilo sustituido con $-CF_3$, tal como, por ejemplo, p–CF_3–fenilo–), y (3) fenilo sustituido con ciano (tal como, por ejemplo, p–CN–fenilo–).

La realización No. 17 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde cada L^1

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es el mismo o diferente halo, y Ar es heteroarilo no sustituido (por ej., piridilo no sustituido).

La realización No. 18 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo o diferente halo, y Ar es heteroarilo no sustituido (por ej., piridilo no sustituido).

La realización No. 19 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo halo, y Ar es heteroarilo no sustituido (por ej., piridilo no sustituido).

La realización No. 20 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es F, y Ar es heteroarilo no sustituido (por ej., piridilo no sustituido).

La realización No. 21 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde cada L^1 es el mismo o diferente halo, y Ar es heteroarilo sustituido (por ej., piridilo sustituido). Los ejemplos de piridilos sustituidos incluyen, por ejemplo, (1) piridilo sustituido con halo (tal como, por ejemplo piridilo sustituido con cloro), (2) piridilo sustituido con haloalquilo (tal como, por ejemplo, piridilo sustituido con $-CF_3$), y (3) piridilo sustituido con ciano.

La realización No. 22 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo o diferente halo, y Ar es heteroarilo sustituido (por ej., piridilo sustituido). Los ejemplos de piridilos sustituidos incluyen, por ejemplo, (1) piridilo sustituido con halo (tales como, por ejemplo piridilo sustituido con cloro), (2) piridilo sustituido con haloalquilo (tales como, por ejemplo, piridilo sustituido con $-CF_3$), y (3) piridilo sustituido con ciano.

La realización No. 23 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2,

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cada L^1 es el mismo halo, y Ar es heteroarilo sustituido (por ej., piridilo sustituido). Los ejemplos de piridilos sustituidos incluyen, por ejemplo, (1) piridilo sustituido con halo (tales como, por ejemplo piridilo sustituido con cloro), (2) piridilo sustituido con haloalquilo (tales como, por ejemplo, piridilo sustituido con $-CF_3$), y (3) piridilo sustituido con ciano.

La realización No. 24 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es F, y Ar es heteroarilo sustituido (por ej., piridilo sustituido). Los ejemplos de piridilos sustituidos incluyen, por ejemplo, (1) piridilo sustituido con halo (tales como, por ejemplo piridilo sustituido con cloro), (2) piridilo sustituido con haloalquilo (tales como, por ejemplo, piridilo sustituido con $-CF_3$), y (3) piridilo sustituido con ciano.

La realización No. 25 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es el mismo halo, y Ar es arilo sustituido seleccionado del grupo que consiste en p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo,

p–CH_3O–fenilo, y p–CF_3CH_2Ofenilo.

La realización No. 26 se refiere a cualquiera de los compuestos de las fórmulas (I), (iI) a (Ivii), (I.A1), (I.A1a) a (I.A1h), (I.A2), y (I.A2a) a (I.A2h), en donde n es 2, cada L^1 es F, y Ar es arilo sustituido seleccionado del grupo que consiste en p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, y p–CF_3CH_2Ofenilo.

La realización No. 27 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^2 es H.

La realización No. 28 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^2 es alquilo.

La realización No. 29 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^2 es metilo.

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La realización No. 30 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es –alquilen–(1,1–dióxido de tetrahidrotiofeno).

La realización No. 31 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es –alquenil–$S(O)_2$–alquilo(C_1–C_6).

La realización No. 32 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es –cicloalquil–$S(O)_2$–alquilo(C_1–C_6).

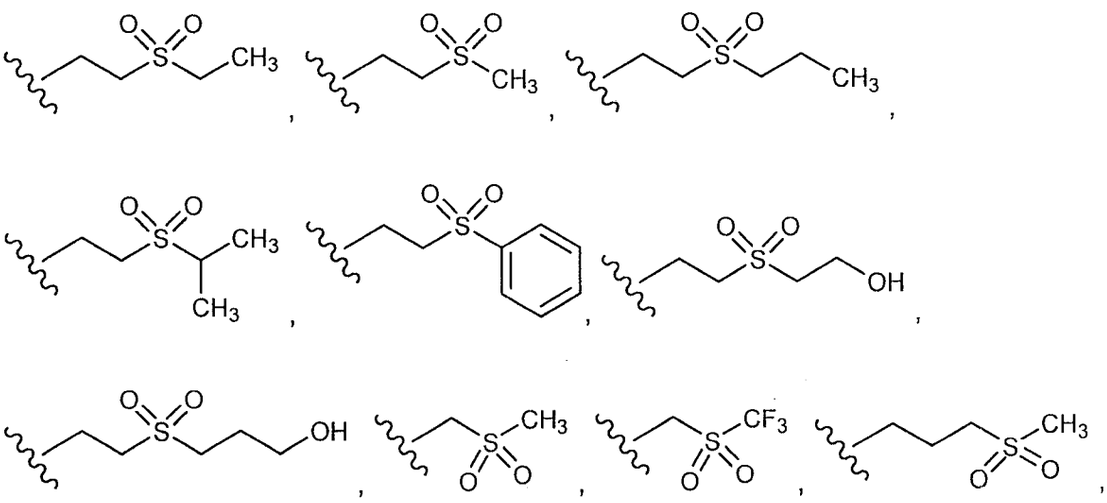
La realización No. 33 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen–$S(O)_2$–alquilo(C_1–C_6).

La realización No. 34 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo(C_1–C_6).

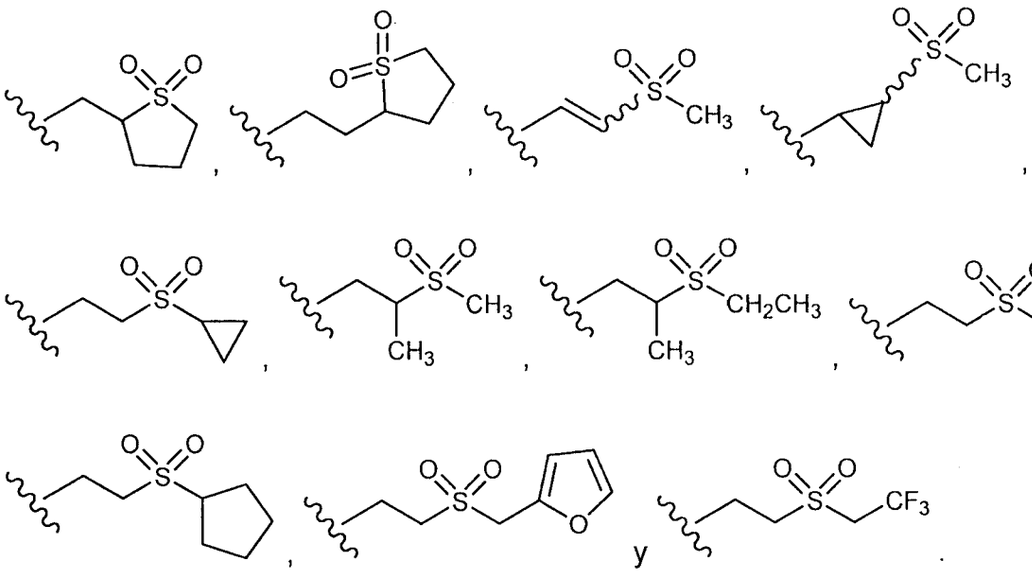
La realización No. 35 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo (C_1–C_3).

La realización No. 36 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –(C_2) alquilen–$S(O)_2$–alquilo(C_1–C_6).

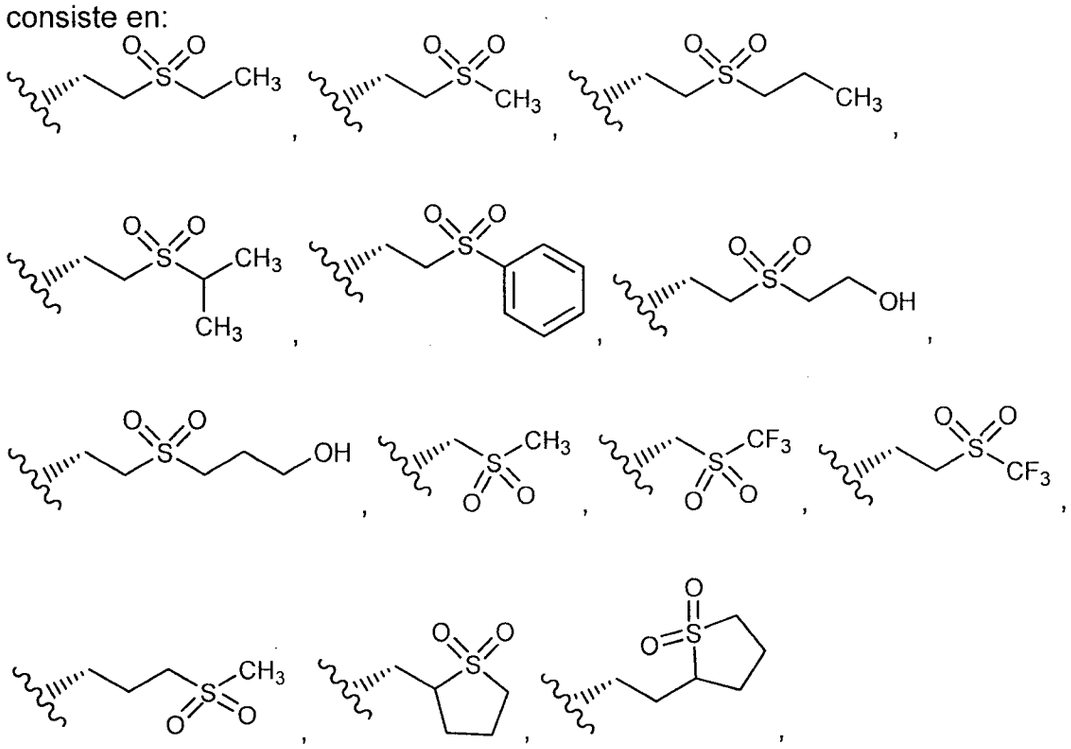
La realización No. 37 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (I), (I.A1), (I.A2), (I.A1a), (I.A1e), (I.A2a) o (I.A2e) en donde R^1 se selecciona del grupo que consiste en:



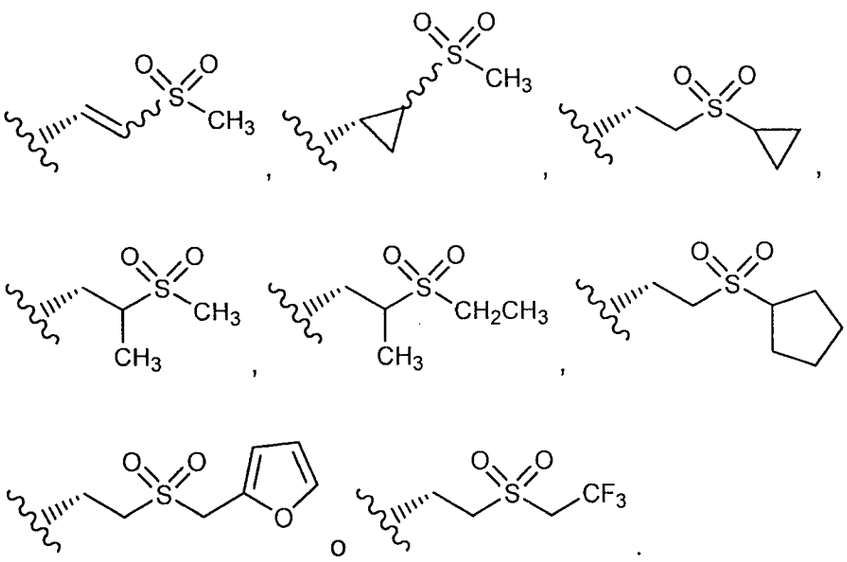
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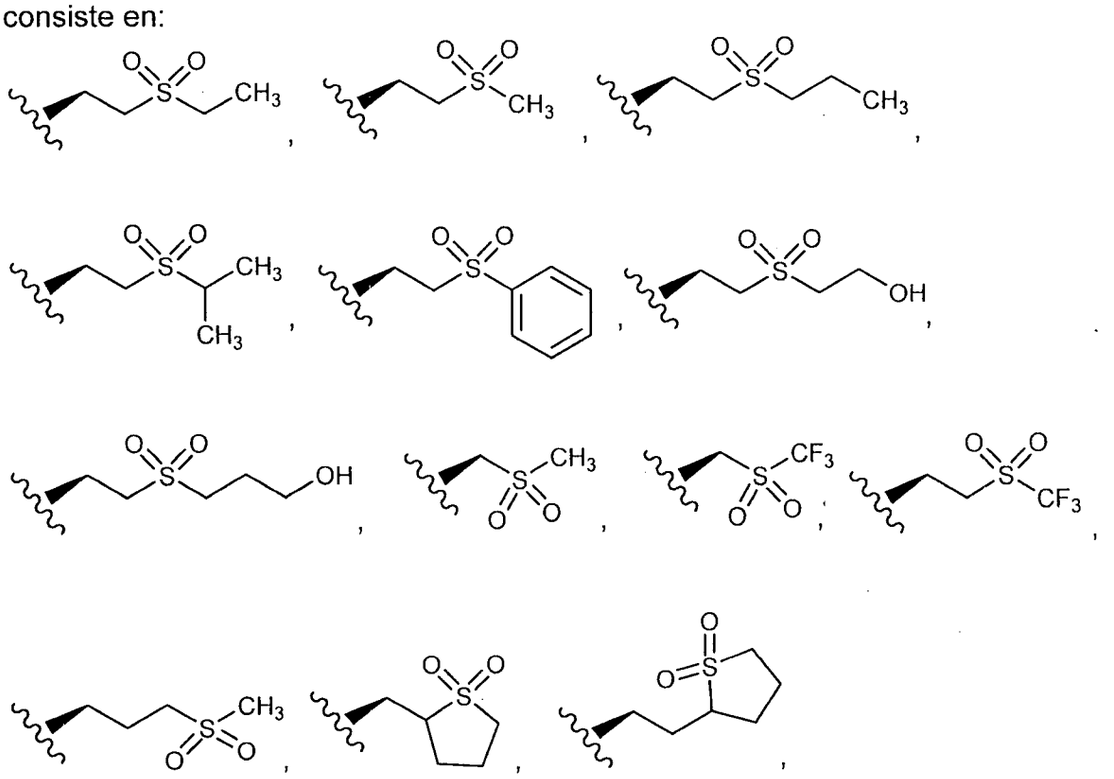
La realización No. 38 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 se selecciona del grupo que consiste en:



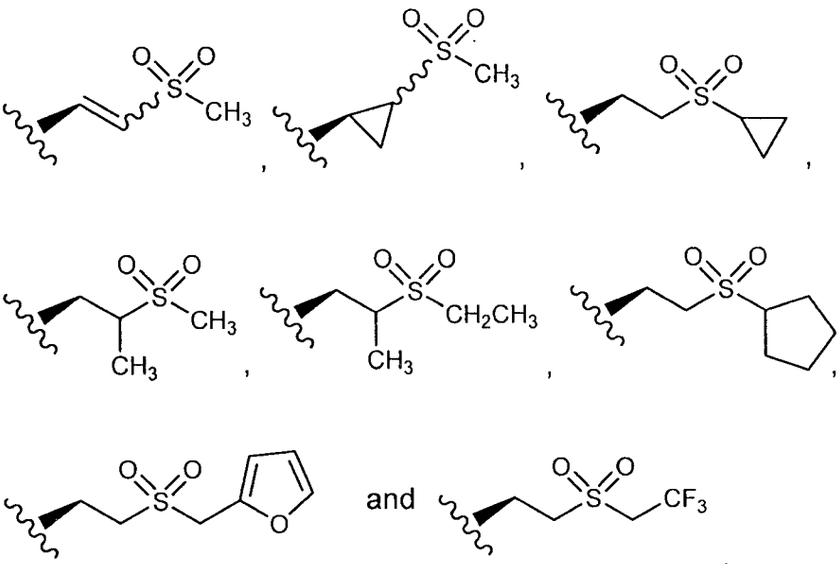
448



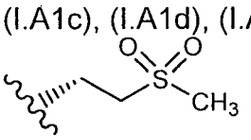
La realización No. 39 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 se selecciona del grupo que consiste en:



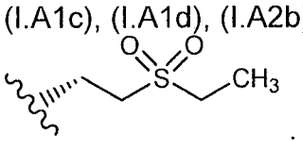
449



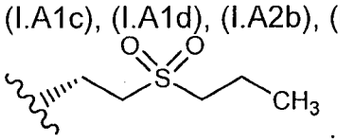
La realización No. 40 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



La realización No. 41 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

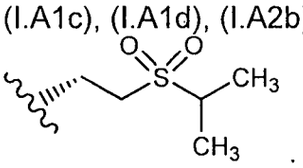


La realización No. 42 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

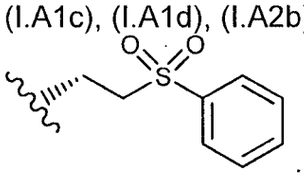


450

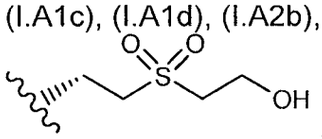
La realización No. 43 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



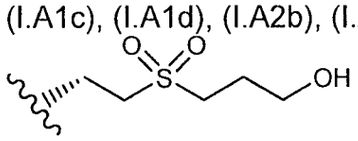
La realización No. 44 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



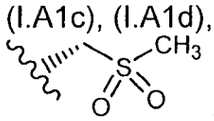
La realización No. 45 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



La realización No. 46 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

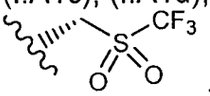


La realización No. 47 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

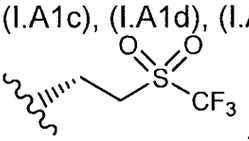


451

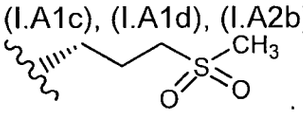
La realización No. 48 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



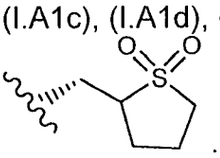
La realización No. 49 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



La realización No. 50 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

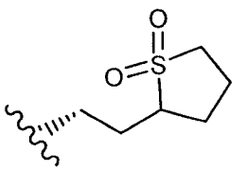


La realización No. 51 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

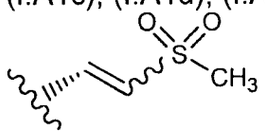


La realización No. 52 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

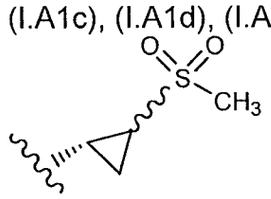
452



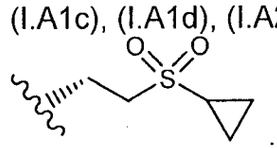
La realización No. 53 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



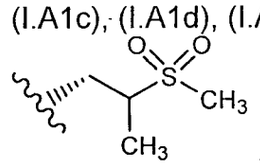
La realización No. 54 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



La realización No. 55 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

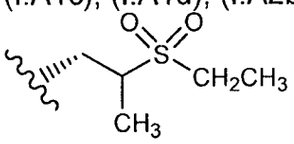


La realización No. 56 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

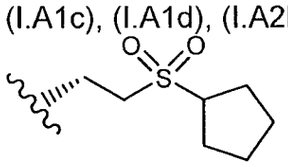


453

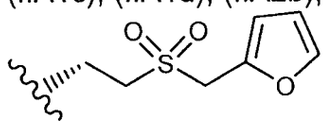
La realización No. 57 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



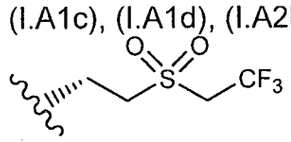
La realización No. 58 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es



La realización No. 59 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

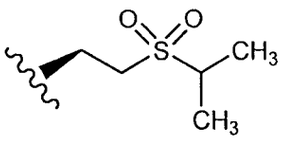


La realización No. 60 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es

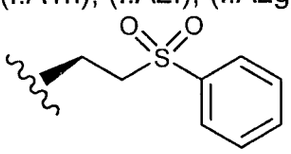


La realización No. 61 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

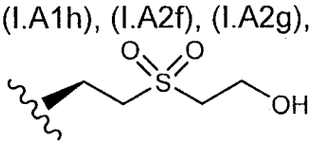
454



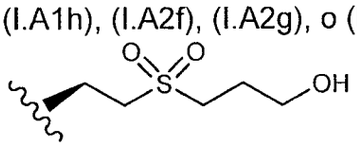
La realización No. 62 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



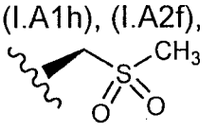
La realización No. 63 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



La realización No. 64 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

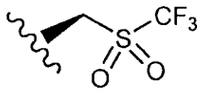


La realización No. 65 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

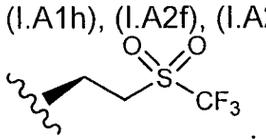


455

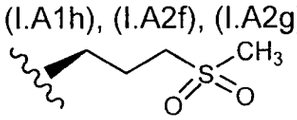
La realización No. 66 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



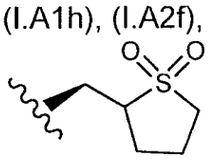
La realización No. 67 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



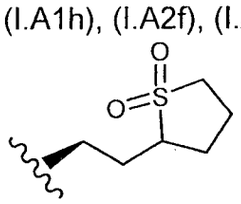
La realización No. 68 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



La realización No. 69 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

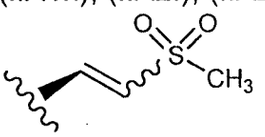


La realización No. 70 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

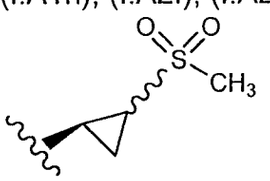


456

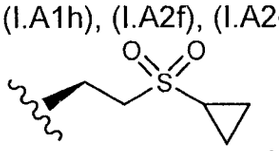
La realización No. 71 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



La realización No. 72 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



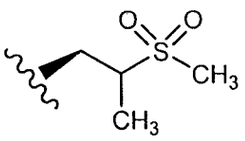
La realización No. 73 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



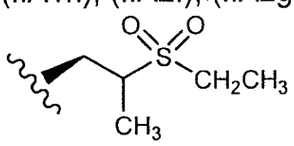
La realización No. 74 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

La realización No. 75 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es

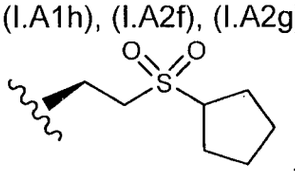
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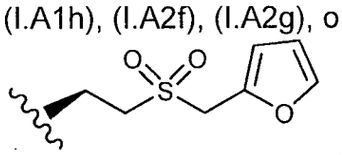
La realización No. 76 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



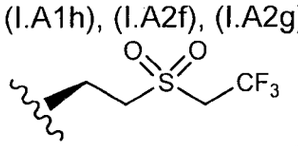
La realización No. 77 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



La realización No. 78 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



La realización No. 79 se refiere a cualquiera de las realizaciones Nos. 1 a 26, en donde el compuesto es un compuesto de la fórmula (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g), o (I.A2h) en donde R^1 es



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La realización No. 80 se refiere a cualquiera de las realizaciones Nos. 37 a 79 en donde R^2 es H.

La realización No. 81 se refiere a cualquiera de las realizaciones Nos. 37 a 79 en donde R^2 es alquilo.

La realización No. 82 se refiere a cualquiera de las realizaciones Nos. 37 a 79 en donde R^2 es metilo.

La realización No. 83 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen–$S(O)_2$–haloalquilo(C_1–C_6).

La realización No. 84 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–haloalquilo (C_1–C_3.

La realización No. 85 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–haloalquilo (C_1–C_2).

La realización No. 86 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –(C_2) alquilen–$S(O)_2$–haloalquilo (C_1–C_2).

La realización No. 87 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es a –alquilen–(1,1–dióxido de tetrahidrotiofeno) group.

La realización No. 88 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquenil–$S(O)_2$–alquilo(C_1–C_6).

La realización No. 89 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –cicloalquil–$S(O)_2$–alquilo(C_1–C_6).

La realización No. 90 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen–$S(O)_2$–haloalquilo(C_1–C_6), en donde el carbono terminal de dicho grupo haloalquilo está sustituido con 1 a 3 de los mismos o diferentes átomos de halo. Los ejemplos de dichos grupos haloalquilo incluyen los grupo en donde el carbono terminal está sustituido con 1 a 3 átomos de F, o 2 a 3 átomos de F, o 3 átomos de F (se prefiere 3 átomos de F).

La realización No. 91 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–haloalquilo (C_1–C_3), en donde el carbono terminal de dicho grupo halolaquilo está sustituido con 1 a 3 de los

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mismos o diferentes átomos de halo. Los ejemplos de dichos grupos haloalquilo incluyen grupos en donde el carbono terminal está sustituido con 1 a 3 átomos de F, o 2 a 3 átomos de F, o 3 átomos de F (se prefiere 3 átomos de F).

La realización No. 92 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–haloalquilo (C_1–C_2), en donde el carbono terminal de dicho grupo halolaquilo está sustituido con 1 a 3 de los mismos o diferentes átomos de halo. Los ejemplos de dichos grupos haloalquilo incluyen los grupos en donde el carbono terminal está sustituido con 1 a 3 átomos de F, o 2 a 3 átomos de F, o 3 átomos de F (se prefiere 3 átomos de F).

La realización No. 93 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –(C_2) alquilen–$S(O)_2$–haloalquilo (C_1–C_2), en donde el carbono terminal de dicho grupo halolaquilo está sustituido con 1 a 3 de los mismos o diferentes átomos de halo. Los ejemplos de dichos grupos haloalquilo incluyen grupos en donde el carbono terminal está sustituido con 1 a 3 átomos de F, o 2 a 3 átomos de F, o 3 átomos de F (se prefiere 3 átomos de F).

La realización No. 94 se refiere a cualquiera de las realizaciones Nos. 83 a 93 en donde el compuesto es un compuesto de fórmula (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d), y R^1 es cualquiera de los grupos R^1 descriptos en cualquiera de las realizaciones Nos. 40 a 60.

La realización No. 95 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen–$S(O)_2$–alquilo(C_1–C_6) sustituido, tal como, por ejemplo, un grupo –alquilen–$S(O)_2$–hidroxialquilo (C_1–C_6).

La realización No. 96 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo (C_1–C_3) sustituido, talecomo, por ejemplo, un grupo –alquilen (C_1 a C_2)–$S(O)_2$–hidroxialquilo (C_1–C_3).

La realización No. 97 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo (C_1–C_2) sustituido, tal como, por ejemplo, un grupo –alquilen (C_1 a C_2)–$S(O)_2$–hidroxialquilo (C_1–C_2).

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La realización No. 98 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –(C_2) alquilen–$S(O)_2$–alquilo (C_1–C_2) sustituido, tal como, por ejemplo, un grupo –(C_2) alquilen–$S(O)_2$–hidroxialquilo (C_1–C_2) sustituido.

La realización No. 99 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen–$S(O)_2$–alquilo (C_1–C_6) sustituido, tal como, por ejemplo, un grupo –alquilen–$S(O)_2$–hidroxialquilo (C_1–C_6), en donde el carbono terminal de dicho grupo alquilo sustituido está sustituido.

La realización No. 100 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo (C_1–C_3) sustituido, tal como, por ejemplo, un grupo –alquilen (C_1 a C_2)–$S(O)_2$–hidroxialquilo (C_1–C_3), en donde el carbono terminal de dicho grupo alquilo está sustituido.

La realización No. 101 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –alquilen (C_1 a C_2)–$S(O)_2$–alquilo (C_1–C_2) sustituido, tal como, por ejemplo, un grupo –alquilen (C_1 a C_2)–$S(O)_2$– hidroxialquilo (C_1–C_2), en donde el carbono terminal de dicho grupo alquilo está sustituido.

La realización No. 102 se refiere a cualquiera de las realizaciones Nos. 1 a 26 en donde R^1 es un grupo –(C_2) alquilen–$S(O)_2$–alquilo (C_1–C_2) sustituido, tal como, por ejemplo, un grupo –alquilen (C_1 a C_2)–$S(O)_2$–hidroxialquilo (C_1–C_2), en donde el carbono terminal de dicho grupo alquilo está sustituido.

La realización No. 103 se refiere a cualquiera de las realizaciones Nos. 83 a 102 en donde R^2 es H.

La realización No. 104 se refiere a cualquiera de las realizaciones Nos. 83 a 102 en donde R^2 es alquilo.

La realización No. 105 se refiere a cualquiera de las realizaciones Nos. 83 a 102 en donde R^2 es metilo.

Como se usó anteriormente, y en toda esta descripción, los siguientes términos, a menos que se indique de otro modo, se considerará que tienen los siguientes significados:

"RAC" (o "rac") significa racemato.

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"Paciente" incluye a seres humanos y animales.

"Mamífero" significas seres humanos y otros animales mamíferos.

"Uno o más" significa al menos uno, por ejemplo, 1, 2 o 3, o 1 o 2, o 1, de este modo, por ejemplo, "uno o más grupos L^3" significa al menos un grupo L^3, y los ejemplos incluyen 1–3 grupos L^3, 1 o 2 grupos L^3, y un grupo L^3.

"Al menos uno" significa que hay al menos uno, y los ejemplos incluyen 1, 2 o 3, o 1 o 2, o 1.

"Alquilo" significa un grupo hidrocarbonado alifático, que puede ser lineal o ramificado y que comprende aproximadamente 1 a aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 a aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo más preferidos contienen aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena, que puede ser lineal o ramificada. El término "alquilo sustituido" significa que el grupo alquilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona de modo independiente del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, –NH(alquilo), –NH(cicloalquilo), $–N(alquilo)_2$, carboxi y –C(O)O–alquilo (a menos que se indique expresamente de otro modo). Los ejemplos no limitantes de grupos alquilo adecuados incluyen metilo, etilo, n–propilo, isopropilo y t–butilo.

"Alquenilo" significa un grupo hidrocarbonado alifático que contiene al menos un doble enlace carbono–carbono y que puede ser lineal o ramificada y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y con más preferencia

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aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etil o propilo están unidos a una cadena alquinilo lineal. El "alquinilo inferior" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena, que puede ser lineal o ramificada. Los ejemplos no limitantes de los grupos alquinilo adecuados incluyen etinilo, propinilo, 2–butinilo y 3–metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona de modo independiente del grupo que consiste en alquilo, arilo y cicloalquilo.

"Alquileno" significa un radical hidrocarbonado alifático divalente derivado de un grupo alquilo, definido anteriormente. Ambas valencias "abiertas" pueden estar en el mismo átomo de carbono, o en diferentes átomos de carbono. Los ejemplos de grupos alquileno incluyne grupos alquileno C_1–C_6, por ejemplo, grupos alquileno C_1 a C_4 y en otro ejemplo, grupos alquileno C_1–C_3, y en otro ejemplo grupos alquileno C_1 a C_2. Los ejemplos no limitantes de grupos alquileno incluyen $–CH_2–$, $–CH_2–CH_2–$, $–CH(CH_3)–$, etc.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene al menos un enlace carbono–carbono triple y que puede ser lineal o ramificado y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y con más preferencia aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena, que puede ser lineal o ramificada. Los ejemplos no limitantes de grupos alquinilo adecuados incluyen etinilo, propinilo, 2–butinilo y 3–metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo puede estar sustituido con uno o más sustituyentes

que pueden ser iguales o diferentes, cada sustituyente se selecciona de modo independiente del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 6 a aproximadamente 14 átomos de carbono, con preferencia aproximadamente 6 a aproximadamente 10 átomos de carbono. El grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se definen en la presente memoria. Los ejemplos no limitantes de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 5 a aproximadamente 14 átomos anulares, con preferencia aproximadamente 5 a aproximadamente 10 átomos anulares, en el que uno o más de los átomos anulares es un elemento diferente que carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos anulares. El "heteroarilo" puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se definen en la presente memoria. El prefijo aza, oxa o tia antes del nombre de la raíz heteroarilo significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como un átomo anular. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al correspondiente N–óxido. Los ejemplos no limitantes de heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridona (que incluye piridonas N–sustituidas), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4–tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2–a]piridinilo, imidazo[2,1–b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo,

isoquinolinilo, benzoazaindolilo, 1,2,4–triazinilo, benzotiazolilo y similares. El término "heteroarilo" también se refiere a restos heteroarilo parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Cicloalquilo" significa un sistema anular no aromático mono o multicíclico que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, con preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 a aproximadamente 7 átomos anulares. El cicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se definieron anteriormente. Los ejemplos no limitantes de cicloalquilos monocíclicos adecuados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares y los ejemplos no limitantes de cicloalquilos multicíclicos adecuados incluyen 1–decalinilo, norbonilo, adamantilo y similares, además de especies parcialmente saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo y similares.

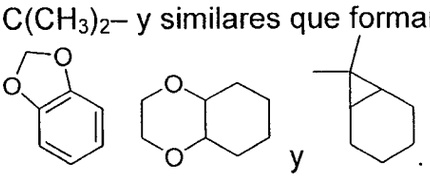
"Halógeno" o "halo" significa flúor, cloro, bromo o yodo. Los preferidos son flúor, cloro y bromo.

"Heteroalquilo" significa un grupo alquilo (definido en la presente memoria) en donde uno o más átomos de carbono se han reemplazado con heteroátomos, tales como, por ejemplo, cada heteroátomo se selecciona de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, O, S(O), y $S(O)_2$.

"Sustituyente del sistema anular" significa un sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular. Los sustituyentes del sistema anular pueden ser iguales o diferentes, cada uno se selecciona de modo independiente del grupo que consiste en alquilo, alquenilo, alquinilo, arilo (sustituido o no sustituido), heteroarilo, (sustituido o no sustituido, alquilen–arilo,

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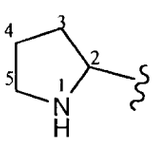
heteroarilalquenilo, heteroarilalquinilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, arilalcoxi susituido, acilo, aroílo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, arilalcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, arilalquiltio, heteroarilalquiltio, cicloalquilo, heterocicloalquilo, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH$(alquilo), Y_1Y_2N-, Y_1Y_2N–alquilo–, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ y $-SO_2NY_1Y_2$, en donde Y_1 y Y_2 puede ser iguales o diferentes y se seleccionan de modo independiente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y –alquilen–arilo (a menos que se definan expresamente de otro modo). El término "sustituyente del sistema anular" también puede significar un resto único que reemplaza en forma simultánea dos hidrógenos disponibles en dos átomos de carbono adyacentes están reemplazados en forma simultánea (por ej., uno H en cada carbono) en un sistema anular. Los ejemplos de dichos residuo son metilendioxi, etilendioxi, $-C(CH_3)_2-$ y similares que forman residuos tales como, por ejemplo:



"Heterocicloalquilo" significa un sistema anular no aromático monocíclico o multicíclico que comprende aproximadamente 3 a aproximadamente 10 átomos anulares, con preferencia aproximadamente 5 a aproximadamente 10 átomos anulares, en los que uno o más de los átomos del sistema anular es un elemento diferente del carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. No existen átomos de oxígeno y/o azufre presentes en el sistema anular. Los heterocicloalquilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos anulares. El prefijo aza, oxa o tia antes del nombre de la raíz heteroarilo significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como un átomo anular. Cualquier –NH de un anillo heterocicloalquilo puede existir en su forma protegida, por ejemplo, como un grupo –N(Boc), –N(CBz), –N(Tos) y similares; dichas formas protegidas

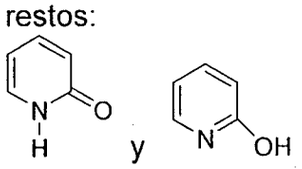
también se consideran parte de esta invención. El heterocicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se definen en la presente memoria.El átomo de nitrógeno o azufre del heterocicloalquilo puede esta ópcionalmente oxidado a los correspondientes N–óxido, S–óxido o S,S–dióxido. Los ejemplos no limitantes de anillos heterocicloalquilo monocíclicos adecuados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4–dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactam, lactona y similares. Los ejemplos no limitantes de anillos heterocicloalquilo monocíclicos no aromáticos insaturados incluyen tiazolinilo, 2,3–dihidrofuranilo, 2,3–dihidrotiofenilo, etc.

Cabe advertir que en los sistemas anulares que contienen heteroátomos de esta invención, no existen grupos hidroxilo en los átomos de carbono adyacentes a N, O o S, además de que no existen grupos N o S en el carbono adyacente a otro heteroátomo. En consecuencia, por ejemplo, en el anillo:



no existe –OH unido directamente a los carbonos marcados 2 y 5.

Se debe indicar que las formas tautoméricas tales como, por ejemplo, los restos:



se consideran equivalentes en ciertas realizaciones de esta invención.

"Hidroxialquilo" significa un grupo alquilo sustituido con aun grupo hidroxilo (–OH) en el que el alquilo es como se definió previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Los ejemplos no limitantes de grupos hidroxialquil adecuados incluyen hidroximetilo y 2–hidroxietilo.

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"Haloalquil" significa un grupo alquilo sustituido con uno o más átomos de halo seleccionados de modo independiente (por ej., F, Cl y Br, y en un ejemplo, uno o más átomos de F), y en donde un ejemplo es $-CF_3$.

"Acilo" significa un grupo H–C(O)–, alquilo–C(O)– o cicloalquilo–C(O)–, en el que varios grupos son como se describieron previamente. El enlace al resto principal es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Los ejemplos no limitantes de grupos acilo adecuados incluyen formilo, acetilo y propanoílo.

"Aroílo" significa un grupo arilo–C(O)– en el que el grupo arilo es como se describió previamente. El enlace al resto principal es a través del carbonilo. Los ejemplos no limitantes de grupos adecuados incluyen benzoílo y 1– naftoílo.

"Alcoxi" significa un grupo alquilo–O– en el que el grupo alquilo es como se describió previamente. Los ejemplos no limitantes de grupos alcoxi adecuados incluyen metoxi, etoxi, n–propoxi, isopropoxi y n–butoxi. El enlace al resto principal es a través del oxígeno del éter.

"Alcoxialquil" significa un grupo –alquilo–O–alquilo en donde alquilo es como se describió previamente.

"Ariloxi" significa un grupo arilo–O– en el que el grupo arilo es como se describió previamente. Los ejemplos no limitantes de grupos ariloxi adecuaos incluyen fenoxi y naftoxi. El enlace al resto principal es a través del oxígeno del éter.

"Alquiltio" significa un grupo alquilo–S– en el que el grupo alquilo es como se describió previamente. Los ejemplos no limitantes de grupos alquiltio adecuados incluyen metiltio y etiltio. El enlace al resto principal es a través del azufre.

Ariltio" significa un grupo arilo–S– en el que el grupo arilo es como se describió previamente. Los ejemplos no limitantes de grupos ariltio adecuados incluyen feniltio y naftiltio. El enlace al resto principal es a través del azufre.

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"Aralquiltio" significa un grupo –S–alquilen–arilo en que los grupos alquileno y arilo son como se describieron previamente. Un ejemplo no limitante de un grupo aralquiltio adecuado es benciltio. El enlace al resto principal es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquilo–O–CO–. Los ejemplos no limitantes de grupos alcoxicarbonilo adecuados incluyen metoxicarbonilo y etoxicarbonilo. El enlace al resto principal es a través del carbonilo.

Ariloxicarbonilo" significa un grupo arilo–O–C(O)–. Los ejemplos no limitantes de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace al resto principal es a través del carbonilo.

"Arilalcoxicarbonilo" significa un grupo –C(O)–O–alquilen–arilo group. Un ejemplo no limitante de un grupo arilalcoxicarbonilo adecuado es benciloxicarbonilo. El enlace al resto principal es a través del carbonilo.

"Alquilsulfonilo" significa un grupo alquilo–$S(O_2)$–. Los grupos preferidos son aquellos en que el grupo alquilo es alquilo inferior. El enlace al resto principal es a través del sulfonilo.

"Arilsulfonilo" significa un grupo arilo–$S(O_2)$–. El enlace al resto principal es a través del sulfonilo.

“Alcanoílo” significa un grupo alquil–C(O)–.

“Carbamoílo” significa un grupo NH_2–C(O)–.

El término “sustituido” significa que uno o más hidrógenos de los átomos designados se reemplaza con una selección del grupo indicado, con la condición que no se exceda la valencia normal del átomo designado en las circunstancias existentes y que la substitución origine un compuesto estable. Las combinaciones de los sustituyentes y/o variables son permisibles solo si dichos compuestos producen compuestos estables. Por “compuesto estable’ o “estructura estable” se entiende un compuesto que es suficientemente robusto para sobrevivir al

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aislamiento en un grado útil de pureza de una mezcla de reacción, y formulación en un agente terapéutico eficaz.

Cuando un grupo está sustituido con "uno o más" sustituyentes, el grupo indicado puede estar sustituido con un sustituyente, dos sustituyentes, etc., con la condición que el grupo sustituido resultante forme una estructura estable, como se describió anteriormente.

El término "opcionalmente sustituido" significa substitución opcional con los grupos, radicales o restos especificados. Por ejemplo, un arilo opcionalmente sustituido con un grupo indicado de sustituyentes incluye arilo no sustituido además de arilo sustituido con cualquiera de los sustituyentes indicados.

El término "aislado" o "en forma y aislada" para un compuesto se refiere al estado físico de dicho compuesto después de aislarse de un proceso sintético o fuente natural o sus combinaciones. el término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto después de obtenerse de un proceso o procesos de purificación descriptos en la presente memoria o bien conocidos por los profesionales expertos (por ej., cromatografía, recristalización y similares), en una pureza suficiente para ser caracterizable por técnicas analíticas estándares descriptas en la presente memoria o bien conocidas por los profesionales expertos.

También cabe indicar que se asume que cualquier carbono además de heteroátomos con valencias insatisfechas del texto, esquemas, ejemplos y Tablas de la presente memoria tiene el número suficiente de átomos de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional de un compuesto se denomina "protegido", esto significa que el grupo está en una forma modificada para evitar reacciones no deseadas en el sitio protegido cuando el compuesto se somete a una reacción. Los grupos protectores adecuados serán reconocidos por los expertos en el arte así también como por referencia a textos estándares tales como, por

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ejemplo, T. W. Greene *et al*, *Protective En organic Synthesis* (1991), Wiley, New York, incorporados en la presente memoria en su totalidad como referencia.

Cuando cualquier variable (por ej., arilo, heterocicloalquilo, L^1, etc.) aparece más de una vez en cualquier constituyente o en la Fórmula I, su definición de cada aparición es independiente de su definición en todas las otras apariciones (a menos que se indique expresamente de otro modo).

Como se usa en la presente memoria, el término "composición" abarca un producto que comprende los componentes especificados en las cantidades especificadas, además de cualquier producto que resulte, en forma directa o indirecta, de la combinación de componentes especificados en las cantidades especificadas.

Un "grupo atrayente de electrones" (abreviado como EWG), usado en la presente es un grupo que atraerá electrones a sí mismo más de lo que lo haría un átomo de hidrógeno si ocupara la misma posición en la molécula (ver, por ejemplo, Jerry March, "Advanced Organic Chemistry", 4th Edition, página 18, John Wiley & Sons, 1992)

Las prodrogas y solvatos de los compuestos de la invención también están contemplados en la presente memoria. El término "prodroga", como se emplea en la presente memoria. indica un compuesto que es un precursor de droga) que después de la administración a un sujeto, experimenta la conversión química por procesos metabólicos o químicos para producir un compuesto de fórmula (I) o una sal y/o solvato de este. Una descripción de prodrogas se proporciona en T. Higuchi y V. Stella, Pro–drogas as Novel Delivery Systems (1987) 14 de la A.C.S. Symposium Series, y en Bioreversible Carriers en Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association y Pergamon Press, las que están incorporadas en la presente memoria como referencia.

"Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física involucra

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variados grados de uniones iónicas y covalentes, que incluyen enlaces hidrógeno. En ciertos casos el solvato será posible de aislamiento, por ejemplo cuando una o más moléculas de solvente se incorporan en la retícula del cristal del sólido cristalino. "Solvato" abarca tanto la fase solución como solvatos aislables. Los ejemplos no limitantes de solvatos adecuados incluyen etanolatos, metanolatos y similares. "Hidrato" es un solvato donde la molécula de solvente es H_2O.

"Cantidad efectiva" o "cantidad terapéuticamente efectiva" significa que describe una cantidad de compuesto o una composición de la presente invención efectiva para inhibir las enfermedades indicadas anteriormente y en consecuencia producir el efecto terapéutico, mejorador, inhibitorio o preventivo deseado.

Los compuestos de fórmula I pueden formar sales que están dentro del alcance de esta invención. La referencia a un compuesto de Fórmula I en la presente memoria se entiende que incluye las referencias a sus sales, a menos que se indique lo contrario. El término "sale(s)", empleado en la presente memoria, indica sales ácidas formadas con ácidos orgánicos y/o inorgánicos, además de sales básicas formadas con bases inorgánicas y/o orgánicas. Además, cuando un compuesto de Fórmula I contiene tanto un resto básico, tal como, pero sin limitación una piridina o imidazol, como un resto ácido tal como, pero sin limitación un ácido carboxílico, se pueden formar zwitteriones ("sales internas") y se incluyen dentro del término "sal(es)" usado en la presente memoria. Las sales aceptables para uso farmacéutico (es decir, no tóxicas, fisiológicamente aceptables) son preferidas, si bien otras sales también son útiles. Las sales de los compuestos de la Fórmula I se pueden formar, por ejemplo, por la reacción de un compuesto de Fórmula I con una cantidad de ácido o base, tal como una cantidad equivalente en un medio tal como uno en el que la sal precipita o en un medio acuoso seguido por liofilización.

Los ejemplos de sales de adición de ácidos incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos,

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canforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos) y similares. Adicionalmente, se describen los ácidos que se consideran generalmente adecuados para la formación de sales farmacéuticamente útiles a partir de compuestos farmacéuticos, por ejemplo, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley–VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1–19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201–217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New Yok; y en *The Orange Book* (Food & Droga Administración, Washington, D.C. en sitio de red). Estas descripciones están incorporadas en la presente memoria como referencia.

Los grupos que contienen nitrógeno básico se puede cuaternizar con agentes tales como haluros de alquilo inferior (por ej., cloruros, bromuros y yoduros de metilo, etilo y butilo), dialquilsulfatos (por ej., sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ej., cloruros, bromuros y yoduros de decilo, laurilo, y estearilo), haluros de aralquilo (por ej., bromuros de bencilo y fenetilo), y otros.

Todas estas sales ácidas y sales básicas son sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales ácidas y básicas se consideran equivalentes a las formas libres de los correspondientes compuestos para los fines de la invención.

Los compuestos de fórmula (I) y una de sus sales, solvatos y prodrogas, pueden existir en forma tautomérica (por ejemplo, como una amida o iminoéter). Todas estas formas tautoméricas están contemplados en la presente memoria como parte de la presente invención.

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Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (que incluyen los de las sales, solvatos, ésteres y prodrogas de los compuestos además de las sales, solvatos, ésteres de las prodrogas), tales como las que pueden existir debido a los carbonos asimétricos de varios sustituyentes, que incluyen formas enantioméricas (que pueden existir aun en la ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros, y formas diastereoméricas, están contempladas dentro del alcance de esta invención, como los isómeros de posición (tales como, por ejemplo, 4–piridilo y 3–piridilo). Los estereoisómeros individuales de los compuestos de la invención, por ejemplo, pueden estar sustancialmente libres de otros isómeros, o se pueden mezclar, por ejemplo, como racematos o con los otros, u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener configuración S o R definida por las recomendaciones de *IUPAC* 1974. Se considera que el uso de los términos "sal", "solvato", "éster", "prodroga" y similares, se aplica igualmente a la sal, solvato, éster y prodroga de los enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros de posición, racematos o prodrogas de los compuestos de la invención.

Las formas polimórficas de los compuestos de fórmula I, y de las sales, solvatos, ésteres y prodrogas de los compuestos de fórmula I, están incluidos en la presente invención.

Los compuestos de acuerdo con la invención pueden tener propiedades farmacológicas; en particular, los compuestos de fórmula (I) pueden inhibir gamma–secretasa, y en consecuencia son útiles en el tratamiento o prevención de enfermedades neurodegenerativas, por ej., Enfermedad de Alzheimer.
Los compuestos representativos de la invención incluyen pero sin limitación a los compuestos y Ejemplos descriptos en la presente memoria.

Las composiciones farmacéuticas pueden comprender uno o más de los compuestos de fórmula (I). Para preparar las composiciones farmacéuticas a

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partir de los compuestos descriptos por esta invención, los vehículos inertes aceptables para uso farmacéutico pueden ser sólidos o líquidos. Las preparaciones en forma sólida incluyen polvos, comprimidos, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y comprimidos pueden estar compuestos de aproximadamente 5 a aproximadamente 95 por ciento de componente activo. Los vehículos sólidos son conocidos en el arte, por ej., carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Se pueden usar comprimidos, polvos, sellos y cápsulas como formas de dosis adecuadas para la administración oral. Los ejemplos de vehículos aceptables para uso farmacéutico y métodos de fabricación para diversas composiciones se pueden hallar en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18^{t} Edición, (1990), Mack Publishing Co., Easton, Pennsilvania, incorporadas en la presente memoria en su totalidad como referencia.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. Son ejemplos agua o soluciones de agua–propilenglicol para inyección parenteral o adición de edulcorantes y opacificantes para las soluciones, suspensiones y emulsiones orales. Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para la inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden estar en combinación con un vehículo aceptable para uso farmacéutico, tal como un gas inerte comprimido, por ej., nitrógeno.

También se incluyen las preparaciones en forma sólida que están destinadas a convertirse, inmediatamente antes de usar, en preparaciones en forma líquida para la administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención también se pueden administrar por vía transdérmica. Las composiciones transdérmicas pueden adoptar la forma de

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cremas, lociones, aerosoles y/o emulsiones y se pueden incluir en un parche transdérmico del tipo matriz o reservorio convencionales en el arte para este propósito.

Con preferencia, la preparación farmacéutica está en una forma de dosis unitaria. En dicha forma, la preparación se subdivide en dosis unitarias de tamaño adecuado que contienen cantidades apropiadas del componente activo, por ej., una cantidad efectiva para lograr el efecto deseado.

El término "composición farmacéutica" también abarca la composición a granel y unidades de dosis individuales compuestas de más de un (por ej., dos) agentes activos para uso farmacéutico tales como, por ejemplo, un compuesto de la presente invención y un agente adicional seleccionado de las listas de los agentes adicionales descriptos en la presente memoria, junto con excipientes inactivos para uso farmacéutico. La composición a granel y cada unidad de dosis individual puede contener cantidades fijas de los precedentes "más de uno de los agentes activos para uso farmacéutico". La composición a granel es material qua aún no se ha formado en unidades de dosis individuales. Una unidad de dosis ilustrativa es una unidad de dosis oral tal como comprimidos, pastillas y similares. De modo similar, el método de descripto en la presente de tratamiento de un paciente por la administración de una composición farmacéutica de la presente invención también abarca la administración de la composición a granel mencionada anteriormente y unidades de dosis individuales.

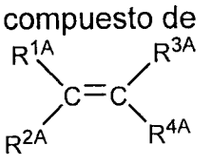
La cantidad del compuesto activo en una dosis unitaria de preparación se puede variar o ajustar de aproximadamente 0,01 mg a aproximadamente 1000 mg, con preferencia de aproximadamente 0,01 mg a aproximadamente 750 mg, con más preferencia de aproximadamente 0,01 mg a aproximadamente 500 mg, y con máxima preferencia de aproximadamente 0,01 mg a aproximadamente 250 mg, de acuerdo con la aplicación particular. La dosis real empleada puede variar de acuerdo con los requerimientos del paciente y la gravedad de la patología tratada. La determinación del esquema de dosis apropiado para una situación particular

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está dentro de la experiencia del arte. Para conveniencia, la dosis diaria total se puede dividir y administrar en porciones durante el día, según corresponda.

La cantidad y frecuencia de administración de los compuestos de la invención y/o sus sales aceptables para uso farmacéutico se regulará de acuerdo con el criterio del médico asistente tomando en consideración factores tales como edad, enfermedad y tamaño del paciente además de la gravedad de los síntomas tratados. Un régimen de dosis diaria recomendada típica para la administración oral puede variar de aproximadamente 0,04 mg/día a aproximadamente 4000 mg/día, en uno a cuatro dosis divididas.

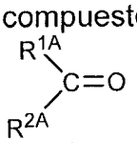
Esta invención también se refiere al proceso (Proceso 1) para preparar un compuesto de la fórmula:



dicho proceso que comprende la reacción:

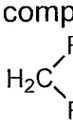
(1) una mezcla que comprende:

(a) un compuesto de la fórmula:



, y

(b) un compuesto de la fórmula:

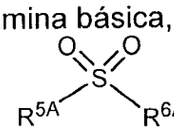


, y

(c) un solvente orgánico adecuado (con preferencia anhidro); con

(2) alguno de:

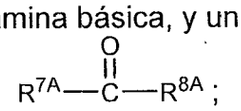
(a) una amina básica, y un compuesto de la fórmula



, o

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(b) una amina básica, y un compuesto de la fórmula



en donde:

Cada R^{1A} y R^{2A} se seleccionan de modo independiente del grupo que consiste en: H, alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, heteroalquilo, arilo, heteroarilo, alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido y heteroarilo sustituido; en donde dichos grupos sustituidos están sustituidos con uno o más (por ej., 1 a 5, 1 a 4, 1 a 3, 1 a 2, o 1) sustituyentes, cada uno seleccionado de modo independiente del grupo que consiste en: $-NO_2$, –NO, $-SO_2R^{7B}$, $-SO_2$–arilo (por ej., $-SO_2$–fenilo), $-SO_2$–heteroarilo (por ej., $-SO_2$–piridilo), $-SO_2OR^{7B}$, –CN, –COOH, halo (por ej., F, Cl, Br, y I), $-CF_3$, –Oaril (por ej., –O–fenilo), –Oheteroaril (por ej., –O–piridilo), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, –CHO, $-OR^{7B}$, $-COR^{7B}$, –SH, $-SR^{7B}$, –OH, arilo (por ej., fenilo), y heteroarilo (por ej., piridilo); y en donde en un ejemplo dichos grupos sustituidos están sustituidos con uno o más (por ej., 1 a 5, 1 a 4, 1 a 3, 1 a 2, o 1) sustituyentes, cada uno se selecciona de modo independiente del grupo que consiste en: halo (por ej., Cl, F, y Br), $-NO_2$, –CN, $-C(O)OR^{12A}$, $-C(O)R^{12A}$, $-CF_3$, –S(O), y $-S(O)_2$; en donde:

(1) los ejemplos de los anillos heterocicloalquilos de dicho anillo heterocicloalquilo R^{1A} o R^{2A}, o de dicho anillo heterocicloalquilo sustituido R^{1A} o R^{2A}, incluyen, pero sin limitación: anillos heterocicloalquilos que comprende un total de 3 a 7 miembros anulares (por ej., 3 a 6, o 3 a 5, o 3 a 4 miembros anulares totales) en donde 1 a 4 (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2) miembros anulares son heteroátomos seleccionados de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, –O–, –S–, –S(O)–, y $-S(O)_2-$; y los ejemplos de dichos

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anillos heterocicloalquilos también incluyen, pero sin limitación: piperidina, piperazina, pirrolidina, azetidina, homopiperazina, tetrahidropirano, tetrahidropirano y oxetano; y los ejemplos de dichos anillos heterocicloalquilos sustituidos incluyen, pero sin limitación: piperidina sustituida, piperazina sustituida, pirrolidina sustituida, azetidina sustituida, homopiperazina sustituida, tetrahidropirano sustituido, tetrahidrofurano sustituido y oxetano sustituido, en donde los sustituyentes se definieron anteriormente para dichos grupos heterocicloalquilos sustituidos R^{1A} y R^{2A};

(2) los ejemplos de los anillos heteroarilo de dicho anillo heteroarilo R^{1A} o R^{2A} , o de dicho anillo heteroarilo sustituido R^{1A} o R^{2A}, incluyen, pero sin limitación: anillos heteroarilo que comprenden un total de 5 a 6 miembros anulares (por ej., 5 miembros anulares totales, o 6 miembros anulares totales) en donde 1 a 4 (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2) miembros anulares son heteroátomos seleccionados de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, –O–, –S–,–S(O)–, y–$S(O)_2$–; y los ejemplos de dichos anillos heteroarilo también incluyen, pero sin limitación: piridina, pirimidina, pirazina, tiofeno, y furano; y los ejemplos de dichos anillos heteroarilo sustituidos incluyen, pero sin limitación: piridina sustituida, pirimidina sustituida, pirazina sustituida, tiofeno sustituido, y furano sustituido, en donde los sustituyentes se definieron anteriormente para dichos grupos heteroarilo sustituidos R^{1A} y R^{2A}; y

(3) los ejemplos del grupo heteroalquilo de dicho grupo heteroalquilo R^{1A} o R^{2A}, o de dicho grupo heteroalquilo R^{1A} o R^{2A} sustituido, incluyen, pero sin limitación: grupos heteroalquilo (C_3 a C_{20}) que comprenden al menos un (por ej., 1 a 3, o 1 a 2, o 1 o 2) heteroátomo, cada uno que se selecciona de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, O, S(O), y $S(O)_2$;

cada R^{3A} y R^{4A} se seleccionan de modo independiente del grupo que consiste en: $-NO_2$, –NO, $-SO_2R^{7B}$, $-SO_2$–arilo (por ej., $-SO_2$–fenilo), $-SO_2$–heteroarilo (por ej., $-SO_2$–piridilo), $-SO_2OR^{7B}$, –CN, –COOH, halo (por ej., F, Cl,

Br, y I), $-CF_3$, –Oarilo (por ej., –O–fenilo), –Oheteroarilo (por ej., –O–piridilo), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, –CHO, $-OR^{7B}$, $-COR^{7B}$, –SH, $-SR^{7B}$, –OH, arilo (por ej., fenilo), y heteroarilo (por ej., piridilo); y en un ejemplo cada R^{3A} y R^{4A} se seleccionan de modo independiente del grupo que consiste en: $-C(O)OR^{12A}$, –CN, $-NO_2$, $-CF_3$, $-C(O)R^{12A}$, –S(O),y $-S(O)_2$;

R^{5A} se selecciona del grupo que consiste en: H, alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, heteroalquilo, arilo, heteroarilo, alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido; y en donde:

dichos grupos alquilos sustituidos están sustituidos con uno o más (por ej., 1 a 5, 1 a 4, 1 a 3, 1 a 2, o 1) sustituyentes, cada uno se selecciona de modo independiente del grupo que consiste en: halo (por ej., Cl, F, y Br), $-NO_2$, –CN, y $-OR^{12A}$; y

dichos grupos alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido están sustituidos con uno o más (por ej., 1 a 5, 1 a 4, 1 a 3, 1 a 2, o 1) sustituyentes, cada uno se selecciona de modo independiente del grupo que consiste en: halo (por ej., Cl, F, y Br), $-NO_2$, –CN, y $-OR^{12A}$, alquilo y halo alquilo sustituido (por ej., alquilo sustituido con F, tal como, por ejemplo, $-CF_3$); y en donde:

(1) los ejemplos del anillo heterocicloalquilo de dicho anillo heterocicloalquilo R^{5A}, o de dicho anillo heterocicloalquilo sustituido R^{5A}, incluyen, pero sin limitación: anillos heterocicloalquilo que comprende un total de 3 a 7 miembros anulares (por ej., 3 a 6, o 3 a 5, o 3 a 4 miembros anulares totales) en donde 1 a 4 (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2) miembros anulares son heteroátomos seleccionados de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, –O–, –S–, –S(O)–, y $-S(O)_2-$; y los ejemplos de dichos anillos

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heterocicloalquilo también incluyen, pero sin limitación: piperidina, piperazina, pirrolidina, azetidina, homopiperazina, tetrahidropirano, tetrahidropirano y oxetano; y los ejemplos de dichos anillos heterocicloalquilo sustituidos también incluyen, pero sin limitación: piperidina sustituida, piperazina sustituida, pirrolidina sustituida, azetidina sustituida, homopiperazina sustituida, tetrahidropirano sustituido, tetrahidrofurano sustituido y oxetano sustituido, en donde los sustituyentes están definidos anteriormente para dichos grupos heterocicloalquilo R^{5A} sustituidos;

(2) los ejemplos del anillo heteroarilo de dichos anillos R^{5A} de dichos anillo heteroarilo, o de dichos anillo heteroarilo R^{5A} sustituidos, incluyen, pero sin limitación: anillos heteroarilo que comprende un total de 5 a 6 miembros anulares (por ej., 5 miembros anulares totales, o 6 miembros anulares totales) en donde 1 a 4 (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2) miembros anulares son heteroátomos seleccionados de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, –O–, –S–,–S(O)–, y–$S(O)_2$–; y los ejemplos de dichos anillos heteroarilo también incluyen, pero sin limitación: piridina, pirimidina, pirazina, tiofeno y furano; y los ejemplos de dichos anillos heteroarilo sustituidos también incluyen, pero sin limitación: piridina sustituida, pirimidina sustituida, pirazina sustituida, tiofeno sustituido, y furano sustituido, en donde los sustituyentes se definieron anteriormente para dichos grupos heteroarilo sustituido R^{5A}; y

(3) los ejemplos del grupo heteroalquilo de dichos grupo heteroalquilo R^{5A}, o de dichos grupo heteroalquilo R^{5A} sustituidos, incluyen, pero sin limitación: grupos heteroalquilo (C_3 a C_{20}) que comprenden al menos un (por ej., 1 a 3, o 1 a 2, o 1 o 2) heteroátomo cada uno se selecciona de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, O, S(O), y $S(O)_2$;

R^{6A} se selecciona del grupo que consiste en: halo (por ej., Cl, F, y Br, y con preferencia Cl), y $-OSO_2R^{5A}$ (y con preferencia R^{6A} es halo);

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R^{7A} se selecciona del grupo que consiste en: arilo no sustituido, arilo sustituido con al menos un (por ej., 1 a 3, o 1 a 2, o 1) grupo atrayente de electrones, heteroarilo y heteroarilo sustituido con al menos un grupo atrayente de electrones (por ej., 1 a 3, o 1 a 2, o 1); y en donde un ejemplo de dicho resto arilo (de dicho arilo R^{7A}, o dichos grupos arilo sustituido R^{7A}) es fenilo; y en donde un ejemplo de dicho resto heteroarilo (de dicho heteroarilo R^{7A}, o dichos grupos heteroarilo R^{7A} sustituidos) es piridilo; y en donde:

(1) en un ejemplo cada grupo atrayente de electrones se selecciona de modo independiente del grupo que consiste en: $-NO_2$, –NO, $-SO_2R^{7B}$, $-SO_2$–arilo (por ej., $-SO_2$–fenilo), $-SO_2$–heteroarilo (por ej., $-SO_2$–piridilo), $-SO_2OR^{7B}$, –CN, –COOH, halo (por ej., F, Cl, Br, y I), $-CF_3$, –Oarilo (por ej., –O–fenilo), –Oheteroarilo (por ej., –O–piridilo), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, –CHO, $-OR^{7B}$, $-COR^{7B}$, –SH, $-SR^{7B}$, –OH, arilo (por ej., fenilo), y heteroarilo (por ej., piridilo); y

(2) en otro ejemplo, cada grupo atrayente de electrones se selecciona de modo independiente del grupo que consiste en: $-NO_2$, –CN, $-CF_3$, $-C(O)R^{12A}$, –S(O), $-SO_2$, y halo (por ej., Cl, F, y Br); y

(3) en otro ejemplo, dicho resto heteroarilo of dicho grupo heteroarilo sustituido R^{7A} comprises 1 a 4 heteroátomos anulares (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2 heteroátomos) en donde each heteroátomo se selecciona de modo independiente del grupo que consiste en: –O–, –S–, –S(O)–, y $-S(O)_2$–, y dicho anillo heteroarilo comprende un total de 5 o 6 miembros anulares;

(4) en otro ejemplo, dicho resto heteroarilo of dicho grupo heteroarilo sustituido R^{7A} comprises 1 a 4 heteroátomos anulares (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2 heteroátomos) en donde each heteroátomo se selecciona de modo independiente del grupo que consiste en: –O–, –S–, –S(O)–, y $-S(O)_2$–, y dicho anillo heteroarilo comprende un total de 5 o 6 miembros anulares, y cada grupo atrayente de electrones se selecciona de modo independiente del grupo que

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consiste en:

$-NO_2$, –NO, $-SO_2R^{7B}$, $-SO_2$–arilo (por ej., $-SO_2$–fenilo), $-SO_2$–heteroarilo (por ej., $-SO_2$–piridilo), $-SO_2OR^{7B}$, –CN, –COOH, halo (por ej., F, Cl, Br, y I), $-CF_3$, –Oaril (por ej., –O–fenilo), –Oheteroaril (por ej., –O–piridilo), $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, –CHO, $-OR^{7B}$, $-COR^{7B}$, –SH, $-SR^{7B}$, –OH, arilo (por ej., fenilo), y heteroarilo (por ej., fenilo); y

(5) en otro ejemplo, dicho resto heteroarilo de dicho grupo heteroarilo sustituido R^{7A} comprende 1 a 4 heteroátomos anulares (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2 heteroátomos) en donde cada heteroátomo se selecciona de modo independiente del grupo que consiste en: –O–, –S–, –S(O)–, y $-S(O)_2$–, y dicho anillo heteroarilo comprende un total de 5 o 6 miembros anulares, y cada grupo atrayente de electrones se selecciona de modo independiente del grupo que consiste en:

$-NO_2$, –CN, $-CF_3$, $-C(O)R^{12A}$, –S(O), $-SO_2$, y halo (por ej., Cl, F, y Br);

Cada R^{7B} se selecciona de modo independiente del grupo que consiste en: alquilo (por ej., C_1 a C_6, o C_1 a C_4, o C_1 a C_2, o metilo, o etilo), cicloalquilo y heteroalquilo;

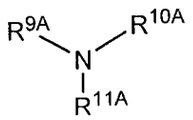
R^{8A} se selecciona del grupo que consiste en: halo (por ej., Cl, F, y Br), y $-OC(O)R^{7A}$;

R^{12A} es alquilo (por ej., C_1 a C_6, o C_1 a C_4, o C_1 a C_2, o metilo, o etilo); y

R^{13A} se selecciona del grupo que consiste en: alquilo, alcoxialquilo, hidroxialquilo, alcanoílo, arilo, heteroarilo, aroílo y carbamoílo, y con preferencia alquilo.

Los ejemplos de la amina básica usados en los procesos de esta invención (ver, por ejemplo, pasos (2)(a) y (2)(b)), incluyen, pero sin limitación: (1) heteroarilos basados en nitrógeno (es decir, el único heteroátomo es N), y (2) aminas de la fórmula:

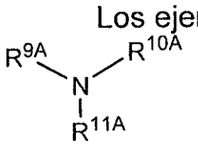
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(en donde R^{9A}, R^{10A} y R^{11A} se definen a continuación).

Los ejemplos de la amina básica del heteroarilo basado en nitrógeno incluyen, pero sin limitación: imidazolilo y piridilo.

Los ejemplos de la amina básica de la fórmula:



incluyen, pero sin limitación trialquilaminas (es decir, cada R^{9A}, R^{10A}, y R^{11A} son alquilo y se seleccionas de modo independiente), tales como, por ejemplo, trietilamina (TEA) y diisopropiletilamina (es decir, dos de grupos R^{9A}, R^{10A}, y R^{11A} son grupos diisopropilo y el grupo restante es un grupo etilo), se prefiere TEA.

Cada R^{9A}, R^{10A}, y R^{11A} se selecciona de modo independiente del grupo que consiste en: alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, heteroalquilo, arilo, heteroarilo, alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido; en donde dichos grupos sustituidos están sustituidos con uno o más (por ej., 1 a 5, 1 a 4, 1 a 3, 1 a 2, o 1) sustituyentes cada uno se selecciona de modo independiente del grupo que consiste en: halo (por ej., Cl, F, y Br), alquilo y alcoxi; en donde:

(1) los ejemplos del anillo heterocicloalquilo de dicho anillo heterocicloalquilo R^{9A}, R^{10A} o R^{11A} o de dicho anillo heterocicloalquilo R^{9A}, R^{10A} o R^{11A} sustituido, incluyen, pero sin limitación: anillos heterocicloalquilo que comprenden un total de 3 a 7 miembros anulares (por ej., 3 a 6, o 3 a 5, o 3 a 4 miembros anulares totales) en donde 1 a 4 (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2) miembros anulares are heteroátomos seleccionados de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, –O–, –S–, –S(O)–, y $-S(O)_2-$; los ejemplos de dichos anillo heterocicloalquilo también incluyen, pero sin limitación: piperidina,

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piperazina, pirrolidina, azetidina, homopiperazina, tetrahidropirano, tetrahidropirano y oxetano; los ejemplos de dicho anillos heterocicloalquilo sustituidos incluyen, pero sin limitación: piperidina sustituida, piperazina sustituida, pirrolidina sustituida, azetidina sustituida, homopiperazina sustituida, tetrahidropirano sustituido, tetrahidrofurano sustituido y oxetano sustituido, en donde los sustituyentes se definieron anteriormente para dichos grupos heterocicloalquilo sustituido R^{9A}, R^{10A} y R^{11A};

(2) los ejemplos de los anillo heteroarilo de dicho anillo heteroarilo R^{9A}, R^{10A} o R^{11A} , o de dichos anillos heteroarilo sustituido R^{9A}, R^{10A}, o R^{11A}, incluyen, pero sin limitación: anillos heteroarilo que comprende un total de 5 a 6 miembros anulares (por ej., 5 miembros anulares totales, o 6 miembros anulares totales) en donde 1 a 4 (por ej., 1 a 4, 1 a 3, 1 a 2, 1, o 2) miembros anulares son heteroátomos seleccionados de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, –O–, –S–,–S(O)–, y–$S(O)_2$–; los ejemplos de dicho anillos heteroarilo también incluyen, pero sin limitación: piridina, pirimidina, pirazina, tiofeno, y furano; los ejemplos de dicho anillos heteroarilo sustituidos incluyen, pero sin limitación: piridina sustituida, pirimidina sustituida, pirazina sustituida, tiofeno sustituido, y furano sustituido, en donde los sustituyentes se definieron anteriormente para dichos grupos heteroarilo sustituido R^{9A}, R^{10A}, y R^{11A}; y

(3) los ejemplos del grupo heteroalquilo de dicho grupo heteroalquilo R^{9A}, R^{10A}, o R^{11A} o de dicho heteroalquilo sustituido R^{9A}, R^{10A}, o R^{11A}, incluyen, pero sin limitación: grupos heteroalquilo (C_3 a C_{20}) que comprenden al menos un (por ej., 1 a 3, o 1 a 2, o 1 o 2) heteroátomo, cada uno que se selecciona de modo independiente del grupo que consiste en: N, $-(NR^{13A})-$, O, S(O), y $S(O)_2$.

Los ejemplos de los grupos alquilo en los procesos de esta invención incluyen, pero sin limitación: alquilo C_1 a C_6, alquilo C_1 a C_4, alquilo C_1 a C_2, etilo y metilo);

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Los procesos de esta invención se realizan en solventes orgánicos adecuados (con preferencia anhidro). Los ejemplos de dichos solventes incluyen, pero sin limitación: (1) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano y tetraclorometano), (2) arilhaluros (tales como, por ejemplo, clorobenceno), (3) DMSO, (4) DMF, (5) THF, (6) éteres (tales como, por ejemplo, éter dietílico), y (7) sus mezclas.

En una realización el solvente orgánico (con preferencia anhidro) se selecciona del grupo que consiste en: diclorometano, dicloroetano, clorobenceno, DMSO, DMF, THF, y éter dietílico.

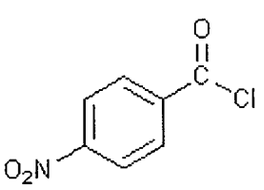
En una realización el solvente es un haloalcano.

En otra realización el solvente es diclorometano.

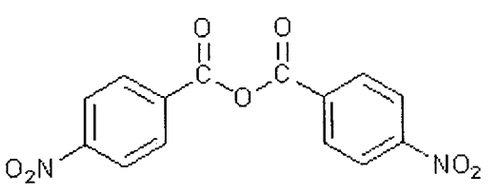
Los ejemplos de la ($–NR^9R^{10}R^{11}$) amina terciaria básica usados en los procesos de esta invención incluyen, pero sin limitación: trietilamina (es decir, TEA), y diisopropiletilamina (es decir, $C_2H_5N(CH_2CH_3)_2$).

En una realización de los procesos de esta invención la amina terciaria básica ($–NR^9R^{10}R^{11}$) es trietilamina (es decir, TEA).

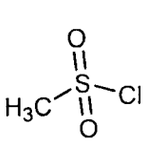
Los ejemplos del resto $R^{7A}C(O)R^{8A}$ incluyen, pero sin limitación:



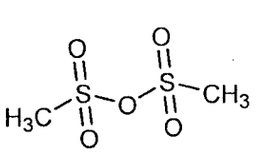
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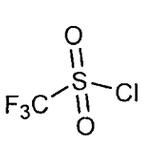
Los ejemplos del resto $R^{5A}S(O)_2R^{6A}$ incluyen, pero sin limitación:



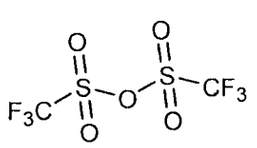
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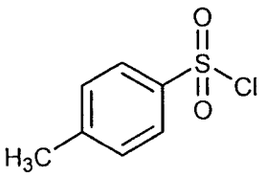
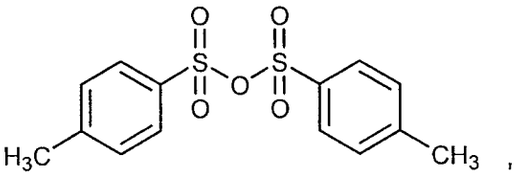
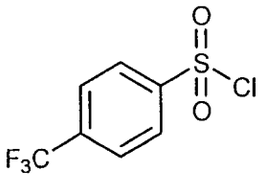
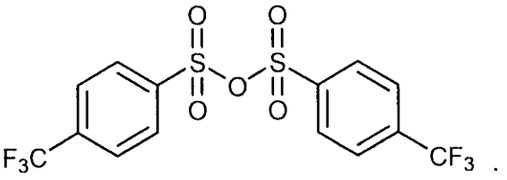
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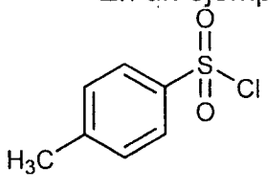
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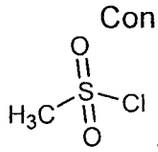
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and


En un ejemplo el resto $R^{5A}S(O)_2R^{6A}$ es



Con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



Los procesos de esta invención se llevan a cabo a una temperatura adecuada. Una temperatura adecuada es una en donde la reacción procede a una tasa razonable, y uno en donde la producción de subproductos o productos de degradación no deseados se minimiza.

En una realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C.

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En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C.

En otra realización del Proceso 1 la amina básica es una trialquilamina.

En otra realización del Proceso 1 la amina básica es TEA.

En otra realización del Proceso 1 la amina básica es diisopropiletilamina.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y la amina básica es una trialquilamina.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, y la amina básica es una trialquilamina.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, y la amina básica es una trialquilamina.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y la amina básica es TEA.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, y la amina básica es TEA.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, y la amina básica es TEA.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y la amina básica es diisopropiletilamina.

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En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, y la amina básica es diisopropiletilamina.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, y la amina básica es diisopropiletilamina.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo,

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diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$),

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triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii)

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DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización de esta invención, el Proceso 1 se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo,

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éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

Otra realización de los procesos de esta invención se refiere a cualquiera de las anteriores realizaciones del procesos en donde la mezcla de (1)(a) y (1)(b) reacciona con (2)(a).

En consecuencia, en otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una

trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

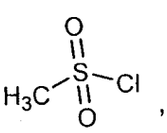
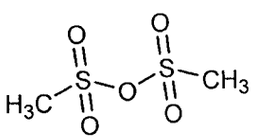
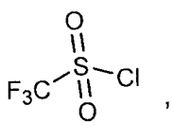
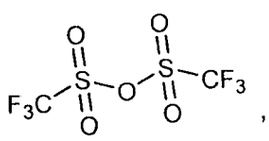
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

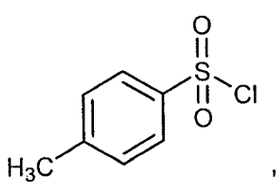
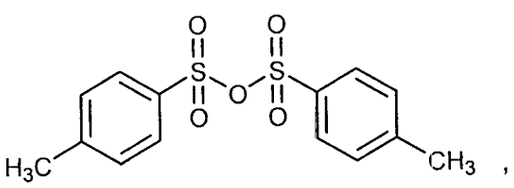
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y

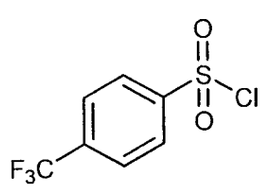
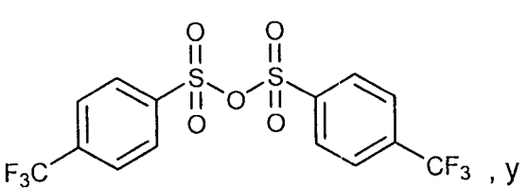
(vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro.

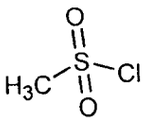
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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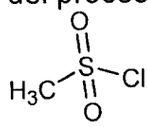

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and

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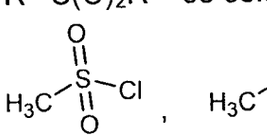
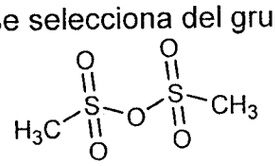
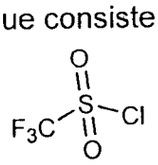
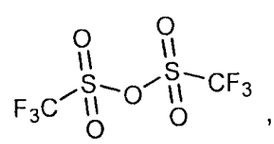
con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:

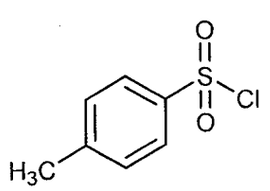
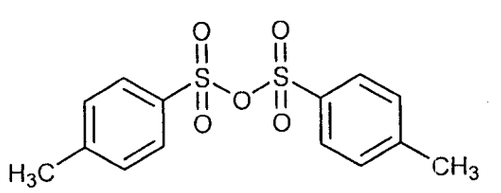


Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:

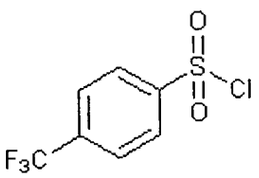


En consecuencia, en otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:

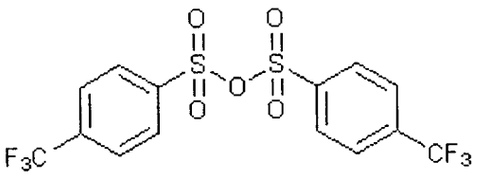

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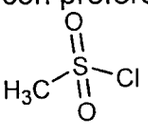


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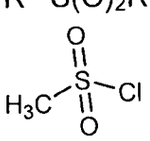
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con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:

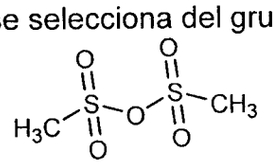


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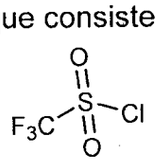
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:



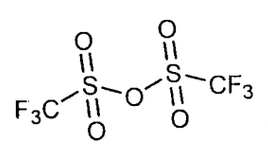
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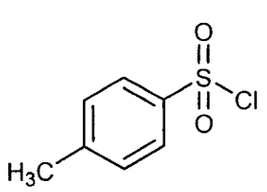
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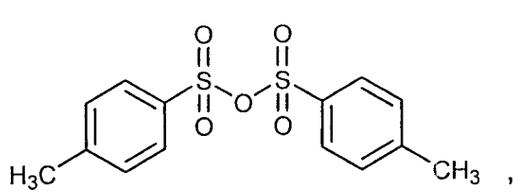
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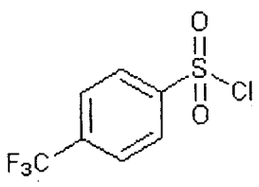
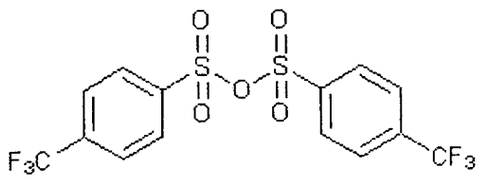
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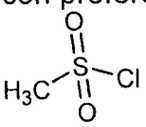
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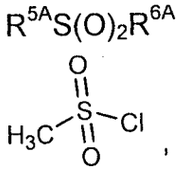
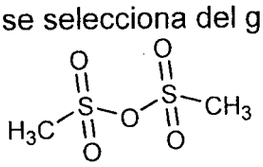
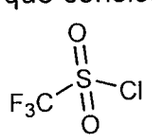
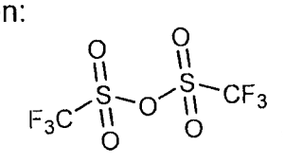
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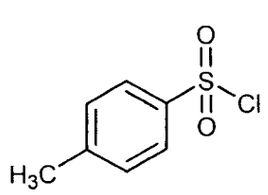
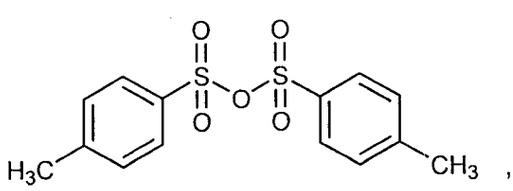

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con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:

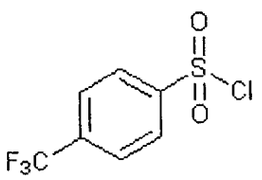
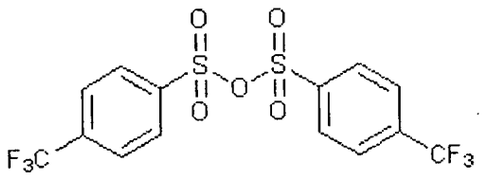


En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ y se selecciona del grupo que consiste en:


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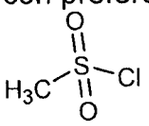

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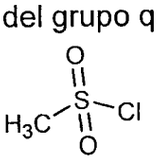
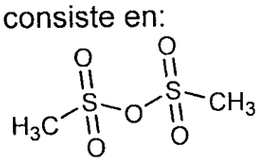
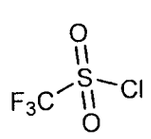
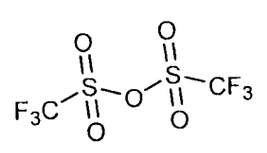



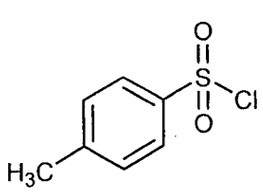
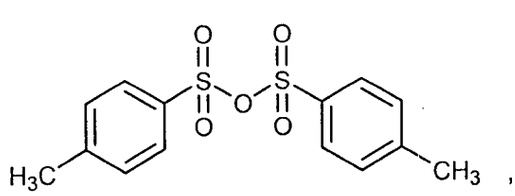
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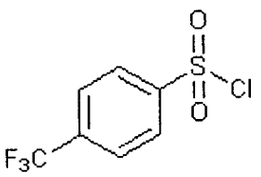
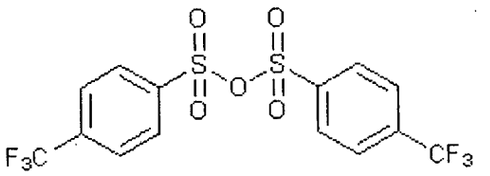
con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



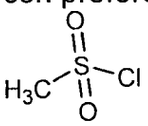
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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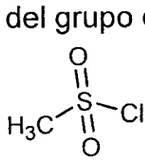
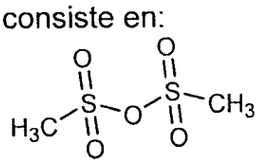
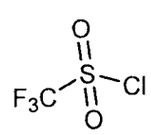
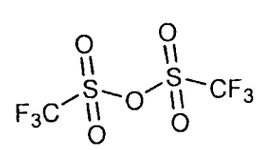

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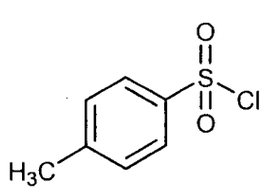
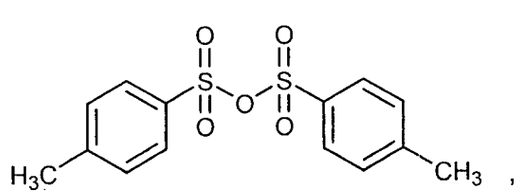

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con preferencia, el resto $R^{5A}S(O)2R^{6A}$ es cloruro de mesilo:

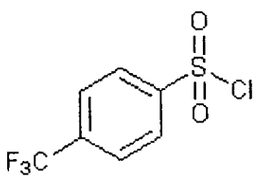


En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:

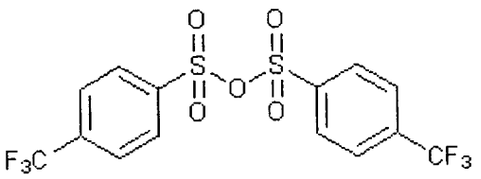

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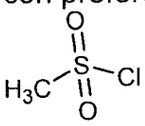


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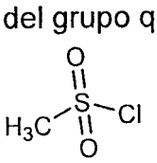
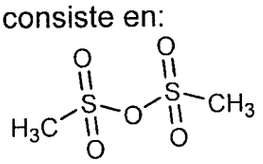
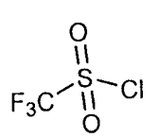
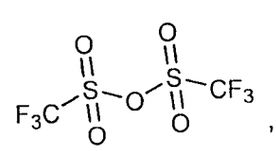


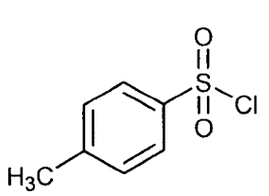
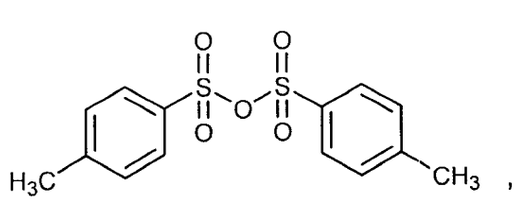
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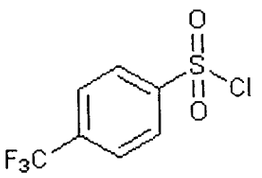
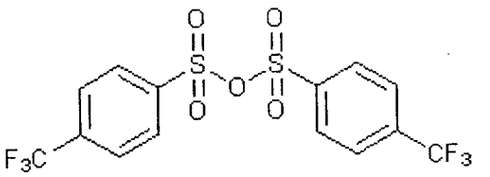
con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



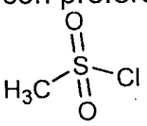
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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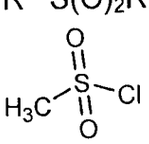
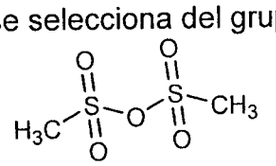
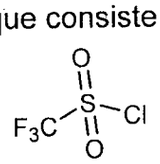
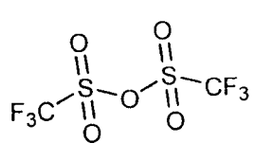

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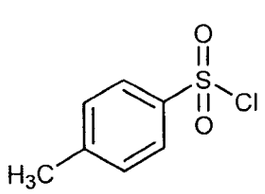
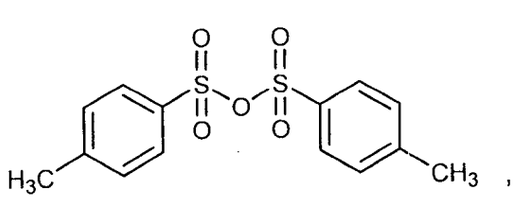

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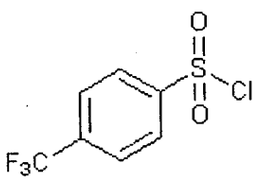
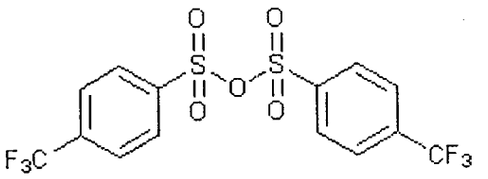
con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



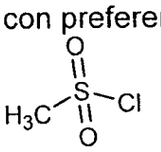
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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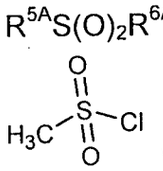
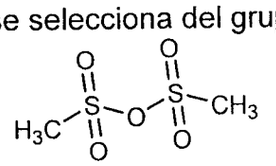
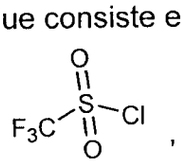
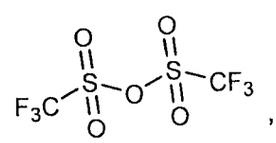

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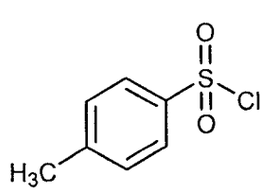
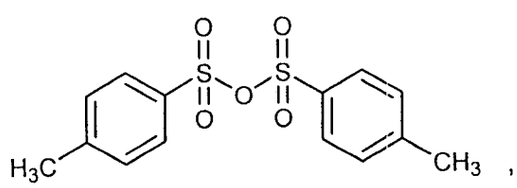

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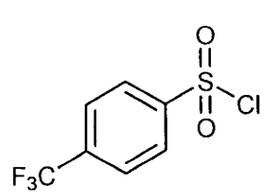
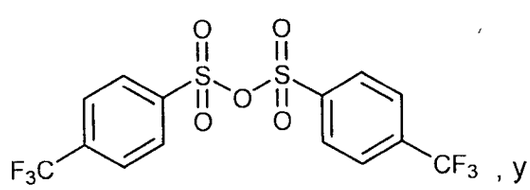
con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:

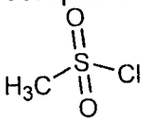

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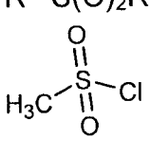

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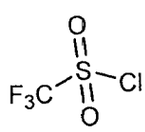
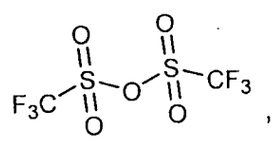
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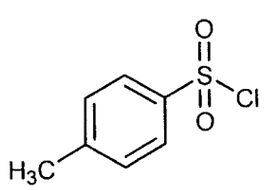
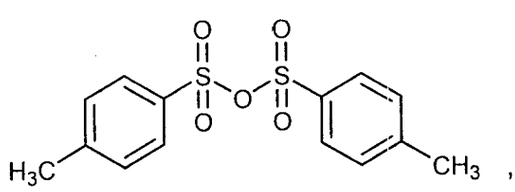
con preferencia, el $R^{5A}S(O)_2R^{6A}$ resto es cloruro de mesilo:



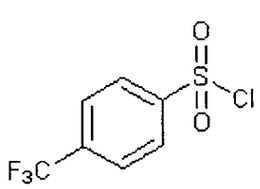
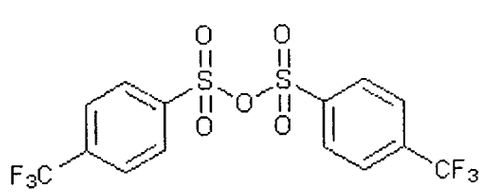
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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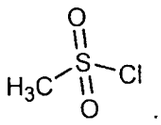
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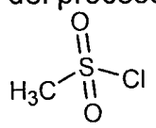
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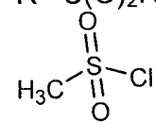
con preferencia, el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde el resto $R^{5A}S(O)_2R^{6A}$ es cloruro de mesilo:



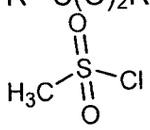
En consecuencia, en otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



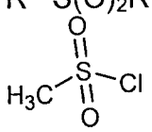
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y

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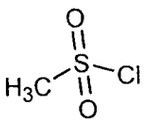
(vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



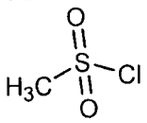
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



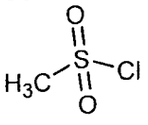
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es

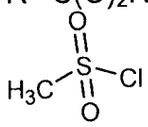


En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es:

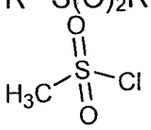


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En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



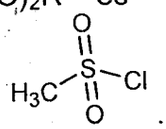
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



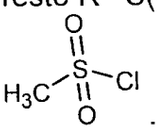
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de

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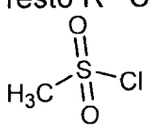
aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia el solvente orgánico es un haloalcano, y con más preferencia el solvente orgánico es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



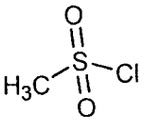
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



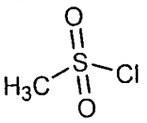
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una

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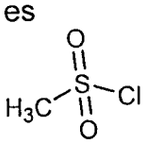
trialquilamina, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



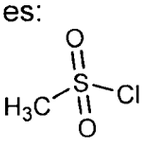
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) (con preferencia es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



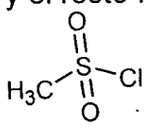
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es TEA, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es:



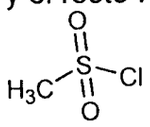
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de

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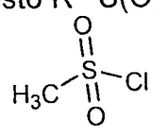
aproximadamente –40°C a aproximadamente 40°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, y el solvente orgánico (paso (1)(c) es diclorometano anhidro, y el resto $R^{5A}S(O)_2R^{6A}$ es



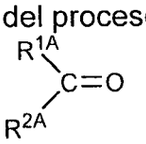
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso descriptas anteriormente en donde uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H.

Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior descriptas anteriormente en donde uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, en donde dicho arilo sustituido está sustituido con uno o más (por ej., 1 a 3, 1 a 2 o 1) sustituyentes

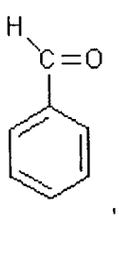
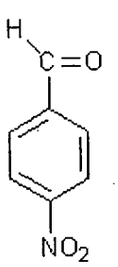
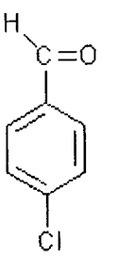
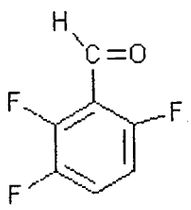
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seleccionados de modo independiente del grupo que consiste en: $-NO_2$ y halo (por ej., Cl y F).

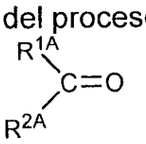
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior descriptas anteriormente en donde



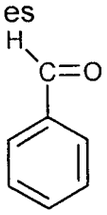
se selecciona del grupo que consiste en:




y


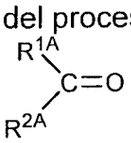
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior descriptas anteriormente en donde



es

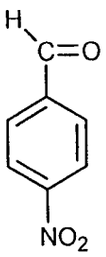


Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior descriptas anteriormente en donde

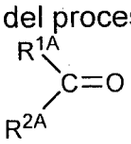


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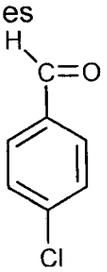
513



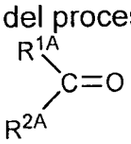
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior descriptas anteriormente en donde



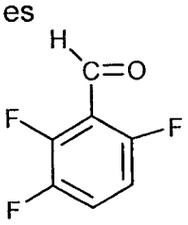
es



Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior descriptas anteriormente en donde



es



Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde R^{3A} y R^{4A} are cada uno se selecciona de modo independiente del grupo que consiste en: $-C(O)OR^{12A}$.

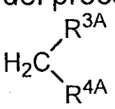
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$.

514

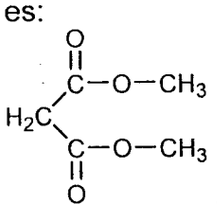
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C_4.

Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es metilo o etilo.

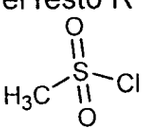
Otra realización del Proceso 1 se refiere a cualquiera de las realizaciones del proceso anterior en donde



es:

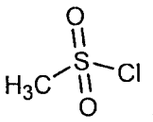


En consecuencia, en Otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es



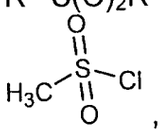
uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es



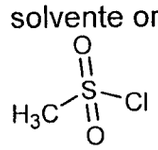
uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una trialquilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es



uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

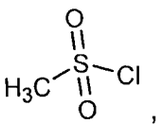
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es



uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

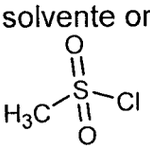
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es

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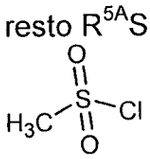
uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es TEA, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es:



uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es diisopropiletilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es

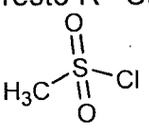


uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es

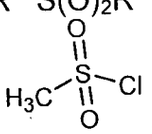
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diisopropiletilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es



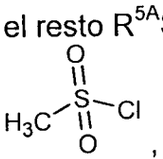
uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es

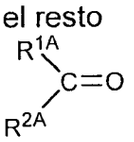


uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo (por ej., fenilo), y arilo sustituido (por ej., fenilo sustituido), y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto $-C(O)OR^{12A}$, y en donde R^{12A} es un alquilo C_1 a C4.

En consecuencia, en Otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es una trialquilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es

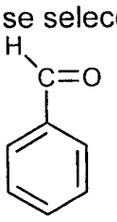
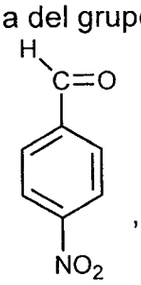
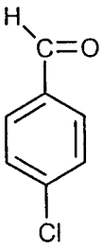
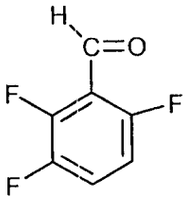


el resto

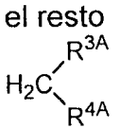


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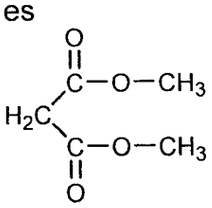
se selecciona del grupo que consiste en:


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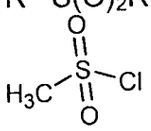
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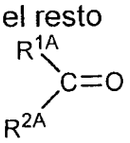
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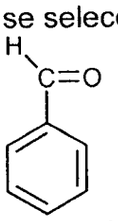
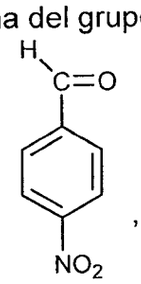
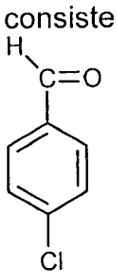
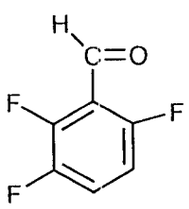
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es


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el resto

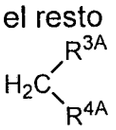


se selecciona del grupo que consiste en:

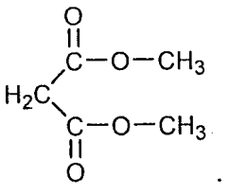

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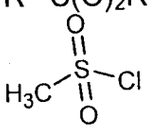
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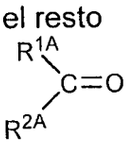


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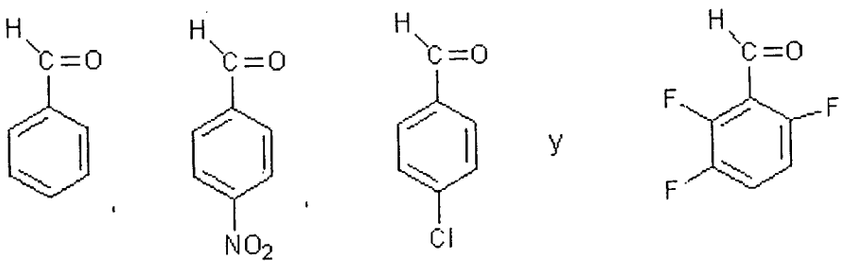


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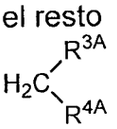
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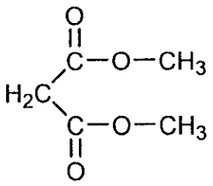
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el resto

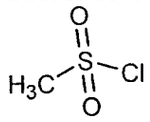


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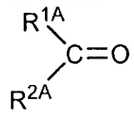


En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, la amina básica es TEA, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es

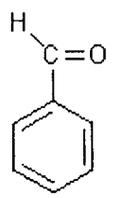


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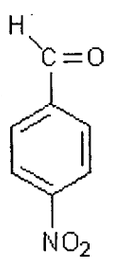
el resto



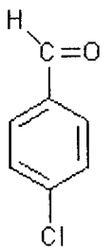
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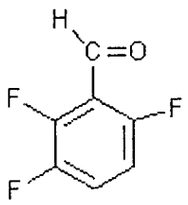
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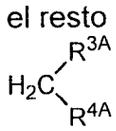


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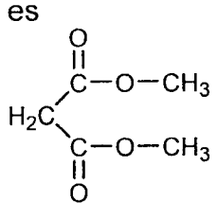


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el resto

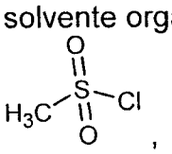


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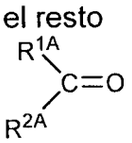


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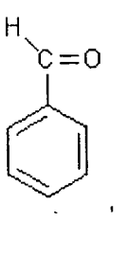
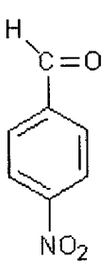
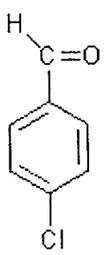
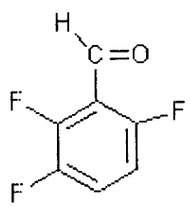
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es TEA, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es



el resto

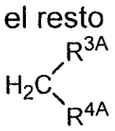


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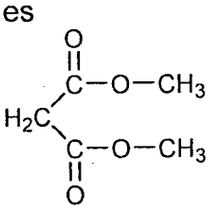



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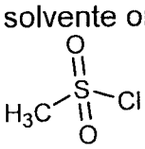
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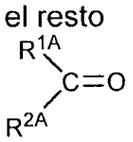


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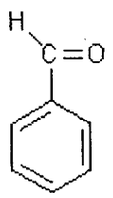
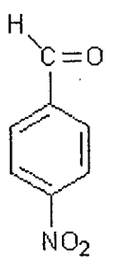
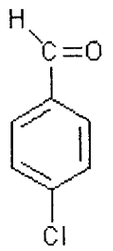
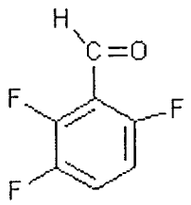


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el resto

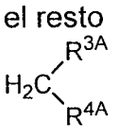


se selecciona del grupo que consiste en:

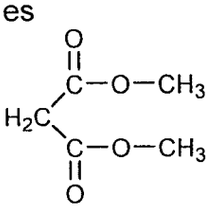



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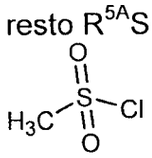
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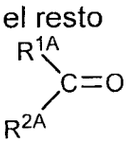


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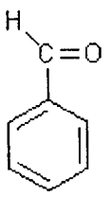
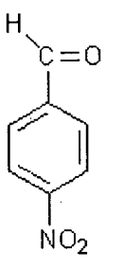
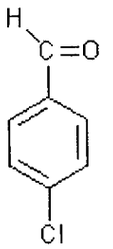
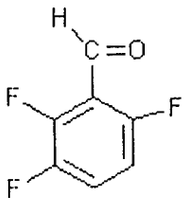
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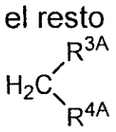


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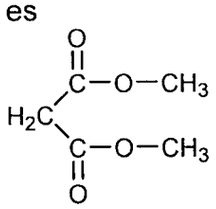
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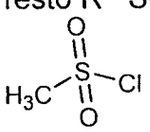
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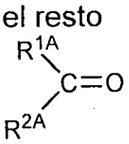
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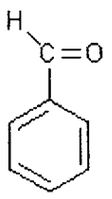
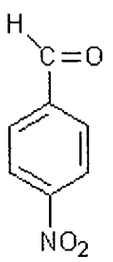
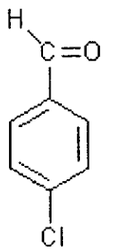
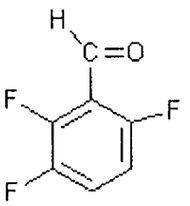

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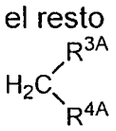


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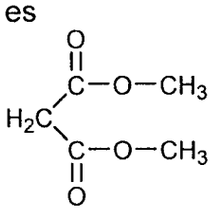
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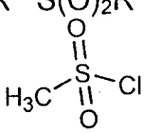
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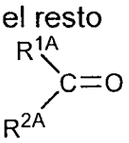
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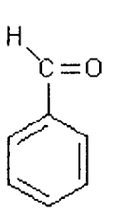
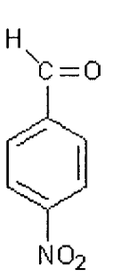
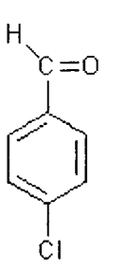
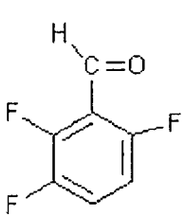
En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es diisopropiletilamina, el solvente orgánico (paso (1)(c) es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ es


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el resto

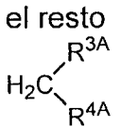


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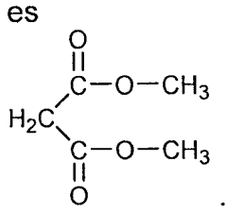

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En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con una amina básica (por ej., una trialquilamina definida anteriormente) y el compuesto $R^{7A}C(O)R^{8A}$.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con una amina básica (por ej., una trialquilamina definida anteriormente) y el compuesto $R^{7A}C(O)R^{8A}$, en donde la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y con preferencia aproximadamente 0°C a aproximadamente 30°C, y con más preferencia aproximadamente 0°C a aproximadamente 10°C.

En otra realización del Proceso 1, la mezcla de (1)(a) y (1)(b) reacciona con una amina básica (por ej., una trialquilamina definida anteriormente) y el compuesto $R^{7A}C(O)R^{8A}$, en donde la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y con preferencia aproximadamente 0°C a aproximadamente 30°C, y con más preferencia aproximadamente 0°C a aproximadamente 10°C, y en donde el solvente orgánico (1)(c) (con preferencia anhidro) se selecciona del grupo que consiste en (i) haloalcanos (tales como, por ejemplo, diclorometano, dicloroetano (por ej., $CH_2Cl–CH_2Cl$), triclorometano, y tetraclorometano), (ii) arilhaluros (tales como, por ejemplo, clorobenceno), (iii) DMSO, (iv) DMF, (v) THF, (vi) éteres (tales

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como, por ejemplo, éter dietílico), y (vii) sus mezclas, y con preferencia un haloalcano, y con más preferencia diclorometano anhidro.

En el Proceso 1 y las realizaciones del Proceso 1 descriptos anteriormente, la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{3A}CH_2R^{4A}$ es usualmente aproximadamente 1:0.8 a aproximadamente 1:1.2, y con preferencia aproximadamente 1:1.

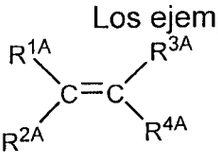
En el Proceso 1 y las realizaciones del Proceso 1 descriptos anteriormente, la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{5A}S(O)_2R^{6A}$ es usualmente aproximadamente 1:1 a aproximadamente 1:4, y con preferencia aproximadamente 1:1.

En el Proceso 1 y las realizaciones del Proceso 1 descriptos anteriormente, la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{7A}C(O)R^{8A}$ es usualmente aproximadamente 1:1 a aproximadamente 1:4, y con preferencia aproximadamente 1:1.

En el Proceso 1 y las realizaciones del Proceso 1 descriptos anteriormente, la relación molar de $R^{5A}S(O)_2R^{6A}$ a la amina básica (por ej., $NR^{9A}R^{10A}R^{11A}$, tal como, por ejemplo, una trialquilamina, tal como, por ejemplo, trietilamina o diisopropiletilamina) es usualmente aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

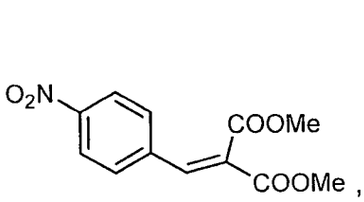
En el Proceso 1 y las realizaciones del Proceso 1 descriptos anteriormente, la relación molar de $R^{7A}C(O)R^{8A}$ a la amina básica (por ej., $NR^{9A}R^{10A}R^{11A}$, tales como, por ejemplo, una trialquilamina, tal como, por ejemplo, trietilamina o diisopropiletilamina) es usualmente aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

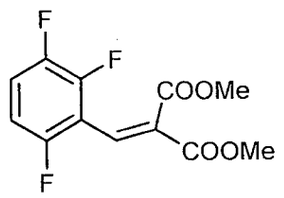
Los ejemplos del compuesto de la fórmula:

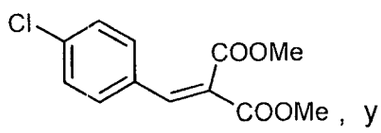


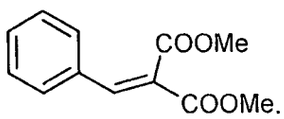
producidos por los procesos de esta invención incluyen, pero sin limitación:

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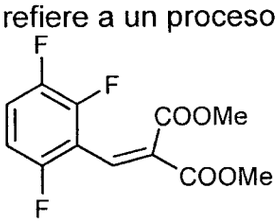


,


,


, y


En consecuencia, otra realización de los procesos de esta invención se refiere a un proceso para preparación un compuesto de la fórmula:



dicho proceso que comprende hacer reaccionar:

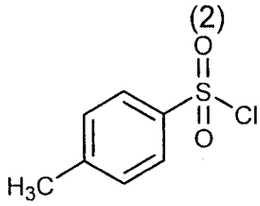
(1) una mezcla que comprende:

(a) 2,3,5–triflorobenzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano (con preferencia anhidro); con

(2) cloruro de mesilo, es decir,



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y con preferencia aproximadamente 0°C a aproximadamente 30°C, y con más preferencia aproximadamente 0°C a aproximadamente 10°C;

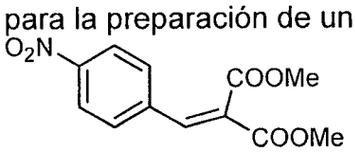
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la relación molar de 2,3,5–triflorobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0.8 a aproximadamente 1:1.2, y con preferencia 1:1;

la relación molar de 2,3,5–triflorobenzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4, y con preferencia 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

Otra realización de los procesos de esta invención se refiere a un proceso para la preparación de un compuesto de la fórmula:



dicho proceso que comprende hacer reaccionar:

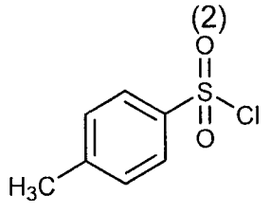
(1) una mezcla que comprende:

(a) 4–nitrobenzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano (con preferencia anhidro); con

(2) cloruro de mesilo, es decir,



;

en donde:

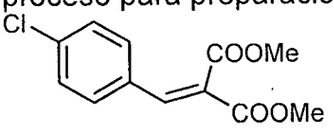
dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y con preferencia aproximadamente 0°C a aproximadamente 30°C, y con más preferencia aproximadamente 0°C a aproximadamente 10°C;

la relación molar de 4–nitrobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0.8 a aproximadamente 1:1.2, y con preferencia 1:1;

la relación molar de 4–nitrobenzaldehído to cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4, y con preferencia 1:1; y

la relación molar de cloruro de mesilo to TEA es aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

Otra realización de los procesos de esta invención es directed to un proceso para preparación un compuesto de la fórmula:



dicho process que comprende reacting:

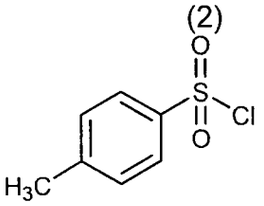
(1) una mezcla que comprende:

(a) 4–clorobenzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano (con preferencia anhidro); with

(2) cloruro de mesilo, es decir,



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y con preferencia aproximadamente 0°C a aproximadamente 30°C, y con más preferencia aproximadamente 0°C a aproximadamente 10°C;

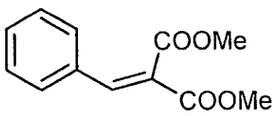
la relación molar de 4–clorobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0.8 a aproximadamente 1:1.2, y con preferencia 1:1;

la relación molar de 4–clorobenzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4, y con preferencia 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

Otra realización de los procesos de esta invención se refiere a un proceso para la preparación de un compuesto de la fórmula:

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dicho proceso que comprende hacer reaccionar:

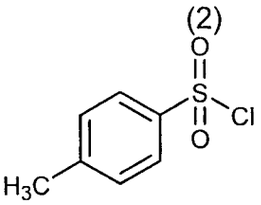
(1) una mezcla que comprende:

(a) benzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano (con preferencia anhidro); con

(2) cloruro de mesilo, es decir,



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C, y con preferencia aproximadamente 0°C a aproximadamente 30°C, y con más preferencia, aproximadamente 0°C a aproximadamente 10°C;

la relación molar de benzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0.8 a aproximadamente 1:1.2, y con preferencia 1:1;

la relación molar de benzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4, y con preferencia 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

Los procesos de esta invención descriptos anteriormente generalmente se llevan a cabo en una atmósfera inerte, tal como, por ejemplo N_2. En consecuencia, por ejemplo la mezcla del compuesto $R^{1A}C(O)R^{2A}$, el compuesto $R^{3A}CH_2R^{4A}$ (por ej., éter dimetílico del ácido malónico) y el solvente orgánico (con preferencia anhidro, por ej., diclorometano anhidro) están bajo N_2, y luego se agrega la amina básica (por ej., TEA), y luego se agrega el compuesto

$R^{5A}S(O)_2R^{6A}$ (por ej., cloruro de mesilo, es decir, cloruro de metansulfonilo). La mezcla de $R^{1A}C(O)R^{2A}$ y $R^{3A}CH_2R^{4A}$ está usualmente a una temperatura baja, tal como, por ejemplo, la temperatura resultante de la mezcla que están en un baño de hielo (por ej., 5°C). En consecuencia, otra realización del Proceso 1 se refiere a cualquiera de las realizaciones descriptas anteriormente en donde la reacción se lleva a cabo bajo una atmósfera inerte, con preferencia N_2.

El compuesto deseado de los procesos de esta invención se puede aislar por técnicas bien conocidas en el arte. Por ejemplo, se puede agregar agua lo que origina una fase orgánica y una acuosa. Las fases se pueden extraer con un solvente orgánico adecuado, con preferencia el solvente orgánico usado en el proceso mismo (por ej., diclorometano). La fase orgánicas se puede lavar con agua, y luego la fase orgánica resultante se puede secar con un agente de secado adecuado, tal como, por ejemplo, sulfato de sodio anhidro. La fase orgánica seca luego se puede concentrar para producir el producto deseado (usualmente como un sólido).

EJEMPLOS

La invención descripta en la presente memoria se ejemplifica con las siguientes preparaciones y ejemplos, que no deben interpretarse como una limitación del alcance de la descripción. Las vías mecanísticas alternativas y las estructuras análogas serán evidentes para los expertos en el arte.

Cuando se presentan datos de RMN, los espectros ^1H se obtuvieron en un Varian VXR–200 (200 MHz, ^1H), Varian Gemini–300 (300 MHz) o XL–400 (400 MHz) y se informan como ppm de campo bajo de Me_4Si con número de protones, multiplicidades y constantes de acoplamiento en Hertz indicados entre paréntesis.

Cuando se presentan datos de LC/MS, los análisis se realizan usando un espectrómetro de masas Applied Biosystems API–100 y columna Shimadzu SCL–10A LC: Altech platino C_{18}, 3 micrones, 33mm x 7mm ID; flujo de gradiente: 0 min

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– 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7,5 min – 10% CH_3CN, 9 min – detención. Se brindan el tiempo de retención y el ion original observado.

Los siguientes solventes, reactivos y condiciones se pueden mencionar por sus abreviaturas entre paréntesis:

Acetilo (Ac), es decir, $CH_3C(O)$–

Butilo (Bu)

Ciclopropilo (Pr–c)

Dicloroetano (DCE)

Diclorometano (DCM)

Éter dietílico (Et_2O)

Hidruro de diisobutilaluminio (DIBAL–H)

Dimetil formamida (DMF)

Etanol (EtOH)

Etilo (Et)

Acetato de etilo (EtOAc)

Espectrometría de masa de alta resolución (HRMS)

Hidruro de aluminio y litio (LAH)

Diisopropilamida de litio (LDA)

Cromatografía líquida/espectrometría de masa (LCMS)

Ácido m–cloroperoxibenzoico (mCPBA)

Mesilo (Ms), es decir, $–S(O)_2CH_3$

Metanol (MeOH)

Metilo (Me)

Espectrometría de resonancia magnética nuclear (RMN)

Cromatografía preparativa en capa delgada (PTLC)

Piridina (Pyr)

Temperatura ambiente (RT)

Ter–butildimetilsililo (TBS)

Fluoruro de tetrabutil amonio (TBAF)

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Tetrahidrofurano (THF)

Ácido trifluoroacético (TFA)

Trimetilsililo (TMS)

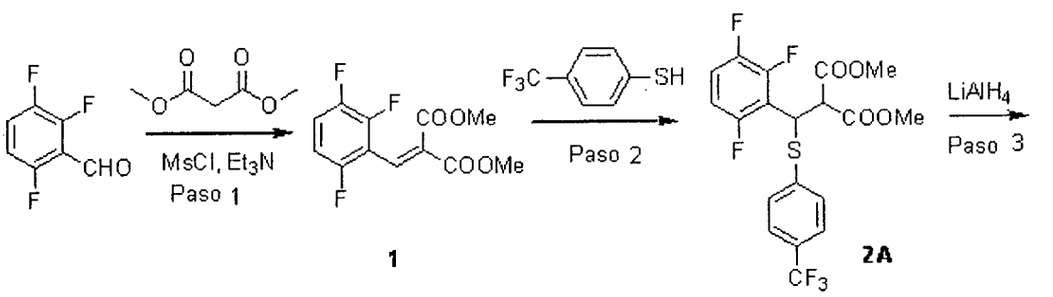
Cloruro de trimetilsililo (TMSCl)

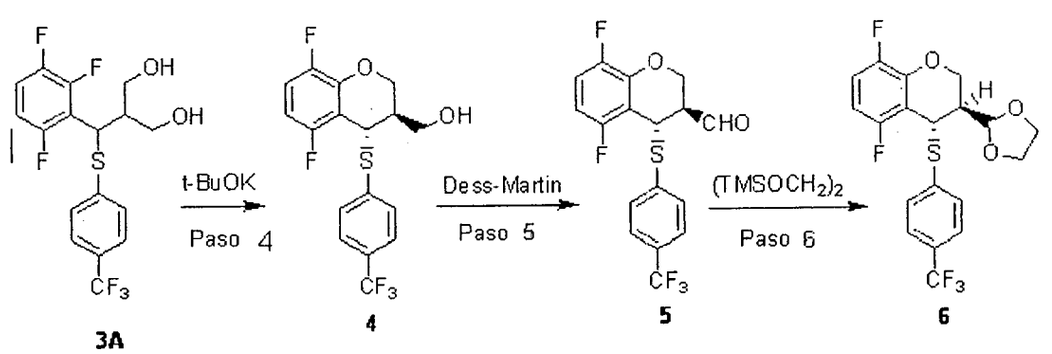
Trietilamina (NEt_3 o Et_3N o TEA)

Los compuestos de fórmula (I) se pueden preparar por diversos métodos bien conocidos en el arte, y por los métodos que se describen a continuación.

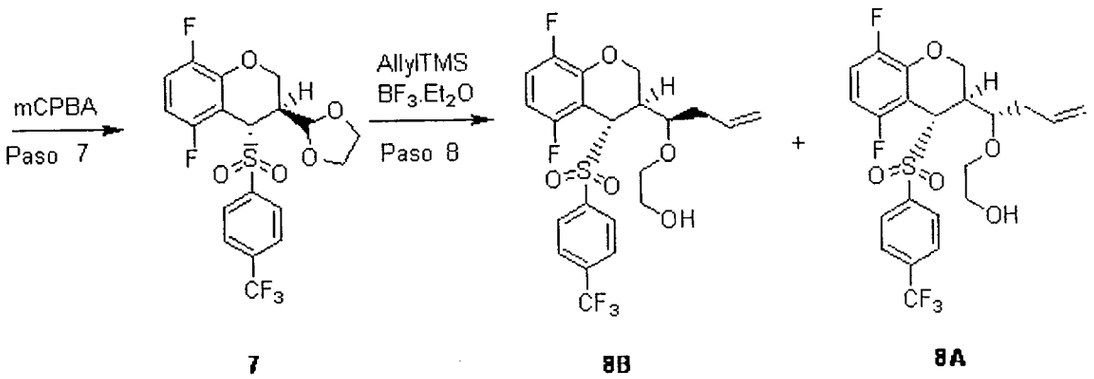
Los compuestos de fórmula (I) se pueden preparar de acuerdo con los procedimientos descriptos en los Esquemas 1 y 2.

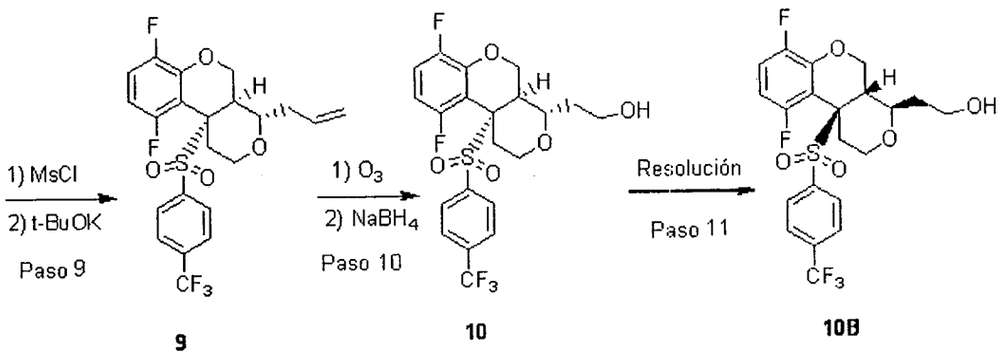
Esquema 1

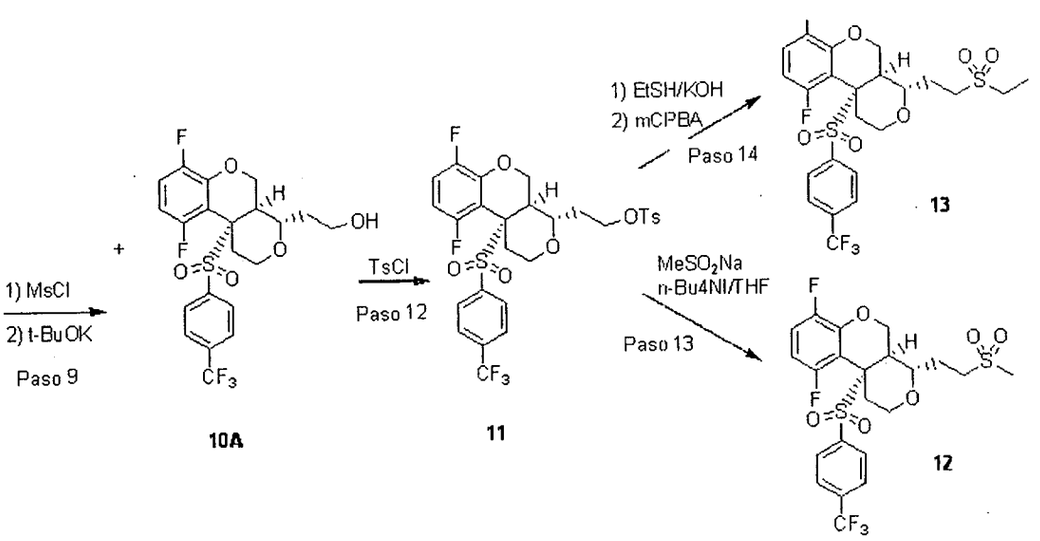




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mCPBA
Paso 7
AllylTMS
$BF_3.Et_2O$
Paso 8
7
8B
8A


1) MsCl
2) t-BuOK
Paso 9
1) O_3
2) $NaBH_4$
Paso 10
Resolución
Paso 11
9
10
10B


1) MsCl
2) t-BuOK
Paso 9
TsCl
Paso 12
1) EtSH/KOH
2) mCPBA
Paso 14
$MeSO_2Na$
n-Bu4NI/THF
Paso 13
10A
11
13
12

Paso 1

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A una solución agitada de 64 g (400 mmol) de 2,3,6–trifluorobenzoaldehído y 53 g (400 mmol) de malonato de dimetilo en 600 ml de diclorometano se agregaron 81 g (800 mmol) de trietilamina a 0°C. Se agregó una solución de 69 g (600 mmol) de cloruro de metansulfonilo en 200 ml de diclorometano durante un período de 1,5 h, con la temperatura mantenida a 0°C. Se agregaron 20 g adicionales (200 mmol) de trietilamina, seguido por la adición de una solución de 23 g (200 mmol) de cloruro de metansulfonilo en 50 ml de diclorometano. La reacción se inactivó con 800 ml de agua, se extrajo con tres porciones de 500 de diclorometano. Los extractos orgánicos combinados se lavaron con 200 ml de bicarbonato de sodio saturado y se concentraron para dar 128 g del compuesto bruto **1**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,70 (s, 1 H), 7,20 (m, 2 H), 6,90 (m, 1 H), 3,87 (s, 3 H), 3,79 (s, 3 H). MS: Calculado para $C_{12}H_{10}F_3O_4$ (MH^+), m/z = 275,1; experimental 275,2. Tiempo de retención: 4,00 min.

Paso 2

A una solución de 124 g (400 mmol) del compuesto **1** y 71,3 g (400 mmol) de 4–(trifluorometil)tiofenol en 1500 ml de tetrahidrofurano se agregaron 55,2 g (400 mmol) de carbonato de potasio. La mezcla se agitó a temperatura ambiente durante 18 h. Se agregaron 29 g adicionales (210 mmol) de carbonato de potasio y 12 g (67 mmol) de 4–trifluorometil tiofenol. Después de 2 h, se inactivó con 800 ml de agua, se extrajo con tres porciones de 600 ml de acetato de etilo. Los extractos orgánicos combinados se concentraron y filtraron. El filtrado se concentró para dar 205 g del compuesto bruto **2A**. ^{1}H RMN ($CDCl_3$ 400 MHz δ 7,50 (m, 4 H), 7,04 (m, 1 H), 6,78 (s, 1 H), 5,22 (d, J = 12 Hz, 1 H), 4,36 (d, J = 12 Hz, 1 H), 3,81 (s, 3 H), 3,66 (s, 1 H). MS: Calculado para $C_{19}H_{15}F_6O_4S$ (MH^+), m/z = 453,1; experimental 453,2. Tiempo de retención: 5,11 min.

Paso 3

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A una suspensión agitada de 32 g (842 mmol) de hidruro de aluminio y litio en 1000 ml de tetrahidrofurano se agregó a 0°C una solución de 200 g (400 mmol) del compuesto **2A** en 500 ml de tetrahidrofurano durante un período de 2 h. Se agitó a temperatura ambiente durante 2 h y se inactivó con 100 ml de agua (enfriado con baño de agua e hielo). Después de la adición de 1500 ml de HCl 6N, se extrajo con cinco por ciones de 600 ml de diclorometano. Los extractos orgánicos combinados se concentraron, y el residuo se purificó por cromatografía eluyendo con un gradiente de 10% a 50% de acetato de etilo en hexanos para dar 55 g del compuesto **3A**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,50 (m, 4 H), 7,03 (m, 1H), 6,78 (m, 1 H), 5,03 (d, J = 12 Hz, 1 H), 4,35 (m, 1 H), 4,20 (dd, J = 11, 2,4 Hz, 1 H), 3,87 (dd, J = 11, 2.,4 Hz, 1 H), 3,50 (dd, J = 11, 4,8 Hz, 1 H), 2,46 (m, 1 H), 2,20 (br, 2 H). MS: Calculado para $C_{17}H_{15}F_6O_2S$ (MH+), m/z = 397,1; experimental 397,2. Tiempo de retención: 4,31 min.

Paso 4

A una solución agitada de 55 g (139 mmol) del compuesto **3A** en 600 ml de tetrahidrofurano enfriado a 10°C se agregó gota a gota una solución de 20 g (179 mmol) de ter-butóxido de potasio en 200 ml de tetrahidrofurano durante un período de 1 h. Se agitó a temperatura ambiente durante adicional 1 h y se inactivó con 500 ml de agua y 80 ml de HCl 1 N. Se separó, la fase acuosa se extrajo con tres porciones de 400 ml de diclorometano. Los extractos orgánicos combinados se concentraron, y el residuo se purificó por cromatografía eluyendo con un gradiente de 15% a 20% de acetato de etilo en hexanos para dar 41 g del compuesto **4**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,58 (s, 4 H), 6,98 (m, 1H), 6,60 (m, 1 H), 4,75 (s, 1 H), 4,63 (dd, J = 12, 2,4 Hz, 1 H), 4,10 (dd, J = 10, 2,4 Hz, 1 H), 3,75 (m, 1 H), 3,55 (m, 1 H), 2,33 (m, 1 H). MS: Calculado para $C_{17}H_{14}F_5O_2S$ (MH^+), m/z = 377,1; experimental 377,2. Tiempo de retención: 4,81 min.

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Paso 5

A una solución agitada de 10 g (26,6 mmol) del compuesto **4** en 250 ml de diclorometano se agregaron 14,2 g (33,5 mmol) de peryodinano de Dess–Martin. La mezcla se agitó a temperatura ambiente durante 2 h y se diluyó con 400 ml de diclorometano. Se agitó con 400 ml de bicarbonato de sodio saturado y 200 ml de solución de tiosulfato de sodio 10% y se separó. Este procedimiento se repitió dos veces con 200 ml de bicarbonato de sodio saturado y 200 ml de solución de tiosulfato de sodio 10%. La fase orgánica se secó con sulfato de sodio y se filtró. El filtrado se concentró para dar 10,1 g de crude aldehído **5**. ^{1}H RMN ($CDCl_3$, 400 MHz) δ 9,74 (s, 1 H), 7,60 (m, 4 H), 6,97 (m, 1 H), 6,64 (m, 1 H), 5,08 (s, 1 H), 4,95 (d, J = 12 Hz, 1 H), 4,75 (dd, J = 12, 2.,4 Hz, 1 H), 2,87 (s, 1 H). MS: Calculado para $C_{17}H_{12}F_5O_2S$ (MH^+), m/z = 375,1; experimental 375,2. Tiempo de retención: 5,00 min.

Paso 6

A una solución agitada de 10 g (26,5 mmol) del compuesto **5** en 150 ml de diclorometano se agregaron 7,14 g (33,5 mmol) de 1,2–bis(trimetilsiloxi)etano y 0,69 g (3,1 mmol) de trifluorometansulfonato de trimetilsililo a –78°C. Después de 30 min, se calentó a temperatura ambiente y se agitó durante 30 min. La reacción se inactivó con 200 ml de bicarbonato de sodio saturado y se extrajo con tres porciones de 200 ml porciones de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 2% to 30% de acetato de etilo en hexanos para dar 9,4 g del compuesto **6**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,60 (m, 4 H), 7,00 (m, 1 H), 6,57 (m, 1 H), 4,90 (s, 1H), 4,79 (d, J = 7,6 Hz, 1 H), 4,60 (m, 1 H), 3,80–4,0 (m, 5 H), 2,18 (m, 1 H). MS: Calculado para $C_{19}H_{16}F_5O_2S$ (MH^+), m/z = 419,1; experimental 419,2. Tiempo de retención: 5,20 min.

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Paso 7

A una solución agitada de 9,8 g (23,4 mmol) del compuesto **6** en 250 ml de diclorometano se agregaron 14,4 g (58,5 mmol) de ácido 3–cloroperoxibenzoico a 0°C. La mezcla se agitó a temperatura ambiente toda la noche. Se diluyó con 400 ml de diclorometano y se inactivó a 0°C con 200 ml de bicarbonato de sodio saturado y 200 ml de tiosulfato de sodio 10%. La fase de diclorometano se lavó con 100 ml de NaOH 1 N, y se secó con sulfato de sodio. Se filtró, se concentró y el residuo se purificó por cromatografía eluyendo con un gradiente de 5% a 45% de acetato de etilo en hexanos para dar 10,1 g del compuesto **7**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,96 (d, J = 8,0 Hz, 2 H), 7,81 (d, J = 8,0 Hz, 2 H), 7,03 (m, 1 H), 6,39 (m, 1 H), 4,89 (dd, J = 12, 4 Hz, 1 H), 4,67 (m, 2 H), 4,64 (dd, J = 6,4, 1,6 Hz, 1 H), 3,8 – 4,0 (m, 4 H), 2,92 (m, 1 H). MS: Calculado para $C_{19}H_{16}F_5O_5S$ (MH^+), m/z = 451,1; experimental 451,2. Tiempo de retención: 4,43 min.

Paso 8

Una solución de 10,0 g (22,2 mmol) del compuesto **7**, 12,7 g (111 mmol) de aliltrimetilsilano y 15,8 g (111 mmol) de eterato de trifluoruro de boro en 120 ml de diclorometano se agitó a reflujo durante 1 día. Se agregaron 5,0 g adicionales (44 mmol) de aliltrimetilsilano y 6,2 g (44 mmol) de eterato de trifluoruro de boro y la mezcla se agitó a reflujo durante otro día. La reacción se inactivó con 200 ml de bicarbonato de sodio saturado, y se extrajo con tres porciones de 150 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 10% a 60% de acetato de etilo en hexanos para dar 2,70 g del compuesto **8A** y 5,3 g de **8B**. **8A**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,97 (d, J = 8,4 Hz, 2 H), 7,82 (d, J = 8,4 Hz, 2 H), 7,03 (m, 1 H), 6,41 (m, 1 H), 5,80 (m, 1 H), 5,18 (d, J = 12,4 Hz, 1 H), 4,97 (s, 1 H), 4,92 (d, J = 9,6 Hz, 1 H), 4,67 (m, 1 H), 4,43 (d, J = 12,4 Hz, 1 H), 3,56 (m, 3 H), 3,24 (m, 1 H), 3,13 (m, 1 H), 2,97 (m, 1 H), 2,57 (m, 1 H), 2,36 (m, 1 H). MS:

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Calculado para $C_{22}H_{22}F_5O_5S$ (MH^+), m/z = 493,1; experimental 493,3. Tiempo de retención: 4,33 min. **8B**: ^1H RMN ($CDCl_3$ 400 MHz) δ 7,95 (d, J = 8,0 Hz, 2 H), 7,82 (d, J = 8,0 Hz, 2 H), 7,05 (m, 1 H), 6,45 (m, 1 H), 5,70 (m, 1 H), 5,0 (m, 2 H), 4,86 (d, J = 5,6 Hz, 1 H), 4,67 (d, J = 11,6 Hz, 1 H), 4,53 (s, 1 H), 3,61 (m, 3 H), 3,47 (m, 1 H), 3,29 (m, 1 H), 2,94 (m, 1 H), 2,37 (m, 1 H), 2,06 (m, 1 H). MS: Calculado para $C_{22}H_{22}F_5O_5S$ (MH^+), m/z = 493,1; experimental 493,3. Tiempo de retención: 4,21 min.

S40

Paso 9

A una solución de 2,68 g (5,44 mmol) del compuesto **8A** en 40 ml de diclorometano se agregaron 1,0 g (10 mmol) de trietilamina y 1,0 g (8,7 mmol) de cloruro de metansulfonilo. La mezcla se agitó a temperatura ambiente durante 1 h. Se inactivó con 80 ml de bicarbonato de sodio saturado y se extrajo con dos porciones de 80 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se disolvió en 100 ml de tetrahidrofurano. A esta solución se agregaron 10 ml (10 mmol) de ter-butóxido de potasio 1 N en THF. La mezcla se agitó a temperatura ambiente durante 15 min., se inactivó con 100 ml de agua y se extrajo con dos porciones de 150 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 2% a 30% de acetato de etilo en hexanos para dar 2,46 g del compuesto **9**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,85 (d, J = 8,4 Hz, 2 H), 7,80 (d, J = 8,4 Hz, 2 H), 7,10 (m, 1 H), 6,46 (m, 1 H), 5,60 (m, 1 H), 5,15 (m, 3 H), 4,47 (d, J = 12,4 Hz, 1 H), 3,93 (m, 1 H), 3,37 (m, 1 H), 3,16 (t, J = 11,6 Hz, 1 H), 2,60 (m, 2 H), 2,40 (m, 3 H). MS: Calculado para $C_{22}H_{20}F_5O_4S$ (MH^+), m/z = 475,1; experimental 475,3. Tiempo de retención: 4,85 min.

Paso 10

A una solución agitada de 6,01 g (12,7 mmol) del compuesto **9** en 125 ml de diclorometano a –78°C se burbujeó con O_3 hasta el color azul sostenido. Se burbujeó con N_2 para eliminar el exceso de O_3. A esta solución se agregaron 3,0 g (75 mmol) de borohidruro de sodio y 25 ml de metanol. La mezcla se agitó a temperatura ambiente toda la noche. Tras la adición de 0,7 g (2,67 mmol) de trifenilfosfina, la reacción se agitó durante 1 día y se diluyó con 200 ml de agua. Se extrajo con tres porciones de 150 ml de diclorometano y los extractos combinados se secaron con sulfato de sodio. Los extractos se filtraron, concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente

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de 5% a 50% de acetato de etilo en hexanos para dar 5,5 g del compuesto **10**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,86 (d, J = 8,4 Hz, 2 H), 7,81 (d, J = 8,4 Hz, 2 H), 7,10 (m, 1 H), 6,40 (m, 1 H), 5,16 (d, J = 12,4 Hz, 1 H), 4,46 (d, J = 12,8 Hz, 1 H), 3,94 (m, 1 H), 3,80 (m, 2 H), 3,50(m, 1 H), 3,19 (t, J = 12 Hz, 1 H), 2,70 (d, J = 10 Hz, 1 H), 2,50 (d, J = 13,6 Hz, 1 H), 2,1 –2,40 (m, 3 H), 1,86 (m, 1 H). MS: Calculado para $C_{21}H_{20}F_5O_5S$ (MH^+) m/z = 479,1; experimental 479,3. Tiempo de retención: 4,20 min.

Paso 11

El compuesto **10** (2,1 g) se resolvió en la columna quiral AS eluyendo con 65% isopropanol en hexanos y tasa de flujo 35 ml/min para dar dos enantiómeros **10B** (0,95 g, tiempo de retención 33,5 –39,1 min, $[\alpha]_D^{20}$ +98,4°) y **10A** (0,98 g, tiempo de retención 41,3 – 49,3 min., $[\alpha]_D^{20}$ –91,4°).

Paso 12

Una solución de 0,98 g (2,05 mmol) del compuesto **10A**, 0,82 g (4,3 mmol) de cloruro de *p*–toluensulfonilo y 0,6 g (6,0 mmol) de trietilamina en 20 ml de diclorometano se agitó a temperatura ambiente durante 18 h. Se inactivó con 80 ml de bicarbonato de sodio saturado, y se extrajo con tres porciones de 80 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 2% a 45% de acetato de etilo en hexanos para dar 1,33 g del compuesto **11**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,84 (d, J = 8,4 Hz, 2 H), 7,80 (d, J = 8,4 Hz, 2 H), 7,74 (d, J = 8,4 Hz, 2 H), 7,30 (d, J = 8,4 Hz, 2 H), 7,14 (m, 1 H), 6,48 (m, 1 H), 5,11 (d, J = 10 Hz, 1 H), 4,32 (d, J = 12,4 Hz, 1 H), 4,16 (m, 2 H), 3,76 (m, 1 H), 3,27 (m, 1 H), 2,96 (t, J = 12 Hz, 1 H), 2,54 (m, 1 H), 2,46 (m, 1 H), 2,42 (s, 3 H), 2,20 (m, 2 H), 1,80 (m, 1 H). MS: Calculado para $C_{28}H_{26}F_5O_7S_2$ (MH^+), m/z = 633,1; experimental 633,3. Tiempo de retención: 4,85 min.

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Paso 13

Una mezcla de 0,90 g (1,42 mmol) del compuesto **11** y 1,59 g (4,3 mmol) de yoduro de tetrabutilamonio en 50 ml de tetrahidrofurano se agitó a reflujo durante 3 h. Tras la adición de 0,56 g (5,5 mmol) de metansulfinato de sodio, la mezcla se agitó a reflujo durante 18 h y se diluyó con 80 ml de agua. Se extrajo con tres porciones de 80 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 10% a 75% de acetato de etilo en hexanos para dar 0,52 g del compuesto **12**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,86 (d, J = 8,4 Hz, 2 H), 7,81 (d, J = 8,4 Hz, 2 H), 7,12 (m, 1 H), 6,48 (m, 1 H), 5,18 (d, J = 10 Hz, 1 H), 4,48 (d, J = 12,8 Hz, 1 H), 3,88 (m, 1 H), 3,0–3,40 (m, 4 H), 2,98 (s, 3 H), 2,61 (d, J = 10 Hz, 1 H), 2,3 – 2,53 (m, 3 H), 2,05 (m, 1 H). MS: Calculado para $C_{22}H_{22}F_5O_6S_2$ (MH^+), m/z = 541,1; experimental 541,3. Tiempo de retención: 4,32 min.

Paso 14

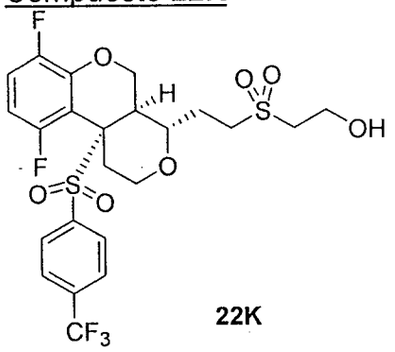
Una mezcla de 0,43 g (0,68 mmol) del compuesto **11**, 0,09 g (1,45 mmol) de 2–etanotiol y 1 ml (1 mmol) de hidróxido de potasio en etanol en 50 ml de etanol se agitó a 70°C durante 40 min. y se concentró. El residuo se disolvió en 40 ml de agua y se extrajo con dos porciones de 50 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el producto sulfuro bruto se disolvió en 30 ml de diclorometano. A esta solución se agregaron 0,42 g (1,7 mmol) de 70% ácido 3–cloroperoxibenzoico. Tras agitar a temperatura ambiente durante 1,5 h, se diluyó con 50 ml de diclorometano, 40 ml de tiosulfato de sodio 10% y 40 ml de bicarbonato de sodio saturado. Se agitó durante 8 min y se separó. La fase orgánica se lavó con 20 ml de hidróxido de sodio 1N y se concentró. El residuo se purificó por cromatografía eluyendo con un gradiente de 10% a 60% de acetato de etilo en hexanos para dar 0,35 g del compuesto **13**. ^{1}H RMN ($CDCl_3$ 400 MHz)

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δ 7,86 (d, J = 8,4 Hz, 2 H), 7,81 (d, J = 8,4 Hz, 2 H), 7,13 (m, 1 H), 6,48 (m, 1 H), 5,17 (d, J = 10 Hz, 1 H), 4,48 (d, J = 12,8 Hz, 1 H), 3,90 (m, 1 H), 3,36 (m, 1 H), 3,20 (m, 2 H), 2,95 (m, 3 H), 2,60 (d, J = 9,6 Hz, 1 H), 2,3 – 2,58 (m, 3 H), 2,05 (m, 1 H), 1,40 (t, J = 7,6 Hz, 3H). MS: Calculado para $C_{23}H_{24}F_5O_6S_2$ (MH^+), m/z = 555,1; experimental 555,3. Tiempo de retención: 4,21 min.

Los siguientes compuestos se prepararon de modo análogo:

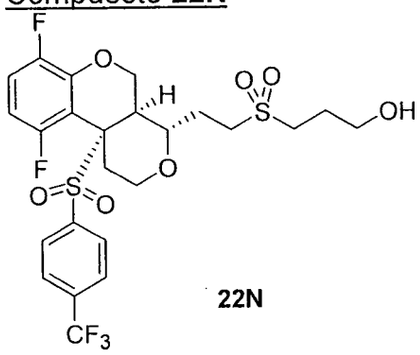
Compuesto **22K**



22K

Compuesto **22K** MS: Calculado para $C_{23}H_{24}F_5O_7S_2$ $(M+1)^+$, m/z = 571,1; experimental 571,3. Tiempo de retención: 3,97 min.

Compuesto **22N**

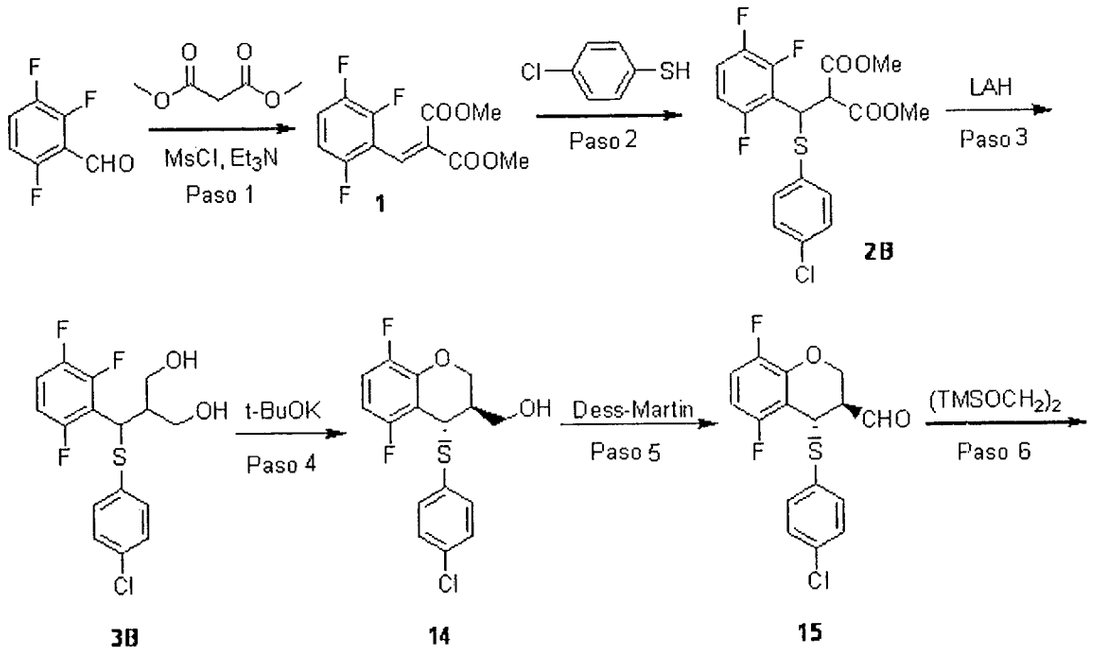


22N

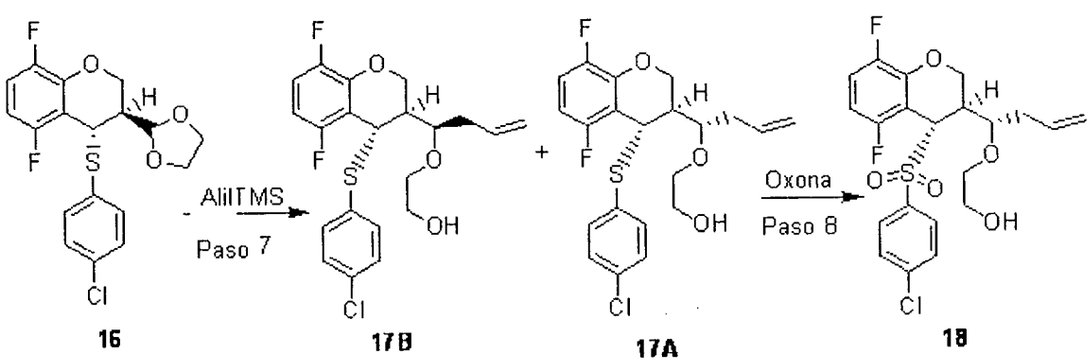
Compuesto **22N** MS: Calculado para $C_{24}H_{26}F_5O_7S_2$ $(M+1)^+$, m/z = 585,1; experimental 585,3. Tiempo de retención: 3,96 min.

Esquema 2:

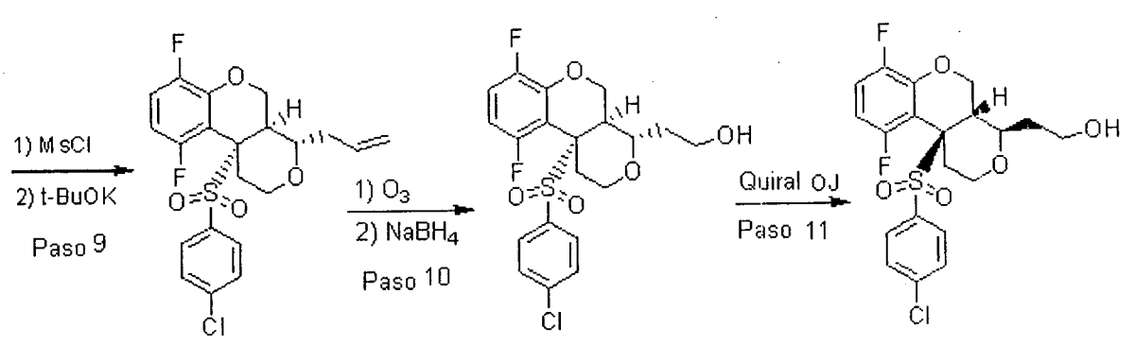
544



1 2B 3B 14 15

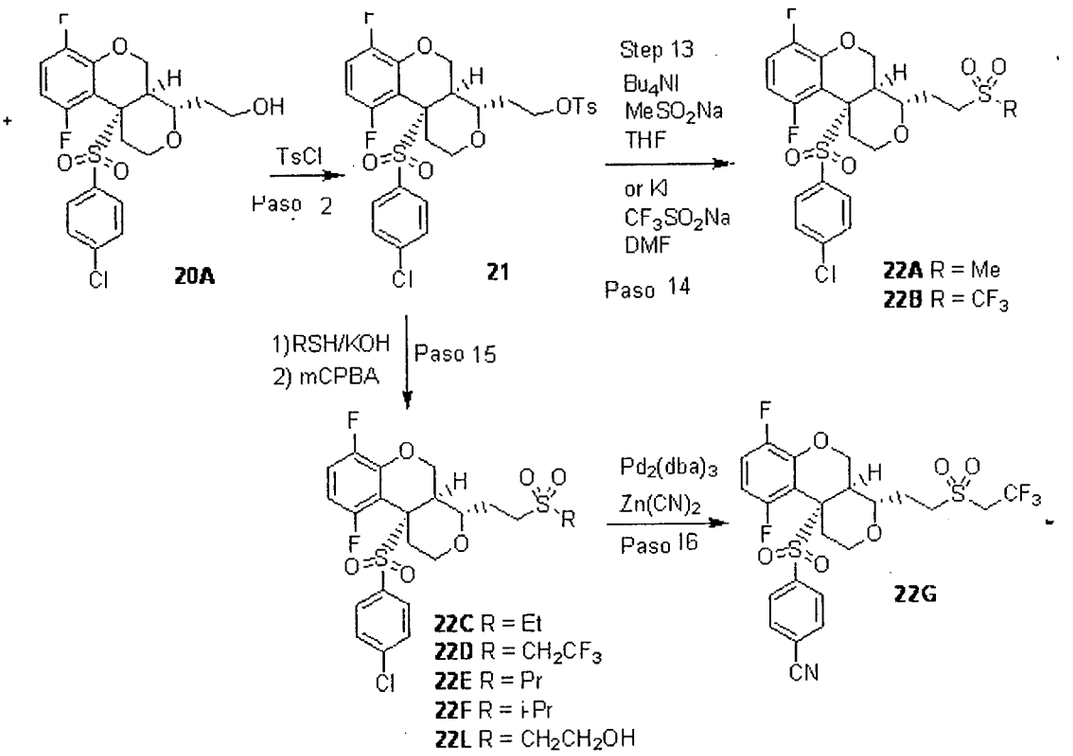


16 17B 17A 18



19 20 20B

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Paso 1

A una solución agitada frío (0°C) de 2,3,5–triflouro–benzaldehído (400 g, 2,5 mol) y dimetilmalonato (280,5 g, 2,875 mol) en diclorometano (7 L) se agregó trietilamina (455 g, 4,5 mol). La mezcla se agitó a 0 a 5°C durante 40 min. Se agregó cloruro de metansulfonilo (430 g, 3,75 mol) durante 2,5 h, se mantiene la temperatura de reacción por debajo de 6 °C. La reacción se agitó durante 30 min. a 0°C. Se agregó trietilamina adicional (126 g, 1,25 mol). La reacción se agitó durante 1 hora a 0°C. El RMN indicó 91% de producto. Se agregaron trietilamina adicional (126 g, 1,25 mol) y cloruro de metansulfonilo (86 g, 0,75 mol). Se agitó a 0°C durante 1 h. La reacción se agitó con agua fría (3 L) y se separó. La fase acuosa se extrajo con diclorometano (2,5 L). Las fases combinadas en diclorometano se lavaron con agua (4 L), HCl 1N (2,5 L) y salmuera (2 L), se secó

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con sulfato de sodio y se filtró. El filtrado se concentró para dar 771 g del producto deseado **1** como un aceite crudo. ^{1}H RMN ($CDCl_3$): δ 3,78 (s, 3H), 3,82 (s, 3H), 6,83 (m, 1H), 7,18 (m, 1H), 7,62 (s, 1H).

Paso 2

A una solución del aceite crudo anterior (771 g, 2,5 mol) y 4–clorotiofenol (366 g, 2,53 mol) en THF (10 L) se agregó carbonato de potasio (345 g, 2,5 mol) a temperatura ambiente. La mezcla se agitó toda la noche. Se agregaron 4–clorotiofenol adicional (37 g, 0,25 mol) y carbonato de potasio (355 g, 0,25 mol). La reacción se agitó 1 hora a temperatura ambiente. La reacción se agitó con acetato de etilo (4 L) y agua (4 L) y se separó. La fase acuosa se extrajo con acetato de etilo (2 L). Las fases orgánicas combinadas se lavaron con salmuera (2 L), se secó con sulfato de sodio y se filtraron. El filtrado se concentró para dar 1152 g del producto deseado **2B** como aceite crudo. ^{1}H RMN ($CDCl_3$): δ 3,58 (s, 3H), 3,80 (s, 3H), 4,35 (d, 2H), 5,08 (d, 2H), 6,75 (m, 1H), 7,00 (m, 1H), 7,22 (m, 4H)

Paso 3

LOs pellet LAH (100 g, 2,62 mol) se suspendieron y agitaron en THF (5 L). A esta suspensión fría se agregó una solución del anterior aceite crudo **2B** (dividir en dos lotes, 560 g, 1,25 mol) en THF (800 ml) durante 1 h por debajo de 7°C. La reacción se agitó a 0°C durante 3 h. Se goteó agua (200 ml) lentamente y la reacción se agitó durante 30 min. Se agregaron HCl 6N (1 L) y hexano (4 L) y la reacción se agitó durante 1h. La fase orgánica se decantó. El sólido residual se agitó con hexano (3 L) y éter etílico (2 L) y se decantó. La fase orgánica combinada se lavó con agua (2 x 3 L). Las fases acuosas combinadas se extrajeron con hexano (2 L) y éter etílico (1 L). Las fases orgánicas combinadas se lavaron con salmuera (1,5 L), se secaron con sulfato de sodio y filtraron. El

filtrado se concentró para dar 430 g de aceite crudo. Este producto crudo se combinó con el otro lote preparado en la misma escala. Los productos brutos combinados se purificaron por cromatografía en gel de sílice (5 Kg) eluyendo con un gradiente de 10% a 50% de acetato de etilo en hexanos para dar 505 g del producto diol **3B**. ^{1}H RMN ($CDCl_3$): δ 2,21 (m, 1H), 2,39 (m, 1H), 2,42 (m, 1H), 3,47 (m, 1H), 3,81 (m, 1H), 4,20 (m, 1H), 4,25 (m, 1H), 4,81 (d, 1H), 6,75 (m, 1H), 6,88 (m, 1H), 7,18 (m, 2H), 7,23 (m, 2H)

Paso 4

A una solución del diol anterior **3B** (530 g, 1,19 mol) en THF se agregó ter-butóxido de potasio 1M (1550 ml, 1,55 mol) en THF durante 1 h manteniendo la temperatura por debajo de 8°C. La reacción se agitó a temperatura ambiente durante 105 min. Se agregó ter-butóxido de potasio 1M adicional (160 ml, 0,16 mol). La reacción se agitó a temperatura ambiente durante 1 h. Se agregaron agua (2 L) y hexano (4 L) a la mezcla de reacción en un baño de hielo y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (1 L) y hexano (1 L). Las fases orgánicas combinadas se lavaron con salmuera (1 L), se secaron con sulfato de sodio, se filtraron y concentraron. El residuo se purificó por cromatografía en gel de sílice (3 Kg) eluyendo con un gradiente de 15% a 50% de acetato de etilo en hexanos para dar 376 g del producto bicíclico deseado **14**. ^{1}H RMN ($CDCl_3$): δ 2,22 (t, 1H), 3,45 (m, 1H), 3,63 (m, 1H), 4,40 (m, 1H), 4,48 (s, 1H), 4,60 (m, 1H), 6,58 (m, 1H), 6,95 (m, 1H), 7,29 (dd, 2H), 7,42 (dd, 2H).

Paso 5

A una solución agitada de 9,1 g (26,5 mmol) del compuesto **14** en 200 ml de diclorometano se agregaron 14,6 g (34,5 mmol) de peryodinano de Dess–Martin. La mezcla se agitó a temperatura ambiente durante 2 h y se diluyó con 400 ml de diclorometano. Se agitó con 400 ml de bicarbonato de sodio saturado y 200 ml de

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solución de tiosulfato de sodio 10% y se separó. Este procedimiento se repitió dos veces con 200 ml de bicarbonato de sodio saturado y 200 ml de solución de tiosulfato de sodio 10%. La fase orgánica se secó con sulfato de sodio y filtraron. El filtrado se concentró para dar 9,0 g de aldehído bruto **15**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 9,69 (s, 1 H), 7,45 (d, J = 8,6 Hz, 2 H), 7,34 (d, J = 8,8 Hz, 2 H), 6,95 (m, 1 H), 6,62 (m, 1 H), 4,91 (m, 2 H), 4,74 (dd, J = 12,5 Hz, 1 H), 2,83 (s, 1 H).

Paso 6

A una solución agitada de 9,0 g (26,5 mmol) del compuesto **15** en 100 ml de diclorometano se agregaron 7,12 g (34,5 mmol) de 1,2–bis(trimetilsiloxi)etano y 0,36 (1,6 mmol) de trifluorometansulfonato de trimetilsililo a –78°C. Después de 30 min., se calentó a temperatura ambiente y se agitó durante 30 min. Se diluyó con 150 ml de diclorometano y se lavó con tres porciones de 200 ml de bicarbonato de sodio saturado. La fase orgánica se secó con sulfato de sodio, se concentró, y el residuo se purificó por cromatografía eluyendo con un gradiente de 2% a 30% de acetato de etilo en hexanos para dar 8,8 g del compuesto **16**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,42 (d, J = 9,0 Hz, 2 H), 7,31 (d, J = 8,6 Hz, 2 H), 6,95 (m, 1 H), 6,57 (m, 1 H), 4,74 (d, J = 7,4 Hz, 1 H), 4,70 (s, 1 H), 4,59 (s, 2 H), 3,80–3,92 (m, 4 H), 2,10 (m, 1 H). MS: Calculado para $C_{18}H_{16}ClF_2O_3S(MH^+)$, m/z = 385,1; experimental 385,2. Tiempo de retención: 5,28 min.

Paso 7

Una solución de 2,9 (7,5 mmol) del compuesto **16**, 3,45 g (30,2 mmol) de aliltrimetilsilano y 4,3 g (30,2 mmol) de dietileterato de trifluoruro de boro en 50 ml de diclorometano se agitó a reflujo durante 1 día. Se inactivó con 50 ml de agua, y 50 ml de diclorometano. La fase orgánica se lavó con dos porciones de 50 ml de bicarbonato de sodio saturado, se concentró, y el residuo se purificó por cromatografía eluyendo con un gradiente de 1% a 30% de acetato de etilo en

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hexanos para dar 1,1 g del compuesto **17A** y 0,63 g de **17B**. **17A**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,45 (d, J = 8,9 Hz, 2 H), 7,31 (d, J = 8,9 Hz, 2 H), 6,95 (m, 1 H), 6,60 (m, 1 H), 5,75 (m, 1 H), 5,10 (d, J = 5,7 Hz, 1 H), 5,07 (s, 1 H), 4,80(m, 1 H), 4,61 (d, J = 12,3 Hz, 1 H), 4,39 (d, J = 11,4 Hz, 1 H), 3,58 (m, 3 H), 3,24 (m, 2 H), 2,52 (m, 1 H), 2,34 (m, 1 H), 2,15 (m, 1 H), 1,60 (m, 1 H). MS: Calculado para $C_{21}H_{22}ClF_2O_3S(MH^+)$, m/z = 427,1; experimental 427,1. Tiempo de retención: 5,04 min. **17B**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,48 (d, J = 8,1 Hz, 2 H), 7,33 (d, J = 8,6 Hz, 2 H), 6,97 (m, 1 H), 6,59 (m, 1 H), 5,50 (m, 1 H), 4,90 (d, J = 10,1 Hz, 1 H), 4,82(d, J = 16,9 Hz, 1 H), 4,63 (m, 2 H), 4,29 (s, 1 H), 3,64 (m, 3 H), 3,43 (m, 1 H), 3,20 (m, 1 H), 2,36 (m, 1 H), 1,90–2,18 (m, 3 H). MS: Calculado para $C_{21}H_{22}ClF_2O_3S(MH^+)$, m/z = 427,1; experimental. Tiempo de retención: 4,32 min.

Paso 8

Una mezcla de 3,6 g (8,4mmol) del compuesto **17A** y 20,7 g (33,6 mmol) de peroxomonosulfato de potasio en 110 ml de acetona y 35 ml de agua se agitó a 50°C durante 3 h. Se concentró, y el residuo se disolvió en 200 ml de agua. Se extrajo con tres porciones de 150 ml de acetato de etilo. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 1% a 10% de acetato de etilo en diclorometano para dar 2,35 g del compuesto **18**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,75 (d, J = 8,6 Hz, 2 H), 7,52 (d, J = 8,1 Hz, 2 H), 7,05 (m, 1 H), 6,45 (m, 1 H), 5,83 (m, 1 H), 5,18 (d, J = 13,5 Hz, 2 H), 4,93 (m, 2 H), 4,40 (d, J = 12,4 Hz, 1 H), 3,55 (m, 3 H), 3,20 (m, 2 H), 2,93 (m, 1 H), 2,54 (m, 1 H), 2,38(m, 1 H), 1,64 (m, 1 H). MS: Calculado para $C_{21}H_{22}ClF_2O_5S(MH^+)$, m/z = 459,1; experimental 459,3. Tiempo de retención: 4,39 min.

Paso 9

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A una solución de 2,33 g (5,1 mmol) del compuesto **18** en 100 ml de diclorometano se agregaron 0,7 g (7,0 mmol) de trietilamina y 0,87 g (7,6 mmol) de cloruro de metansulfonilo. La mezcla se agitó a temperatura ambiente durante 1,5 h. Se diluyó con 100 ml de diclorometano y se lavó con dos porciones de 80 ml de agua, y 80 ml de bicarbonato de sodio saturado. La fase orgánica se concentró y el residuo se disolvió en 100 ml de tetrahidrofurano. A esta solución se agregaron 12,7 ml (12,7 mmol) de ter-butóxido de potasio 1 N en tetrahidrofurano. La mezcla se agitó a temperatura ambiente durante 30 min., se inactivó con 50 ml de agua, y se extrajo con porciones de 250 ml de diclorometano. El extracto orgánico se concentró y el residuo se purificó por cromatografía eluyendo con un gradiente de 1% a 30% de acetato de etilo en hexanos para dar 1,59 g del compuesto **19**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,63 (d, J = 8,0 Hz, 2 H), 7,50 (d, J = 7,3 Hz, 2 H), 7,08 (m, 1 H), 6,46 (m, 1 H), 5,85 (m, 1 H), 5,15 (m, 3 H), 4,45 (d, J = 12,4 Hz, 1 H), 3,91 (m, 1 H), 3,37 (m, 1 H), 3,17 (t, J = 11,6 Hz, 1 H), 2,61 (m, 2 H), 2,25–2,54 (m, 3 H). MS: Calculado para $C_{21}H_{20}ClF_2O_4S(MH^+)$, m/z = 441,1; experimental 441,1. Tiempo de retención: 4,20 min.

Paso 10

A una solución agitada de 5,0 g (11,4 mmol) del compuesto **19** en 150 ml de diclorometano a –78°C se burbujeó con O_3 hasta color azul sostenido. Se burbujeó con N_2 has que la solución se vuelve incolora. A esta solución se agregaron 1,3 g (34,2 mmol) de borohidruro de sodio y 15 ml de metanol. La mezcla se agitó a temperatura ambiente toda la noche. Tras la adición de 3,0 g (11,4 mmol) de trifenilfosfina, se agitó durante 1 h y se diluyó con 200 ml de agua. La mezcla se extrajo con tres porciones de 150 ml de diclorometano, y los extractos combinados se secaron con sulfato de sodio. Los extractos orgánicos combinados se filtraron, se concentraron, y el residuo se purificó por

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cromatografía eluyendo con un gradiente de 5% a 60% de acetato de etilo en hexanos para dar 4,6 g del compuesto **20**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,64 (d, J = 8,5 Hz, 2 H), 7,51 (d, J = 8,9 Hz, 2 H), 7,12 (m, 1 H), 6,45 (m, 1 H), 5,16 (d, J = 10,0 Hz, 1 H), 4,43 (d, J = 13,5 Hz, 1 H), 3,92 (m, 1 H), 3,79 (m, 2 H), 3,51 (m, 1 H), 3,20 (t, J = 11,6 Hz, 1 H), 2,65 (d, J = 11,0 Hz, 1 H), 2,53 (d, J = 12,9 Hz, 1 H), 2,34 (m, 2 H), 2,15 (m, 1 H), 1,85 (m, 1 H). MS: Calculado para $C_{20}H_{20}ClF_2O_5S(MH^+)$ m/z = 445,1; experimental 445,2 Tiempo de retención: 3,40 min.

Paso 11

El compuesto **20** (1,8 g) se resolvió en una columna quiral OJ eluyendo con 70% isopropanol en hexanos y 28 ml/min de velocidad de flujo para dar dos enantiómeros **20A** (0,67 g, tiempo de retención 41 min, $[\alpha]_D^{20}$ –136,6°) y **20B** (0,70 g, tiempo de retención 50 min., $[\alpha]_D^{20}$ +132,5°).

Paso 12

Una solución de 1,5 g (3,37 mmol) del compuesto **20A**, 1,27 g (6,7 mmol) de cloruro de p–toluensulfonilo y 0,68 g (6,7 mmol) de trietilamina en 30 ml de diclorometano se agitó a temperatura ambiente durante 65 h. Se inactivó con 80 ml de bicarbonato de sodio saturado, y se extrajo con tres porciones de 100 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 2% a 40% de acetato de etilo en hexanos para dar 1,95 g del compuesto **21**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,74 (d, J = 8,4 Hz, 2 H), 7,61 (d, J = 8,4 Hz, 2 H), 7,51 (d, J = 8,8 Hz, 2 H), 7,30 (d, J = 8,4 Hz, 2 H), 7,12 (m, 1 H), 6,48 (m, 1 H), 5,10 (d, J = 12,8 Hz, 1 H), 4,29 (d, J = 12,8 Hz, 1 H), 4,19 (m, 2 H), 3,76 (m, 1 H), 3,24 (m, 1 H), 2,96 (t, J = 11,6 Hz, 1 H), 2,51 (m, 2 H), 2,42 (s, 3 H), 2,20 (m, 2 H), 1,80 (m, 1 H). MS: Calculado

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para $C_{27}H_{26}ClF_2O_7S_2(MH^+)$, m/z = 599,1; experimental 599,3. Tiempo de retención: 4,82 min.

Paso 13

Una mezcla de 3,15 g (5,26 mmol) del compuesto **21** y 5,83 g (15,8 mmol) de yoduro de tetrabutilamonio en 80 ml de tetrahidrofurano se agitó a reflujo durante 2 h. Tras la adición de 2,15 g (21,0 mmol) de metansulfinato de sodio, la mezcla se agitó a reflujo toda la noche y se diluyó con 100 ml de agua. Se extrajo con tres porciones de 100 ml de acetato de etilo. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 5% a 75% de acetato de etilo en hexanos para dar 2,44 g del compuesto **22A**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,64 (d, J = 8,8 Hz, 2 H), 7,52 (d, J = 8,8 Hz, 2 H), 7,10 (m, 1 H), 6,48 (m, 1 H), 5,18 (d, J = 13,2 Hz, 1 H), 4,45 (d, J = 12,4 Hz, 1 H), 3,90 (m, 1 H), 3,0–3,40 (m, 4 H), 2,92 (s, 3 H), 2,2 – 2,60 (m, 4 H), 2,05 (m, 1 H). MS: Calculado para $C_{21}H_{22}ClF_2O_6S_2$ (MH^+), m/z = 507,1.; experimental 507,3. Tiempo de retención: 4,22 min.

A partir de alcohol racémico **20**, y mediante procedimiento del Esquema 2, pasos 12 y 13 se proporcionó compuesto racémico **22A–rac:** MS: Calculado para $C_{21}H_{22}ClF_2O_6S_2$ (MH^+), m/z = 507,0; experimental 507,3. Tiempo de retención: 4,20 min.

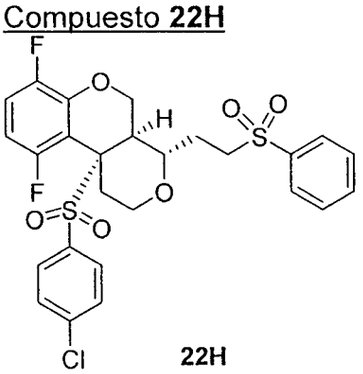
Paso 14

Una mezcla de 0,12 g (0,2 mmol) del compuesto **21**, 0,10 g (0,6 mmol) de yoduro de potasio y 0,10 g (0,6 mmol) de trifluorometilsulfinato de sodio en 6 ml de DMF se agitó a 120°C for 6 h. Se diluyó con 25 ml de agua y se extrajo contres porciones de 40 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el residuo se purificó por TLC preparativa eluyendo con 30% de acetato de etilo en hexanos para dar 0,045 g del compuesto **22B**. ^{1}H RMN ($CDCl_3$

400 MHz) δ 7,63 (d, J = 8,8 Hz, 2 H), 7,52 (d, J = 8,8 Hz, 2 H), 7,12 (m, 1 H), 6,48 (m, 1 H), 5,19 (d, J = 12,8 Hz, 1 H), 4,42 (d, J = 12,4 Hz, 1 H), 3,92 (m, 1 H), 3,1–3,54 (m, 4 H), 2,50 (m, 2 H), 2,30 (m, 2 H), 2,10 (m, 1 H). MS: Calculado para $C_{21}H_{19}ClF_5O_6S_2$ (MH^+), m/z = 561,0; experimental 561,3. Tiempo de retención: 4,80 min.

Los siguientes compuestos se prepararon de modo análogo:

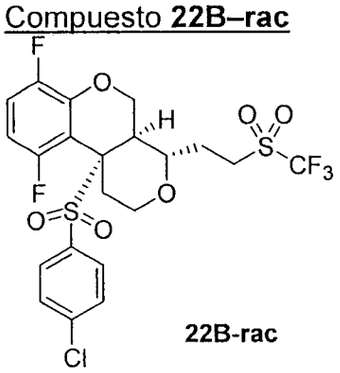
Compuesto **22H**



22H

Compuesto **22H**: MS: Calculado para $C_{26}H_{24}ClF_2O_6S_2(MH^+)$, m/z = 569,1; experimental 569,3. Tiempo de retención: 4,71 min.

Compuesto **22B–rac**



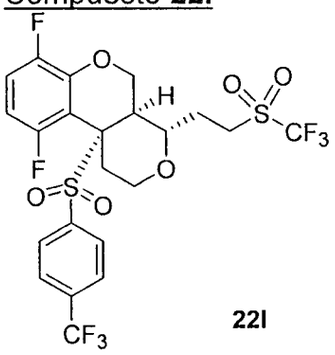
22B-rac

A partir de alcohol racémico **20**, y mediante el procedimiento del Esquema 2, pasos 12 y 14 se proporcionó compuesto racémico **22B–rac:** MS: Calculado para $C_{21}H_{19}ClF_5O_6S_2$ (MH^+), m/z = 561,0; experimental 561,3. Tiempo de retención: 4,89 min.

Los siguientes compuestos se prepararon de modo análogo a a partir del compuesto **11** (Esquema 1) sustituyendo Bu_4NI con KI:

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Compuesto **22I**



22I

Compuesto **22I**: MS: Calculado para $C_{22}H_{19}ClF_8O_6S_2(M+H)^+$, m/z = 595,0 experimental 595,3. Tiempo de retención: 5,06 min.

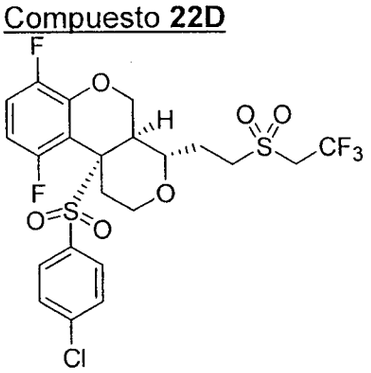
Paso 15

Una mezcla de 0,2 g (0,33 mmol) del compuesto **21**, 0,04 g (0,67 mmol) de 2–etanotiol 0,5 ml (1 mmol) de hidróxido de potasio en etanol en 5,5 ml de etanol se agitó a 70°C durante 25 min. y se concentró. El residuo se disolvió en 15 ml de agua y se extrajo con 30 ml de diclorometano. El extracto orgánico se concentró y el producto sulfuro bruto se disolvió en 10 ml de diclorometano. A esta solución se agregaron 0,17 g (1,0 mmol) de 70% de ácido 3–cloroperoxibenzoico. Tras agitar a temperatura ambiente durante 1 h, se diluyó con 30 ml de diclorometano. Se lavó con tres porciones de 20 ml de bicarbonato de sodio saturado. La fase orgánica se concentró, el residuo se purificó por cromatografía eluyendo con un gradiente de 5% a 80% de acetato de etilo en hexanos para dar 0,14 g del compuesto **22C**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,63 (d, J = 7,8 Hz, 2 H), 7,51 (d, J = 8,9 Hz, 2 H), 7,13 (m, 1 H), 6,47 (m, 1 H), 5,16 (d, J = 15,3 Hz, 1 H), 4,45 (d, J = 12,2 Hz, 1 H), 3,89 (d, J = 10,2, 1 H), 3,36 (m, 1 H), 3,20 (m, 2 H), 2,96 (m, 3 H), 2,5 (m, 2 H), 2,40 (m, 1 H), 2,29 (m, 1 H), 2,02 (m, 1 H), 1,40 (t, J = 7,4 Hz, 3 H). MS: Calculado para $C_{22}H_{24}ClF_2O_6S_2(MH^+)$, m/z = 521,1; experimental 521,3 Tiempo de retención: 4,35 min.

Los siguientes compuestos se prepararon de modo análogo:

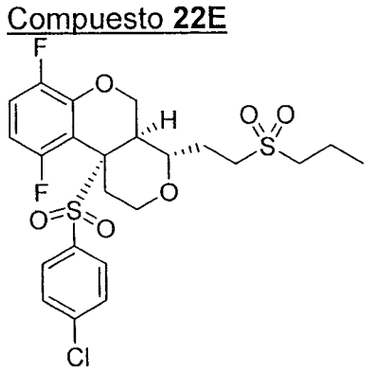
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Compuesto **22D**



Compuesto **22D**: 7,62 (d, J = 8,0 Hz, 2 H), 7,54 (d, J = 8,4 Hz, 2 H), 7,13 (m, 1 H), 6,45 (m, 1 H), 5,19 (d, J = 15 Hz, 1 H), 4,42 (d, J = 12 Hz, 1 H), 3,92 (d, J = 10 Hz, 1 H), 3,79 (m, 2 H), 3,40 (m, 2 H), 3,19 (m, 2 H), 2,56 (m, 3 H), 2,34 (m, 1 H), 2,10 (m, 1 H). MS: Calculado para $C_{22}H_{21}ClF_5O_6S_2(MH^+)$, m/z = 575,0; experimental 575,3. Tiempo de retención: 4,76 min.

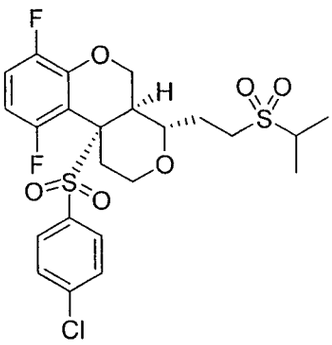
Compuesto **22E**



Compuesto **22E**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,62 (d, J = 8,0 Hz, 2 H), 7,52 (d, J = 8,4 Hz, 2 H), 7,10 (m, 1 H), 6,44 (m, 1 H), 5,18 (d, J = 15 Hz, 1 H), 4,42 (d, J = 12 Hz, 1 H), 3,88 (m, 1 H), 3,37 (m, 1 H), 3,18 (m, 2 H), 2,95 (m, 3 H), 2,55 (m, 1 H), 2,42 (m, 1 H), 2,28 (m, 1 H), 2,02 (m, 1 H), 1,88 (m, 2 H), 1,08 (t, J = 7,4 Hz, 3 H). MS: Calculado para $C_{23}H_{26}ClF_2O_6S_2(MH^+)$, m/z = 535,1; experimental 535,3. Tiempo de retención: 4,53 min.

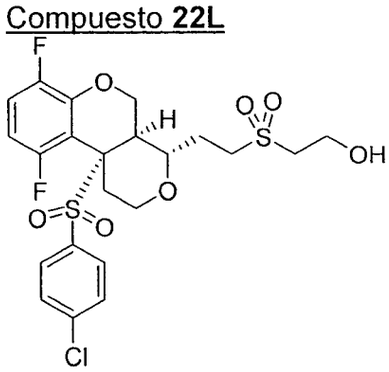
Compuesto **22F**

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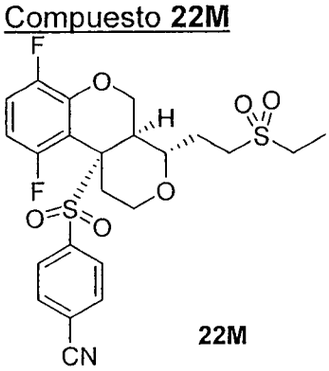
Compuesto **22F**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,64 (d, J = 8,8 Hz, 2 H), 7,52 (d, J = 8,6 Hz, 2 H), 7,13 (m, 1 H), 6,48 (m, 1 H), 5,17 (d, J = 15,3 Hz, 1 H), 4,47 (d, J = 8,5 Hz, 1 H), 3,89 (d, J = 10,2 Hz, 1 H), 3,36 (m, 1 H), 3,17 (m, 3 H), 2,92 (m, 1 H), 2,56 (d, J = 12,6 Hz, 2 H), 2,46 (m, 1 H), 2,29 (m, 1 H), 2,01 (m, 1 H), 1,40 (t, J = 8,0 Hz, 6H). MS: Calculado para $C_{23}H_{26}ClF_2O_6S_2(MH^+)$, m/z = 535,1; experimental 535,3. Tiempo de retención: 4,23 min.

Compuesto **22L**



Compuesto **22L**: MS: Calculado para $C_{22}H_{24}ClF_2O_7S_2(M+1)^+$, m/z = 537,1, experimental 537,3. Tiempo de retención: 3,86 min.

Compuesto **22M**



22M

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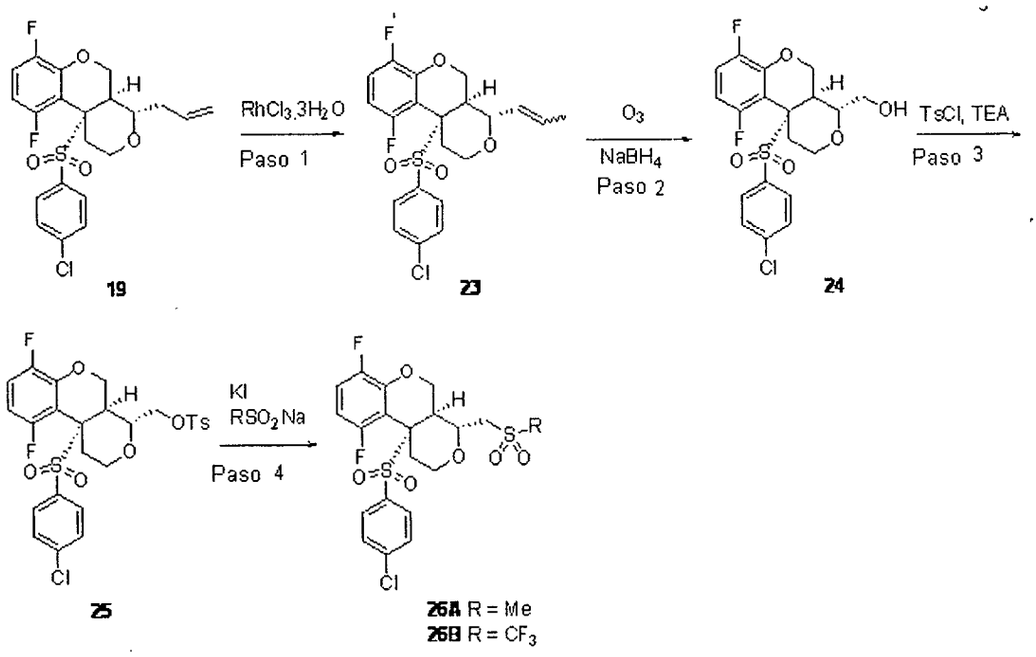
Compuesto **22M** se preparó de modo análogo a partir de tosilato **30** (ver Esquema 6): MS: Calculado para $C_{23}H_{24}F_2NO_6S_2(M+1)^+$, m/z = 512,1, experimental 512,3. Tiempo de retención: 3,73 min.

Paso 16

Una mezcla de 0,049 g (0,085 mmol) del compuesto **22D**, 0,007 g (0,009 mmol) de bis(dibencilidenacetona)paladio ($Pd_2(dba)_3$), 0,008 g (0,013 mmol) de 1,1'–bis(difenilfosfino)ferroceno (dppf), 0,010 g (0,085 mmol) de cianuro de zinc y 0,002 g (0,03 mmol) de polvo de zinc en 3 ml de N,N–dimetilacetamida en un tubo sellado se calentó a 150°C durante 1 h en microondas (Biotage). Se diluyó con 20 ml de agua, y se extrajo con 20 ml de diclorometano. El extracto orgánico se concentró, el residuo se purificó por TLC preparativa eluyendo con 30% acetato de etilo en hexanos para dar 0,006 g del compuesto **22G**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,82 (s, 4 H), 7,12 (m, 1 H), 6,46 (m, 1 H), 5,16 (d, J = 10 Hz, 1 H), 4,46 (d, J = 12 Hz, 1 H), 3,92 (m, 1 H), 3,80 (m, 3 H), 3,40 (m, 2 H), 3,16 (m, 2 H), 2,63 (m, 1 H), 2,46 (m, 1 H), 2,32 (m, 1 H), 2,08 (m, 1 H). MS: Calculado para $C_{23}H_{21}F_5NO_6S_2(MH^+)$,
m/z = 566,1; experimental 566,3 Tiempo de retención: 4,66 min.

Esquema 3:

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Paso 1

Una mezcla de 2,2 g (5 mmol) del compuesto **19** y 0,052 (0,25 mmol) de $RhCl_3,3H_2O$ en 80 ml de etanol se agitó a reflujo durante 3 h, luego se concentró. El residuo se purificó por cromatografía eluyendo con 10 – 40% de acetato de etilo en hexanos para dar 2,1 g (95%) de olefina **23**. MS: Calculado para $C_{21}H_{20}ClF_2O_4S$ $(M+1)^+$ m/z = 441,1, experimental 441,2, Rt = 4,94 min.

Paso 2

Se obtuvieron la ozonolisis de la olefina y la posterior reducción usando un procedimiento análogo al que se muestra en el Paso 10 del Esquema 2 para dar alcohol **24**: MS: Calculado para $C_{19}H_{18}ClF_2O_5S$ $(M+1)^+$ m/z = 431,1, experimental 431,2, Rt = 3,93 min.

Paso 3

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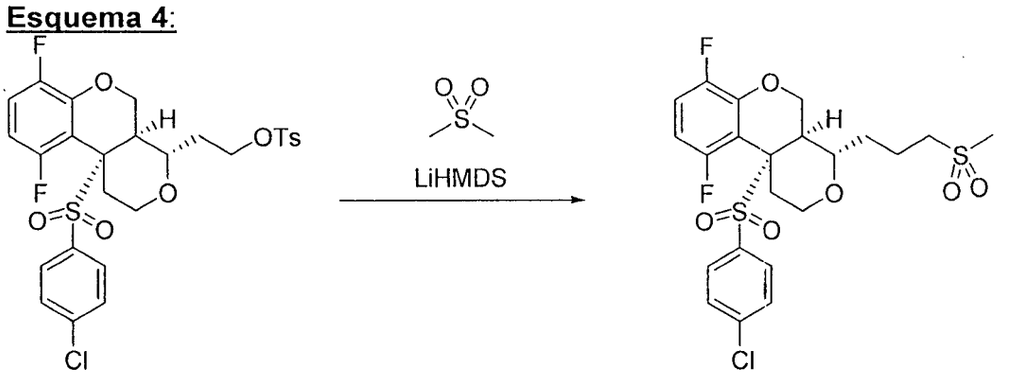
La tosilación del alcohol se logró usando un procedimiento análogo al que se muestra en el Paso 12 de Esquema 2 para dar tosilato **25**: MS: Calculado para $C_{26}H_{24}ClF_2O_7S_2$ $(M+1)^+$ m/z = 585,1, experimental 585,3, Rt = 4,93 min.

Paso 4

El desplazamiento del tosilato se obtuvo mediante un procedimiento análogo al que se muestra en el Paso 13 del Esquema 2 mediante metilsulfinato de sodio para dar sulfona **26A** (R = Me): MS: Calculado para $C_{20}H_{20}ClF_2O_6S_2$ $(M+1)^+$ m/z = 493,0, experimental 493,3, Rt = 4,14 min.

El desplazamiento del tosilato también se obtuvo mediante un procedimiento análogo al que se muestra en Paso 14 de Esquema 2 usando trifluorometilsulfinato de sodio para dar sulfona **26B** (R = CF_3): MS: Calculado para $C_{20}H_{17}ClF_5O_6S_2$ $(M+1)^+$ m/z = 547,1, experimental 371,2 $(M–ClPhSO_2–)^+$, Rt = 4,90 min.

Esquema 4:



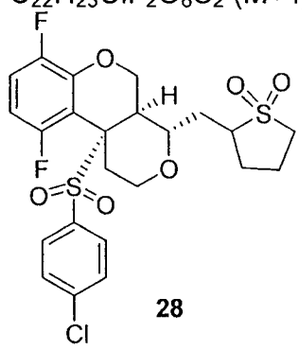
(±)-**21** **27**

Paso 1

A una solución de dimetilsulfona en 20 ml de THF se agregó LiHMDS en THF (1,0M) a –78°C. Después de 30 min., se agregó una solución de 0,12 g (0,2 mmol) del compuesto **21** en 5 ml de THF. La mezcla se calentó a temperatura ambiente toda la noche. Se diluyó con 50 ml de HCl 1N, se extrajo con tres porciones de 50 ml de cloruro de metileno. Los extractos orgánicos combinados

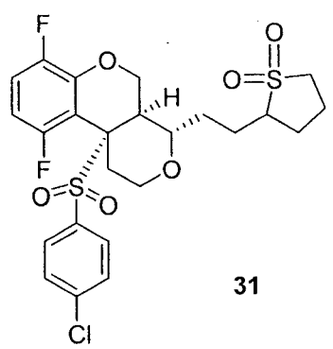
560

se concentraron, el residuo se purificó por TLC preparativa eluyendo con 50% acetato de etilo en hexanos para dar 0,032 g del compuesto **27**. MS: Calculado para $C_{22}H_{23}ClF_2O_6S_2$ $(M+1)^+$ m/z = 521,1, experimental 521,3, Rt = 4,03 min.



28

Mediante un procedimiento similar al Esquema 4, paso 1 a partir del compuesto **25** y sulfolano se proporcionó el compuesto **28**: MS: Calculado para $C_{23}H_{24}ClF_2O_6S_2$ $(M+1)^+$ m/z = 533,1, experimental 533,3, Rt = 4,36 min.

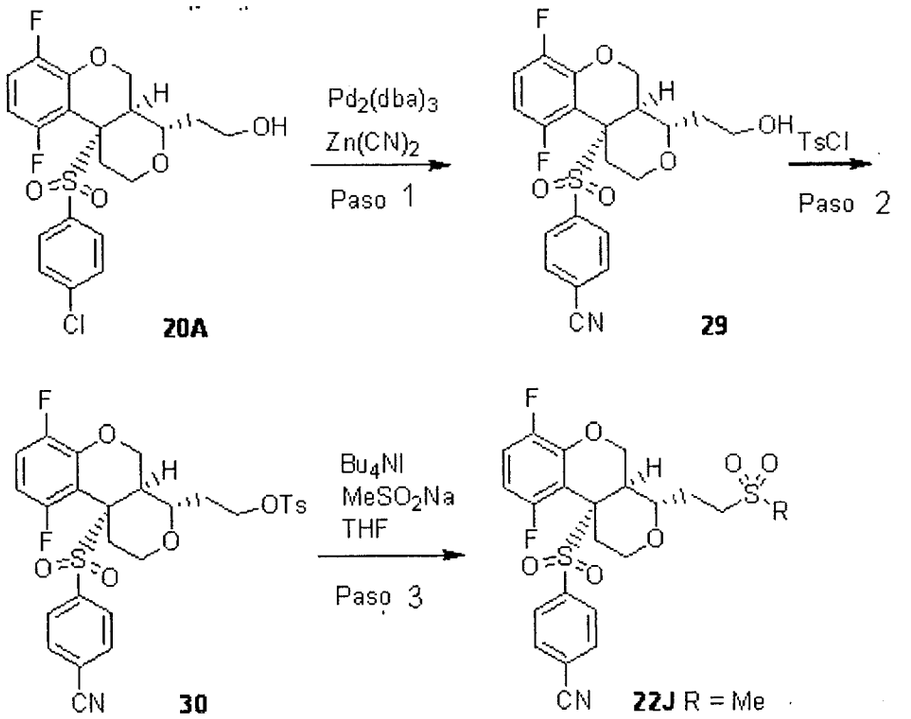


31

Mediante un procedimiento similar al Esquema 4, paso 1 a partir del compuesto **30** y sulfolano se proporcionó el compuesto **31**: MS: Calculado para $C_{24}H_{26}ClF_2O_6S_2$ $(M+1)^+$ m/z = 547,1, experimental 547,3, Rt = 4,23 min.

Esquema 5:

561



Paso 1

Clorofenilsulfona **20A** se convirtió en el análogo de cianofenilo **29** usando un procedimiento análogo al usado en el Esquema 2, Paso 16. MS: Calculado para $C_{21}H_{20}F_2NO_5S$ $(M+1)^+$ m/z = 436,1, experimental 436,3, Rt = 3,36 min.

Paso 2

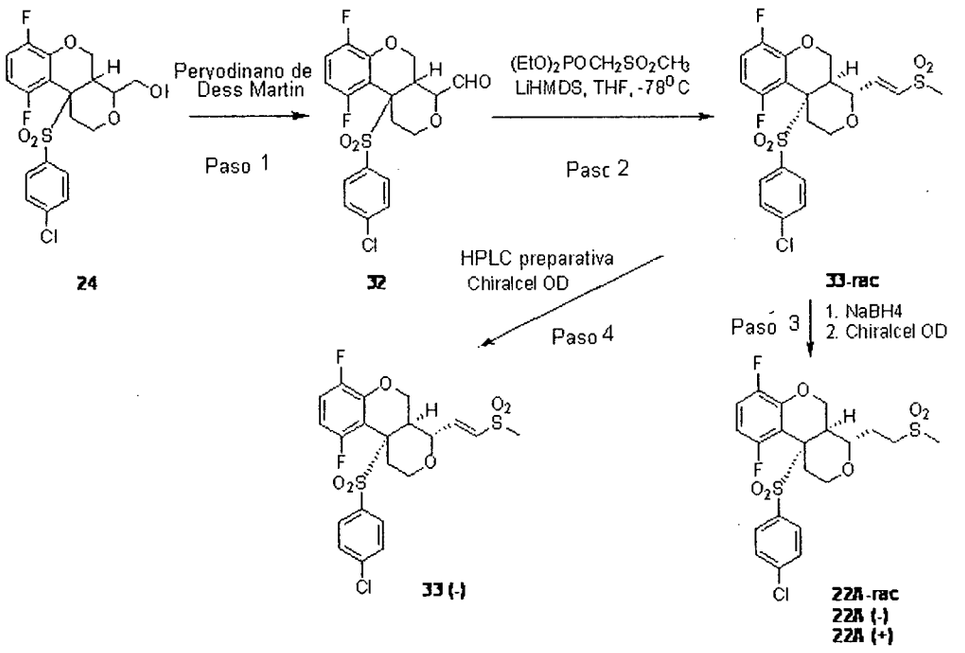
El Alcohol **29** se convirtió en el tosilato **30** mediante un procedimiento análogo al usado en Esquema 2, Paso 12. MS: Calculado para $C_{28}H_{26}F_2NO_7S_2$ $(M+1)^+$ m/z = 590,1, experimental 590,3, Rt = 4,43 min.

Paso 3

El tosilato **30** se convirtió en metilsulfona **22J** mediante un procedimiento análogo al usado en Esquema 2, Paso 13. MS: Calculado para $C_{22}H_{22}ClF_2NO_6S_2$ $(M+1)^+$ m/z = 498,1, experimental 498,3, Rt = 3,85 min.

562

Esquema 6:



Paso 1

El peryodinano de Dess–Martin (0,895 g, 2,11 mmol) se agregó en porciones a una solución agitada de compuesto hidroximetilo **24** (0,700 g, 1,62 mmol) en diclorometano (35 ml) a temperatura ambiente. La reacción se completó después de 2,5 horas (tlc: 30% EtOAc/hexano). La reacción se diluyó con 100 ml de diclorometano repartido con tiosulfato de sodio 10%/bicarbonato de sodio sat (3 80 ml porciones de una mezcla 1:1). El diclorometano se secó con anhidro sulfato de sodio y se concentró in vacuo para producir el compuesto **32** (0,680 g, 97%). MS: Calculado para $C_{19}H_{16}ClF_2O_5S$ $(M+1)^+$ m/z = 429,0, experimental 429, Rt = 4,10 min.

Paso 2

A una solución de 34,5 g (150 mmol) de dietil metilsulfonometil–fosfonato [ref:G. H. Posner y D. J. Brunelle *J. Org. Chem.* **1972**, *37*, 3547] en 500 ml de THF se agregaron 145 ml (145 mmol) de LiHMDS en THF a –78°C. Después de

563

40 min., se agregó una solución de 31,5 g (73,5 mmol) del aldehído **32** en 60 ml de THF y la mezcla se agitó a –78°C durante 5h. Se inactivó con 200 ml de NH_4Cl saturado acuoso y 500 ml de agua, y se extrajo con cuatro porciones de 500 ml de acetato de etilo. Los extractos orgánicos combinados se secaron con Na_2SO_4, filtraron y se concentraron para dar vinilsulfona bruta **33–rac**. MS: Calculado para $C_{21}H_{20}ClF_2O_6S_2$ $(M+1)^+$ m/z = 505,0, experimental 505, Rt = 4,20 min.

Paso 3

A una solución del anterior intermediario racémico **33–rac** en 400 ml de THF se agregaron 5,0 g (132 mmol) de $NaBH_4$ y 100 ml de etanol. La mezcla se agitó a temperatura ambiente durante 4 h. Se inactivó con 200 ml de agua, y los solventes orgánicos se evaporaron. A este residuo se agregaron 300 ml de agua y 50 ml de HCl 1N. Luego se extrajo con cuatro porciones de 500 ml de acetato de etilo. Los extractos orgánicos se secaron con $NaSO_4$, filtraron y concentraron. El residuo se agitó con 300 ml de acetato de etilo y se filtró para dar 17,1 g del compuesto **22A–rac**. MS: Calculado para $C_{21}H_{22}ClF_2O_6S_2$ $(M+1)^+$ m/z = 507,1, experimental 507,3, Rt = 4,23 min.

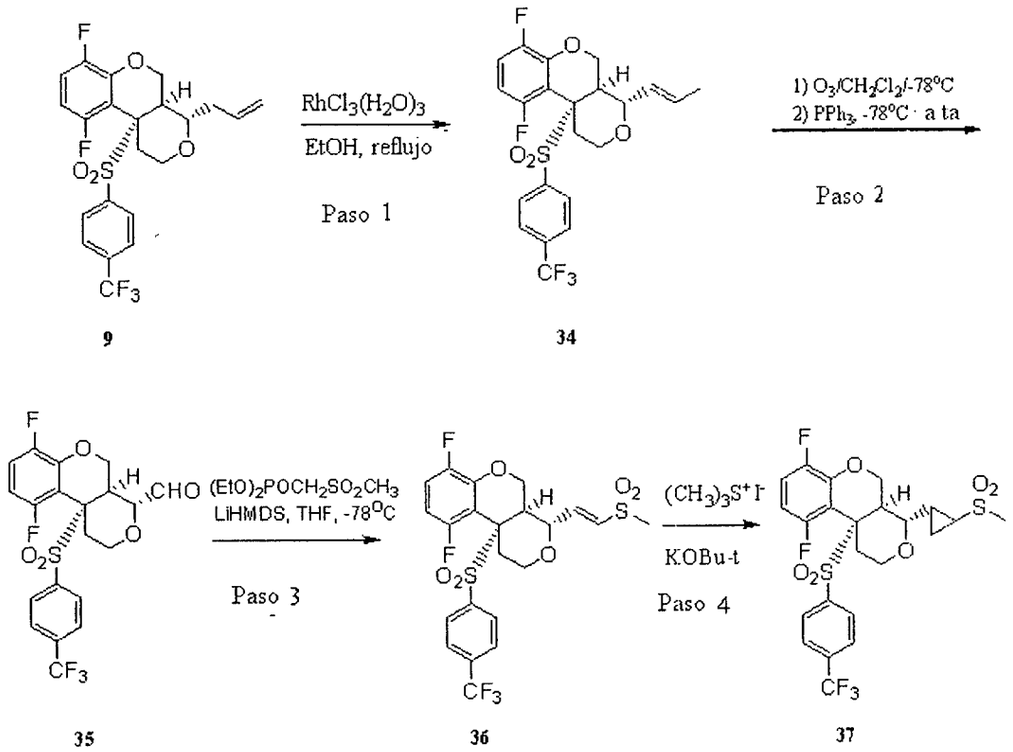
El racemato **22A–rac** se podría resolver en una columna Chiralcel OD eluyendo con 75% de alcohol isopropílico en hexanos para dar **22A (–)** (pico 1, tiempo de retención = 40,2 min, $[\alpha]_D^{20}$ –144,2°, conc = 1,000 M en diclorometano) y **22A (+)** (pico 2, tiempo de retención = 47,4 min, $[\alpha]_D^{20}$ –139,3°, conc = 1,000 M en diclorometano).

Paso 4

Los enantiómeros de vinilsulfona se separaron por HPLC preparativa en una columna Chiralcel OD eluyendo con 60% de isopropanol/hexano a 40 ml/min para dar **33 (–)** (0,139 g). El isómero deseado presentó un tiempo de retención de 56,6 min. MS: Calculado para $C_{21}H_{20}ClF_2O_6S_2$ $(M+1)^+$ m/z = 505,0, experimental 505,3, Rt = 4,33 min.

569

Esquema 7:



Paso 1

El derivado alilo **9** se isomerizó usando $RhCl_3$ como para el Esquema 3, paso 1 para dar la olefina **34**. En consecuencia, una mezcla agitada de **9** (0,413 g, 0,87 mmol) e hidrato de cloruro de rodio (III) (0,020 g, 0,096 mmol) en 10 ml de etanol se calentó a reflujo durante 1 hora (tlc: 20% EtOAc/hexano). El EtOH se evaporó al vacío para dar 0,442 g del producto bruto. Este material se purificó por cromatografía en columna flash en gel de sílice, eluyendo con un gradiente de solventes de 1% de EtOAc/hexano a 40% de EtOAc/hexano durante 30 min para producir **34** (0,343 g, 85%). MS: Calculado para $C_{22}H_{20}F_5O_4S$ $(M+1)^+$m/z = 475,1, experimental 475,3, Rt = 5,05 min.

Paso 2

Una solución agitada de **34** (0,322 g, 0,678 mmol) en 50 ml de diclorometano se enfrió a –78°C. Una corriente de O_3 se burbujeó a través la

solución hasta que un color azul del exceso O_3 persistió. La mezcla se agitó durante 5–10 min adicionales. UNa corriente de N_2 se burbujeó a través de la solución hasta que se volvió incolora. Se agregó trifenilfosfina (0,268 g, 1,02 mmol) en una porción, y la reacción se agitó a --78°C durante 10 min y a temperatura ambiente durante 16 horas (tlc: 20% EtOAc/hexano). El solvente se evaporó para dar 0,730 g de un aceite. El aceite se purificó por cromatografía en columna flash en gel de sílice, eluyendo con un gradiente de solventes de 1% de EtOAc/hexano a 40% de EtOAc/hexano durante 20 min para dar aldehído **35** (0,277 g, 88%). MS: Calculado para $C_{20}H_{16}F_5O_5S$ $(M+1)^+$m/z = 463,1, experimental 463,3, Rt = 4,05 min.

Paso 3

El aldehído **35** se convirtió en la vinilsulfona **36** usando un procedimiento análogo al descripto en Esquema 6, paso 2 (74% de rendimiento). MS: Calculado para $C_{22}H_{20}F_5O_6S_2$ $(M+1)^+$ m/z = 539,1, experimental 539,3, Rt = 4,36 min.

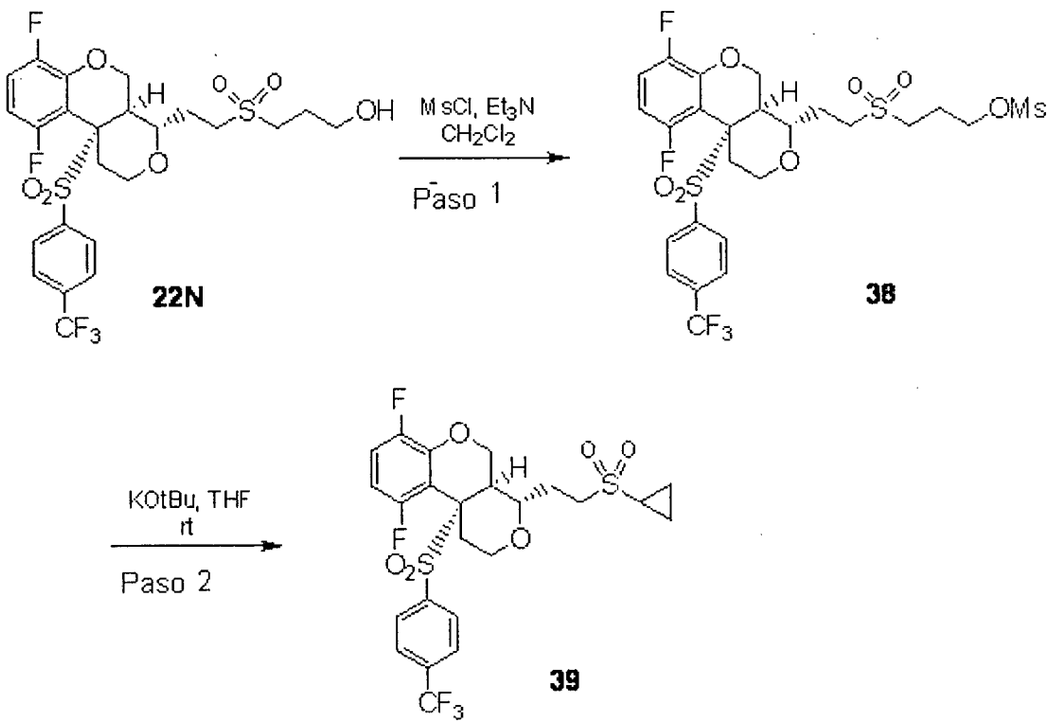
Paso 4

A una mezcla agitada de KOtBu (0,014 g, 0,121 mmol) en 1,5 ml de DMSO se agregó yoduro de trimetil sulfonio (0,027 g, 0,121 mmol). La solución se agitó a temperatura ambiente bajo argón durante 1 hora. Una solución de **36** (0,050 g, 0,093 mmol) en 0,75 ml de DMSO se agregó gota a gota. La agitación continuó toda la noche a temperatura ambiente (tlc: 40% EtOAc/hexano). La reacción se agregó a agua agitada (40–50 ml) y se extrajo con 2 40–ml porciones de EtOAc. Las fases EtOAc combinadas se lavaron con 20 ml de agua y 20 ml de salmuera. La fase en EtOAc se secó con anhidro sulfato de sodio y se evaporó para dar 0,050 g del producto deseado. El producto se purificó por cromatografía en columna flash en gel de sílice, eluyendo con un gradiente de solventes de 10% de EtOAc/hexano a 80% EtOAc/hexano durante 30 min para dar 0,037 g de

566

ciclopropilsulfona **37** (73%). MS: Calculado para $C_{23}H_{22}F_5O_6S_2$ $(M+1)^+$ m/z = 553,1, experimental 553,3, Rt = 4,28 min.

Esquema 8:



Paso 1

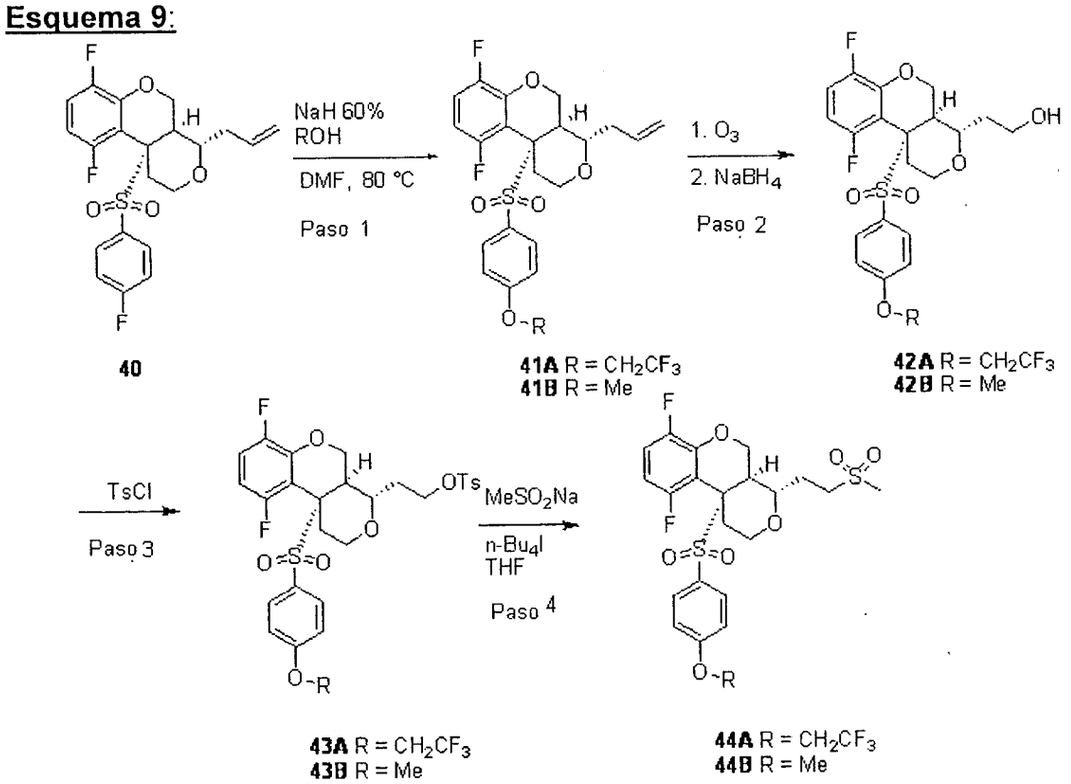
Se agregó trietilamina (0,012 g, 0,123 mmol) a una solución agitada de **22N** (0,048 g, 0,082 mmol) y MsCl (0,014 g, 0,123 mmol) en 1 ml de diclorometano a temperatura ambiente. Después de 1 hora la reacción finalizó (tlc: 50%EtOAc/hexano).La reacción se diluyó con 15 ml de diclorometano y se lavó con bicarbonato de sodio saturado (10 ml), agua (10 ml) y salmuera (10 ml). La fase de diclorometano se secó con anhidro sulfato de sodio y evaporó para dar **38** (0,048 g, 90%). Este material se usó directamente en la próxima reacción.

Paso 2

Se agregó KOtBu 1M en THF (0,054 mls, 0,054 mmol) gota a gota a una solución agitada de **38** (0,024 g, 0,036 mmol) en 50 ml de THF a temperatura ambiente. La reacción finalizó después de 30 min (tlc: 30% EtOAc/hexano). La

reacción se inactivó con la adición gota a gota de agua (1ml). La mezcla se diluyó con diclorometano (20 ml) y se dividió en agua (10 ml). La fase de diclorometano se secó con anhidro sulfato de sodio y se evaporó a 0,020 g del compuesto ciclopropilo deseado. La purificación por TLC preparativa en gel de sílice (50% de EtOAc/hexano) dio 0,018 g de compuesto deseado **39** (85%). MS: Calculado para $C_{24}H_{24}F_5O_6S_2$ $(M+1)^+$ m/z = 567,1, experimental 567,3, Rt = 4,60 min

Esquema 9:



40

41A R = CH_2CF_3
41B R = Me

42A R = CH_2CF_3
42B R = Me

43A R = CH_2CF_3
43B R = Me

44A R = CH_2CF_3
44B R = Me

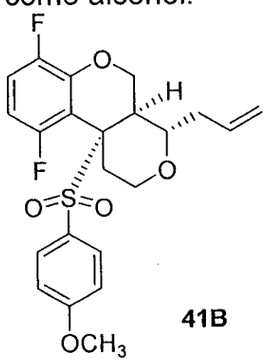
Paso 1

Una solución de trifluoroetanol (34 µL, 0,47 mmol) en 3 ml de DMF se trató con 60% de NaH (5,0 mg, 0,23 mmol) y se agitó durante 20 min. 4–Alil–7,10–difluoro–10–b–(4 fluoro–bencenosulfonil)–1,4a,5,10b–tetrahidro–2*H*,4*H*–piran[3,4–*c*] cromeno **40** (100 mg, 0,23 mmol, preparado de modo análogo al compuesto **19** del Esquema 2 usando 4–fluorofenilsulfuro del Paso 2) se agregó a

568

2 ml de DMF y la reacción se calentó a 80°C durante 18 h. La mezcla de reacción se diluyó con NH_4Cl saturado acuoso y se extrajo con diclorometano (3x). Los extractos orgánicos combinados se lavaron con H_2O, se secó con $MgSO_4$, y se concentró in vacuo. El residuo se purificó por cromatografía flash eluyendo con 15% de EtOAc/hexanos para proporcionar el compuesto deseado **41A** (80%) ^1H RMN ($CDCl_3$ 400 MHz) δ 7,67 (d, J = 8,7 Hz, 2H), 7,13–6,98 (m, 3H), 6,44 (m, 1H), 5,86 (m, 1H), 5,21–5,03 (m, 3H), 4,51–4,38 (m, 3H), 3,91 (m, 1H), 3,36 (m, 1H), 3,15 (t, J = 11,7 Hz, 1H), 2,66–2,47 (m, 3H), 2,45–2,24 (m, 2H).

El siguiente compuesto (**41B**) se preparó de modo análogo usando metanol como alcohol:



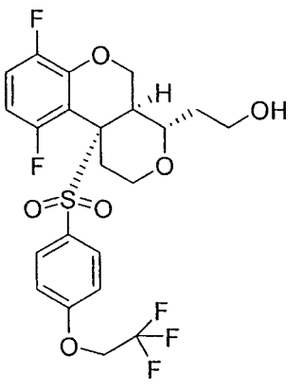
41B

^1H RMN ($CDCl_3$ 400 MHz) δ 7,60(d, J = 8,7 Hz, 2H), 7,06 (m, 1H), 6,97 (d, J = 8,05 Hz, 2H), 6,44 (m, 1H), 5,85 (m, 1H), 5,20–5,08 (m, 3H), 4,42 (d, J = 12,4 Hz, 1H), 3,88 (s, 4H), 3,35 (m, 1H), 3,15 (t, J = 11,7 Hz, 1H), 2,66–2,50 (m, 3H), 2,39 (m, 1H), 2,27 (m, 1H).

Paso 2

El alcohol **42A** se preparó de modo análogo al Esquema 1, Paso 10:

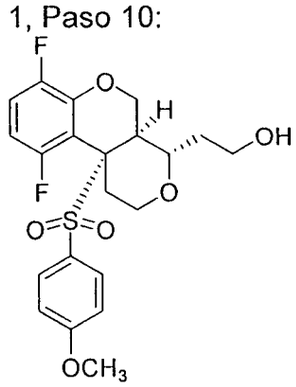
569



42A

^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,67 (d, J = 8,7 Hz, 2H), 7,16–6,98 (m, 3H), 6,44 (m, 1H), 5,86 (d, J= 12,44 Hz, 1H), 4,50–4,36 (m, 3 H), 3,91 (m, 1H),3,81–3,74 (m, 2H), 3,49 (m, 1 H), 3,19 (t, J = 11,7 Hz, 1 H), 2,65–2,49 (m, 3H), 2,37–2,23 (m, 1 H),2,11 (m, 1H), 1,78 (m, 1H).

De modo análogo, el alcohol **42B** se preparó de modo análogo al Esquema 1, Paso 10:



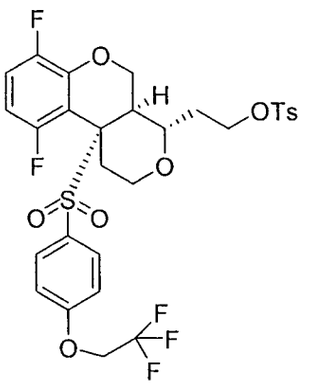
42B

^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,60(d, J = 8,7 Hz, 2H), 7,06 (m, 1H), 6,97 (d, J = 8,05 Hz, 2H), 6,44 (m, 1H), 5,17 (d, J = 12,4 Hz, 1H), 4,40 (d, J = 12,4 Hz, 1H), 3,88 (s, 4H), 3,81–3,73 (m, 2H),3,49 (m, 1H), 3,19 (t, J = 11,7 Hz, 1H), 2,58 (d, J = 12,4 Hz, 2H), 2,37–2,24 (m, 2H), 2,10 (m, 1H), 1,81 (m, 1H).

Paso 3

Tosilato **43A** se preparó de modo análogo al método descripto en el Esquema 1, Paso 12.

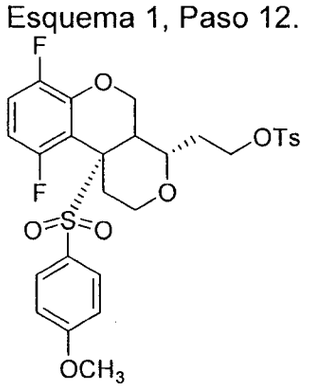
570



43A

^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,72 (d, J = 8,7 Hz, 2H),7,64 (d, J = 8,7 Hz, 2H),7,29 (d, J = 8,05 Hz, 2H), 7,15–7,06 (m, 1 H), 7,03 (d, J = 9,5 Hz, 2H), 6,45 (m, 1H), 5,10 (d, J= 10,2 Hz, 1H), 4,50–4,38 (m, 2H), 4,27 (d, J = 13,2 Hz,1H), 4,22–4,07 (m, 2H), 3,75 (m, 1H), 3,23 (m, 1H), 2,97 (t, J = 12,4 Hz, 1H), 2,54–2,43 (m, 2H), 2,42 (s, 3 H), 2,26–2,10 (m, 2H), 1,78 (m, 1H).

El compuesto **43B** se preparó de modo análogo al método descripto en el Esquema 1, Paso 12.



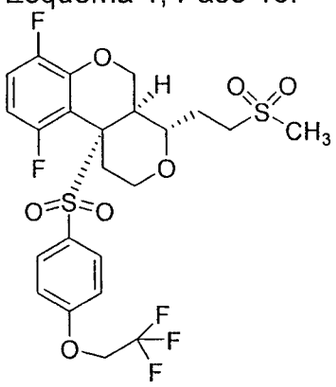
43B

^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,72 (d, J = 8,7 Hz, 2H),7,64 (d, J = 8,7 Hz, 2H),7,29 (d, J = 8,05 Hz, 2H), 7,15–7,06 (m, 1 H), 7,03 (d, J = 9,5 Hz, 2H), 6,45 (m, 1H), 5,10 (d, J= 9,50 Hz, 1H), 4,25 (d, J = 13,2 Hz,1H), 4,21–4,07 (m, 3H), 3,88 (s, 3H), 3,74 (m, 1H), 3,22 (m, 1H), 2,94 (t, J = 12,4 Hz, 1H), 2,53 (d, J = 13,9 Hz, 2H), 2,47–2,37 (m, 2H), 2,26–2,09 (m, 2H), 1,78 (m, 1H).

Paso 4

571

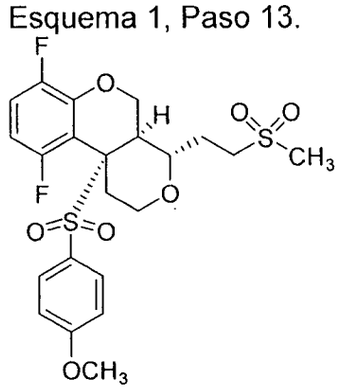
La sulfona **44A** se preparó de modo análogo al método descripto en el Esquema 1, Paso 13.



44A

^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,64 (d, J = 8,7 Hz, 2H), 7,08 (m, 1H), 7,04 (d, J = 9,5 Hz, 2H), 6,45 (m, 1H), 5,19 (d, J= 10,25 Hz, 1H), 4,49–4,38 (m, 3H), 3,89 (m, 1H),3,38–3,21 (m, 2H), 3,19 (t, J = 11,7 Hz, 1H), 3,00 (m, 1H), 2,90 (s, 3H), 2,62–2,50 (m, 2H), 2,43 (m, 1H), 2,28 (m, 1H), 2,02 (m, 1H). MS: Calculado para $C_{23}H_{23}F_5O_7S_2$ $(M+1)^+$, m/z = 571,3; experimental 571,3. Tiempo de retención 4,26 min.

La sulfona **44B** también se preparó de modo análogo al método descripto en Esquema 1, Paso 13.



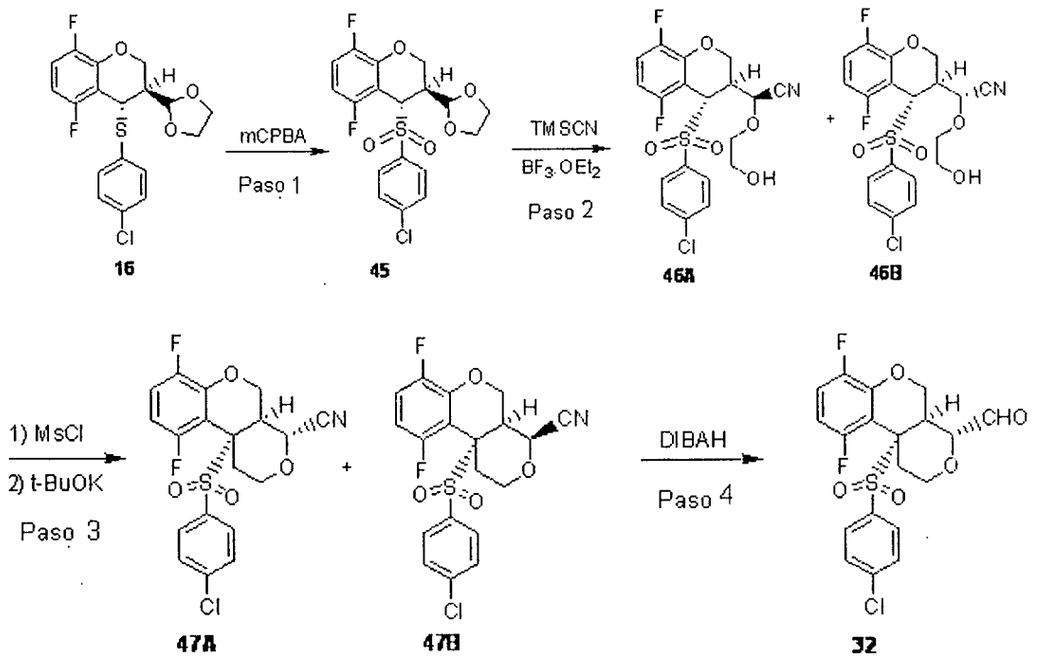
44B

^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,61 (d, J = 8,7 Hz, 2H), 7,08 (m, 1H), 6,98 (d, J = 8,7 Hz, 2H), 6,46 (m, 1H), 5,20 (d, J= 10,25 Hz, 1H), 4,41 (d, J = 12,4 Hz, 1H), 3,90 (s, 4H), 3,47 (m, 1H), 3,37–3,22 (m, 2H), 3,14 (t, J = 11,7 Hz, 1H), 2,99 (m, 1H), 2,89(s, 3H), 2,60 (m, 1H), 2,49 (m, 1H), 2,27 (m, 1H), 2,01(m, 1H). MS: Calculado

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para $C_{22}H_{24}F_2O_7S_2$ $(M+1)^+$, m/z = 503,3; experimental 503,3. Tiempo de retención 3,92 min.

Esquema 10:



Paso 1

A una solución agitada de 10,0 g (26,0 mmol) del compuesto **16** en 250 ml de diclorometano se agregaron 14,5 g (64,7 mmol) de 77% ácido 3–cloroperoxibenzoico a 0°C. La mezcla se agitó a temperatura ambiente toda la noche. Se diluyó con 400 ml de diclorometano y se inactivó a 0°C con 200 ml de bicarbonato de sodio saturado y 200 ml de tiosulfato de sodio 10%. La fase de diclorometano se lavó con 100 ml de 1 N NaOH, y se secó con sulfato de sodio. Se filtró, se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 5% a 45% de acetato de etilo en hexanos para dar 10,0 g del compuesto **45**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,74 (d, J = 8,0 Hz, 2 H), 7,51 (d, J = 8,0 Hz, 2 H), 7,01 (m, 1 H), 6,40 (m, 1 H), 4,88 (dd, J = 12, 4 Hz, 1 H),

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4,60–4,75 (m, 3 H), 3,75–4,0 (m, 4 H), 2,89 (m, 1 H)). MS: Calculado para $C_{18}H_{16}ClF_2O_5S$ (MH^+), m/z = 417,0; experimental 417,2. Tiempo de retención: 4,62 min.

Paso 2

A una solución de 3,99 g (9,58 mmol) del compuesto **45** en 60 ml de diclorometano a 0°C se agregaron 2,40 ml (17,95 mmol) de cianuro de trimetilsililo seguido por 1,60 ml (12,5 mmol) de eterato de trifluoruro de boro y la reacción se dejó calentar a temperatura ambiente y se agitó 90 min. La mezcla final se inactivó con agua, y se extrajo con tres porciones de 50 ml de diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentraron y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 20% a 100% de acetato de etilo en hexanos para proporcionar 3,80 g de **46A** y **46B** como una mezcla ~1:1. Estos compuestos se usaron directamente en la próxima reacción. MS: Calculado para $C_{19}H_{17}ClF_2NO_5S$ (MH^+), m/z = 444,0; experimental 444,2. Tiempo de retención: 3,93 min.

Paso 3

A una solución de 3,80 g (8,56 mmol) de una mezcla ~1:1 de los compuestos **46A** y **46B** en 20 ml de diclorometano a 0°C se agregaron 0,76 ml (9,84 mmol) de cloruro de metansulfonilo seguido por 1,40 ml (10,0 mmol) de trietilamina y la reacción se dejó calentar a temperatura ambiente toda la noche. La mezcla final se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 100% de acetato de etilo en hexanos para proporcionar 4,14 g de intermediario de metansulfonilo como una mezcla ~1:1. Una solución de 2,45 g (4,70 mmol) de este intermediario sulfonilo en 50 ml de tetrahidrofurano a 0°C se trató con 5,0 ml (5,0 mmol) de una solución 1 N de ter-butóxido de potasio en tetrahidrofurano. La mezcla se dejó a calentar

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lentamente a temperatura ambiente y se agitó a esta temperatura durante 2,5 h luego se inactivó con 100 ml de agua y se extrajo con tres porciones de 50 ml de diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 0% a 15% de acetato de etilo en diclorometano para dar 1,62 g del compuesto **47A** y 0,30 g del compuesto **47B**. **47A**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,63 (d, J = 8 Hz, 2 H), 7,53 (d, J = 8 Hz, 2 H), 7,15 (m, 1 H), 6,51 (m, 1 H), 5,25 (dd, J = 13, 3 Hz, 1 H), 4,60 (d, J = 12 Hz, 1 H), 4,15 (d, J = 11 Hz, 1 H), 4,00 (m, 1 H), 3,21 (t , J = 12 Hz, 1 H), 3,04 (br d, J = 12 Hz, 1 H), 2,58 (d, J = 14 Hz, 1 H), 2,38 (m, 1 H), MS: Calculado para $C_{19}H_{15}ClF_2NO_4S$ (MH^+), m/z = 426,0; experimental 426,2. Tiempo de retención: 4,61 min. **47B**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,55 (d, J = 8 Hz, 2 H), 7,50 (d, J = 8 Hz, 2 H), 7,15 (m, 1 H), 6,46 (m, 1 H), 5,22 (dd, J = 12, 4 Hz, 1 H), 4,93 (d, J = 6 Hz, 1 H), 4,35 (d, J = 13 Hz, 1 H), 3,95 (m, 1 H), 3,61 (t, J = 12 Hz, 1 H), 3,20 (t, J = 5 Hz, 1 H), 2,63 (d, J = 14 Hz, 1 H), 2,44 (m, 1 H), MS: Calculado para $C_{19}H_{15}ClF_2NO_4S$ (MH^+), m/z = 426,0; experimental 426,2. Tiempo de retención: 4,43

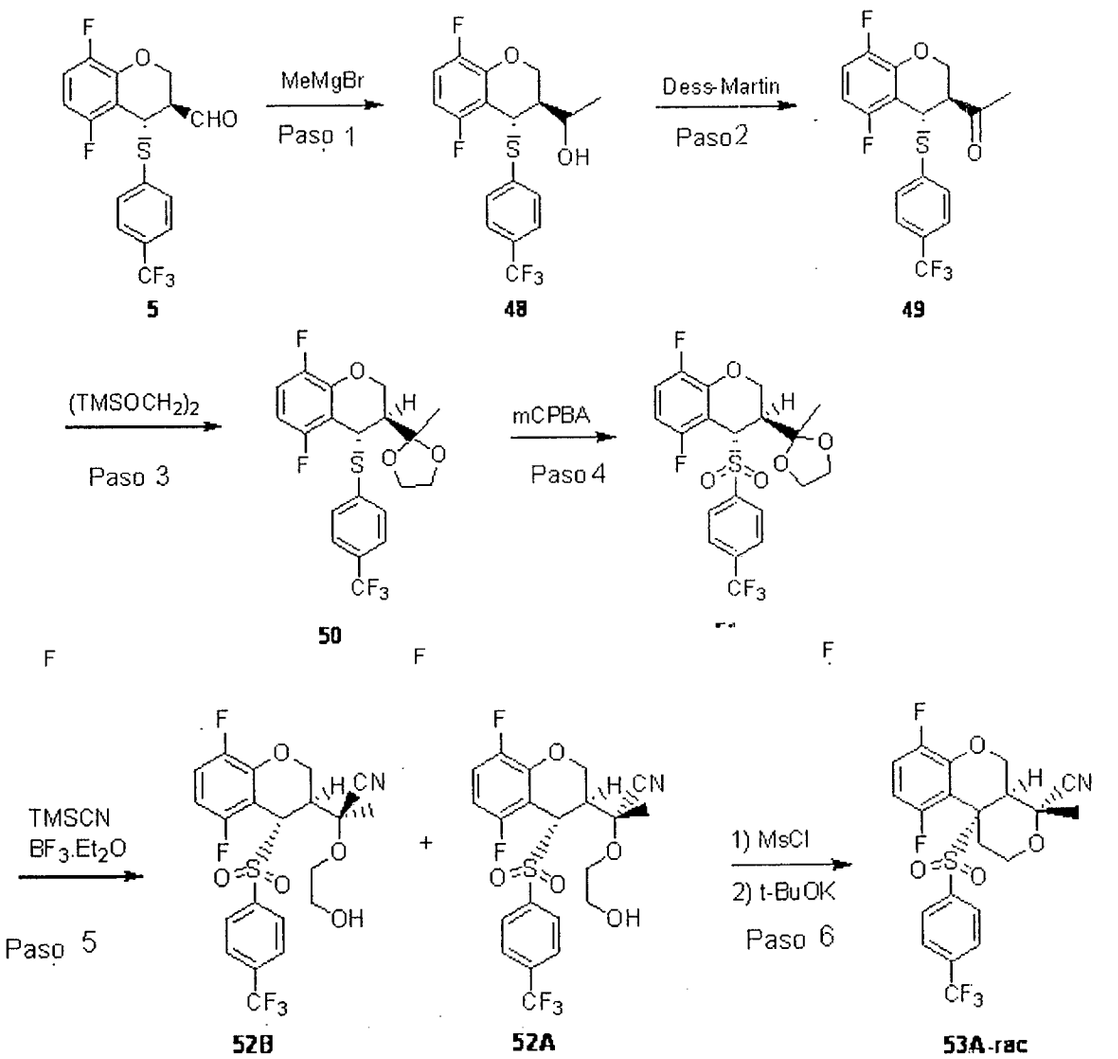
Paso 4

A una solución de 0,75 g (1,76 mmol) del compuesto **47A** en 15 ml de diclorometano a –78°C se agregaron 1,85 ml (1,85 mmol) de una solución 1N de hidruro de diisobutilaluminio en hexanos y la reacción se agitó 2 h a esta temperatura, luego se dejó calentar a temperatura ambiente durante 1 h. La mezcla se inactivó con 0,3 ml de metanol luego se vertió en ácido clorhídrico 1N y se agitó 25 min. La mezcla luego se extrajo con diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentraron para dar 0,63 g de aldehído **32**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 9,62 (s, 1 H), 7,63 (d, J = 8 Hz, 2 H), 7,51 (d, J = 8 Hz, 2 H), 7,11 (m, 1 H), 6,47 (m, 1 H), 5,07 (dd, J = 13, 2 Hz, 1 H), 4,67 (d, J = 12 Hz, 1 H), 4,02 (m, 1 H), 3,71 (d, J = 11 Hz, 1 H), 3,25 (t, J = 12 Hz, 1 H), 2,87 (d, J = 11 Hz, 1 H), 2,61 (d, J = 13 Hz, 1 H), 2,33 (m, 1 H). MS:

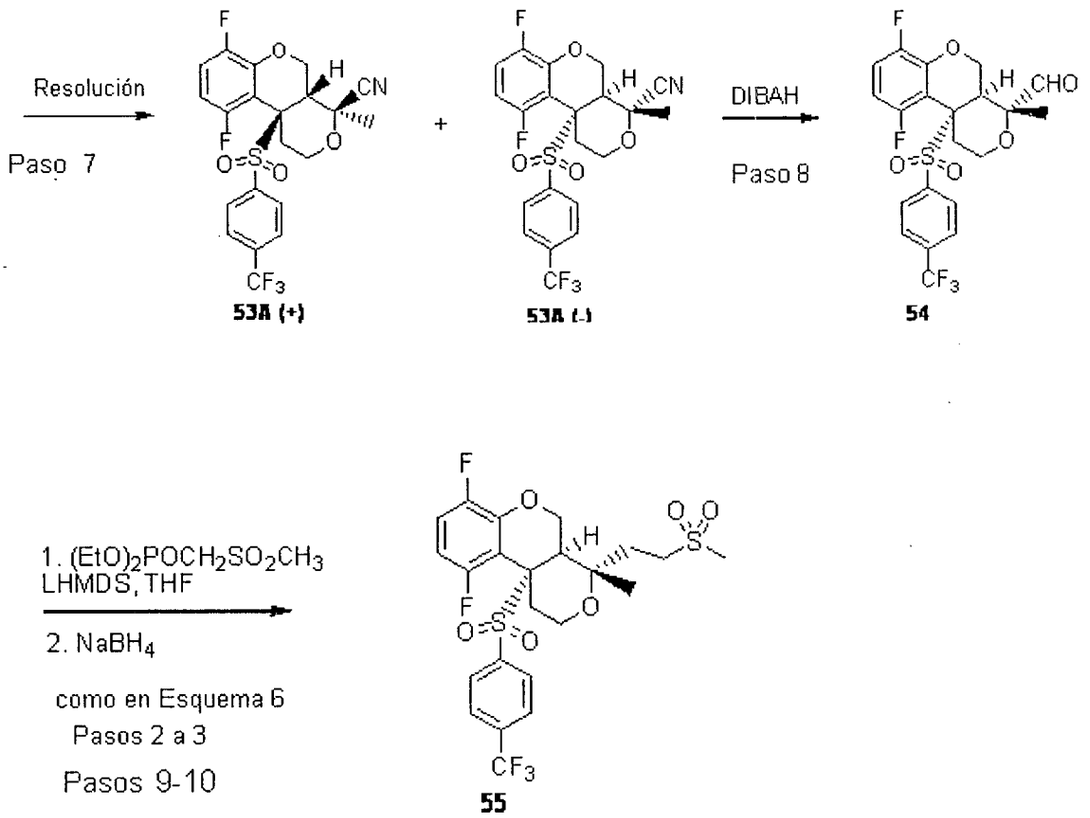
575

Calculado para $C_{19}H_{16}ClF_2O_5S$ (MH^+), m/z = 429,0; experimental 429,2. Tiempo de retención: 3,95 min.

Esquema 11:



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Paso 1

A una suspensión de 29,6 g (120 mmol) de cloruro de cerio (III) en 120 ml de tetrahidrofurano a 0°C durante 90 min se agregaron 40 ml (120 mmol) de bromuro de metilmagnesio 3 N en éter dietílico y la reacción se agitó 1 h a 0°C. Se agregó una solución de 15,0 g (40,1 mmol) del compuesto **5** en 60 ml de tetrahidrofurano y la reacción se agitó 1 h a 10°C. La mezcla final se vertió en cloruro de amonio saturado, se extrajo con acetato de etilo, se secó con sulfato de sodio y se concentró. El residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 40% de acetato de etilo en hexanos para dar 12,1 g del compuesto **48**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,59 (m, 4 H), 6,98 (m, 1 H), 6,61 (m, 1 H), 5,15 (s, 1 H), 4,35–4,75 (m, 2 H), 3,74 (m, 1 H), 1,95 (m, 1 H), 1,36 y 1,16 (t, J = 7 Hz, 3 H), MS: Calculado para $C_{18}H_{15}F_5O_2S$ (MH^+), m/z = 391,1; experimental 391,2. Tiempo de retención: 4,98 min.

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Paso 2

A una solución agitada de 12,1 g (30,9 mmol) del compuesto **48** en 150 ml de diclorometano se agregaron 15,7 g (37,0 mmol) de peryodinano de Dess–Martin. La mezcla se agitó a temperatura ambiente durante 1 h luego se filtró. El filtrado se concentró y se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 40% de acetato de etilo en hexanos para dar 9,96 g del compuesto **49**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,59 (d, J = 8 Hz, 2 H), 7,54 (d, J = 8 Hz, 2 H), 6,98 (m, 1 H), 6,62 (m, 1 H), 5,12 (s, 1 H), 4,86 (d, J = 12 Hz, 1 H), 4,75 (d, J = 12 Hz, 1 H), 2,89 (s, 1 H), 2,28 (s, 3 H), MS: Calculado para $C_{18}H_{14}F_5O_2S$ (MH^+), m/z = 389,1; experimental 389,2. Tiempo de retención: 5,14 min.

Paso 3

A una solución de 6,98 g (18,0 mmol) del compuesto **49** en 60 ml de diclorometano se agregaron 7,90 ml (32,5 mmol) de 1,2–bis(trimetilsiloxi)etano y 0,25 ml (1,50 mmol) de trifluorometansulfonato de trimetilsililo a –78°C. Después de 30 min, la solución se calentó a temperatura ambiente y se agitó durante 48 h. La reacción se inactivó con bicarbonato de sodio saturado y se extrajo con diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentraron y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 100% de diclorometano en hexanos para dar 7,37 g del compuesto **50**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,60 (m, 4 H), 6,98 (m, 1 H), 6,58 (m, 1 H), 4,86 (s, 1 H), 4,60 (m, 2 H), 3,80–3,95 (m, 3 H), 3,59 (m, 1 H), 2,17 (s, 1 H), 1,20 (s, 3H), MS: Calculado para $C_{20}H_{18}F_5O_3S$ (MH^+), m/z = 433,1; experimental 433,3. Tiempo de retención: 5,48 min.

Paso 4

A una solución de 8,92 g (20,6 mmol) del compuesto **50** en 130 ml de diclorometano se agregaron 13,4 g (60,0 mmol) de 77% de ácido 3–cloroperoxibenzoico a 0°C. La mezcla se agitó a temperatura ambiente toda la

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noche luego se filtró, se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 100% de diclorometano en hexanos para dar 9,13 g del compuesto **51**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,95 (d, J = 8,0 Hz, 2 H), 7,80 (d, J = 8,0 Hz, 2 H), 7,01 (m, 1 H), 6,38 (m, 1 H), 4,81 (dd, J = 12, 5 Hz, 1 H), 4,74 (s, 1H), 4,66 (d, J = 12 Hz, 1 H), 2,93 (d, J = 4 Hz, 1 H), 1,13 (s, 3 H), MS: Calculado para $C_{20}H_{18}F_5O_5S$ (MH^+), m/z = 465,1; experimental 465,3. Tiempo de retención: 4,74 min.

Paso 5

A una solución de 9,13 g (19,6 mmol) del compuesto **51** en 100 ml de diclorometano a 0°C se agregaron 4,10 ml de cianuro de trimetilsililo (30,8 mmol) seguido por 2,55 ml (20,3 mmol) de eterato de trifluoruro de boro gota a gota y la reacción se dejó calentar a temperatura ambiente y se agitó 2 h. La mezcla se inactivó con agua y se extrajo con diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentraron y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 50% de acetato de etilo en hexanos para proporcionar 4,27 g del compuesto **52A** y 3,50 g del compuesto **52B**. **52A**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,96 (d, J = 8 Hz, 2 H), 7,82 (d, J = 8 Hz, 2 H), 7,05 (m, 1 H), 6,42 (m, 1 H), 4,93 (dd, J = 13, 4 Hz, 1 H), 4,82 (s, 1 H), 4,74 (d, J = 13 Hz, 1 H), 3,71 (m, 2 H), 3,65 (m, 2 H), 3,37 (m, 1 H), 1,56 (m, 1 H), 1,42 (s, 3 H), MS: Calculado para $C_{21}H_{19}F_5NO_5S$ (MH^+), m/z = 492,1; experimental 492,3. Tiempo de retención: 4,23 min. **52B**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,95 (d, J = 8 Hz, 2 H), 7,82 (d, J = 8 Hz, 2 H), 7,07 (m, 1 H), 6,46 (m, 1 H), 4,86 (dd, J = 13, 5 Hz, 1 H), 4,82 (s, 1 H), 4,67 (d, J = 13 Hz, 1 H), 3,68 (m, 4 H), 3,22 (m, 1 H), 1,64 (br s, 1 H), 1,56 (s, 3 H), MS: Calculado para $C_{21}H_{19}F_5NO_5S$ (MH^+), m/z = 492,1; experimental 492,3. Tiempo de retención: 4,22 min.

Paso 6

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A una solución de 4,27 g (8,69 mmol) del compuesto **52A** en 40 ml de diclorometano se agregaron 1,40 ml (10,0 mmol) de trietilamina y 0,78 ml (10,0 mmol) de cloruro de metansulfonilo. La mezcla se agitó a temperatura ambiente toda la noche luego se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 50% de acetato de etilo en hexanos para proporcionar 4,91 g del intermediario metansulfonilo. Una solución de 4,91 g (8,73 mmol) de este intermediario metansulfonilo en 70 ml de tetrahidrofurano a 0°C se trató con 10,5 ml (10,5 mmol) de una solución de ter-butóxido de potasio 1N en tetrahidrofurano. La mezcla se dejó calentar lentamente a temperatura ambiente y se agitó a esta temperatura durante 30 min luego se inactivó con 100 ml de agua y se extrajo con dos porciones de 150 ml de diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentraron y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 50% de acetato de etilo en hexanos para proporcionar 1,77 g del compuesto **53A–rac** y 0,42 g de intermediario metansulfonilo recuperado. **53A–rac**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,80 (m, 4 H), 7,13 (m, 1 H), 6,44 (m, 1 H), 5,20 (dd, J = 13, 4 Hz, 1 H), 4,64 (d, J = 13 Hz, 1 H), 3,95 (m, 1 H), 3,44 (m, 1 H), 3,36 (d, J = 4 Hz, 1 H), 2,60 (m, 2 H), 1,52 (s, 3 H), MS: Calculado para $C_{21}H_{17}F_5NO_4S$ (MH^+), m/z = 474,1; experimental 474,3. Tiempo de retención: 4,78 min.

Paso 7

El Compuesto **53A–rac** (1,7 g) se resolvió en un columna Chiral OD eluyendo con 60% de isopropanol en hexanos y 35 ml /min de velocidad de flujo para dar dos enantiómeros **53A (–)**(0,82 g, $[\alpha]_D^{20}$ –94,4°) y **53A (+)** (0,88 g, $[\alpha]_D^{20}$ +90,3°).

Paso 8

A una solución de 200 mg (0,42 mmol) del compuesto **53A (–)** en 8 ml de diclorometano a –78°C se agegaron 0,89 ml (0,89 mmol) de una solución 1N de

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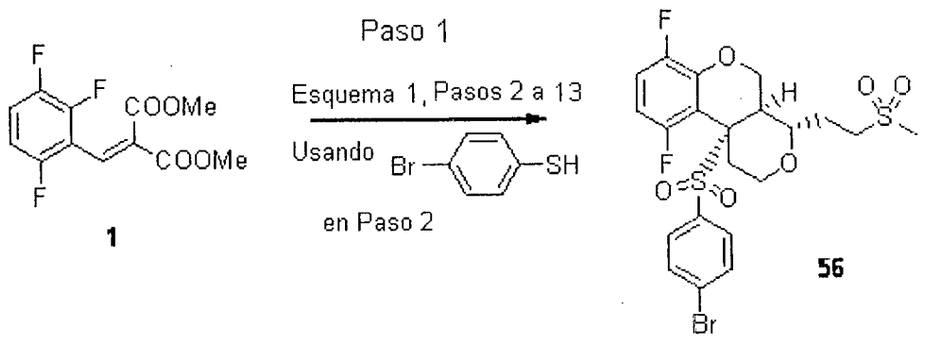
hidruro de diisobutil aluminio en hexanos y la reacción se agitó 1 h a esta temperatura. La mezcla se inactivó con 0,2 ml de metanol luego se diluyó con diclorometano y salmuera. Se agregó celite y la suspensión se agitó a temperatura ambiente durante 15 min. La mezcla se filtró en celite luego se extrajo con diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentraron y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 50% de acetato de etilo en hexanos para proporcionar 92 mg del compuesto **54 (–)**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 9,43 (s, 1 H), 7,78 (m, 4 H), 7,12 (m, 1 H), 6,42 (m, 1 H), 5,06 (dd, J = 12, 5 Hz, 1 H), 4,49 (d, J = 12 Hz, 1 H), 3,90 (m, 1 H), 3,49 (m, 1 H), 3,04 (d, J = 4 Hz, 1 H), 2,58 (m, 1 H), 2,42 (m, 1H), 1,13 (s, 3 H), MS: Calculado para $C_{21}H_{18}F_5O_5S$ (MH^+), m/z = 477,1; experimental 477,3. Tiempo de retención: 4,46 min.

Pasos 9–10

El Compuesto **54 (–)** se sometió a las condiciones análogas a las descriptas en el Esquema 6, Pasos 2 a 3, con la exclusión del la purificación final de HPLC quiral proporcionar el compuesto **55**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,76 (m, 4 H), 7,11 (m, 1 H), 6,40 (m, 1 H), 5,17 (dd, J = 13, 5 Hz, 1 H), 4,45 (d, J = 13 Hz, 1 H), 3,74 (m, 1 H), 3,37 (t, J = 12 Hz, 1 H), 3,23 (m, 1 H), 3,14 (m, 1 H), 2,95 (s, 3 H), 2,74 (d, J = 4 Hz, 1 H), 2,54 (d, J = 14 Hz, 1 H), 2,34 (m, 1 H), 2,24 (m, 1 H), 2,16 (m, 1 H), 1,01 (s, 3 H). MS: Calculado para $C_{23}H_{24}F_5O_6S_2$ (MH^+), m/z = 555,1; experimental 555,3. Tiempo de retención: 4,50 min.

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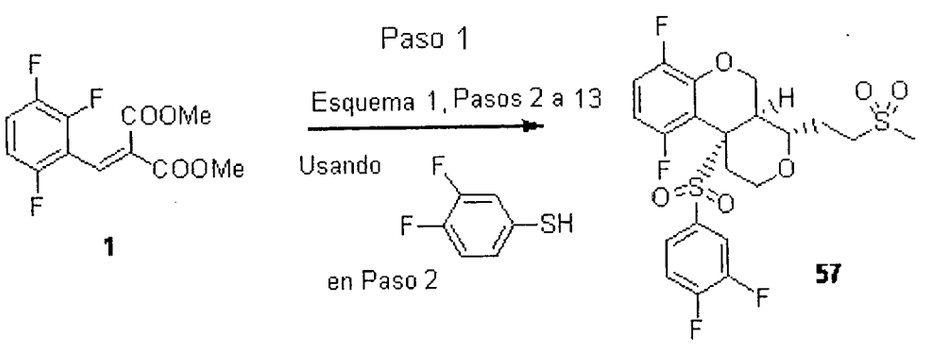
Esquema 12:



Paso 1

El Compuesto **1** se sometió a las condiciones análogas a las descriptas en el Esquema 1, Pasos 2 a 13, y usando 4–bromotiofenol en vez de 4–clorotiofenol del Paso 2, para proporcionar el compuesto **56**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,68 (d, J = 8 Hz, 2 H), 7,55 (d, J = 8 Hz, 2 H), 7,10 (m, 1 H), 6,48 (m, 1 H), 5,17 (dd, J = 12, 2,4 Hz, 1 H), 4,44 (d, J = 12 Hz, 1 H), 3,90 (br d, J = 12 Hz, 1 H), 3,34 (m, 1 H), 3,27 (m, 1 H), 3,14 (m, 1 H), 3,02 (m, 1 H), 2,91 (s, 3 H), 2,50–2,60 (m, 2 H), 2,44 (m, 1 H), 2,29 (m, 1 H), 2,03 (m, 1 H). MS: Calculado para $C_{21}H_{22}BrF_2O_6S_2$ (MH+), m/z = 551,0; experimental 551,3. Tiempo de retención: 4,34 min.

Esquema 13:



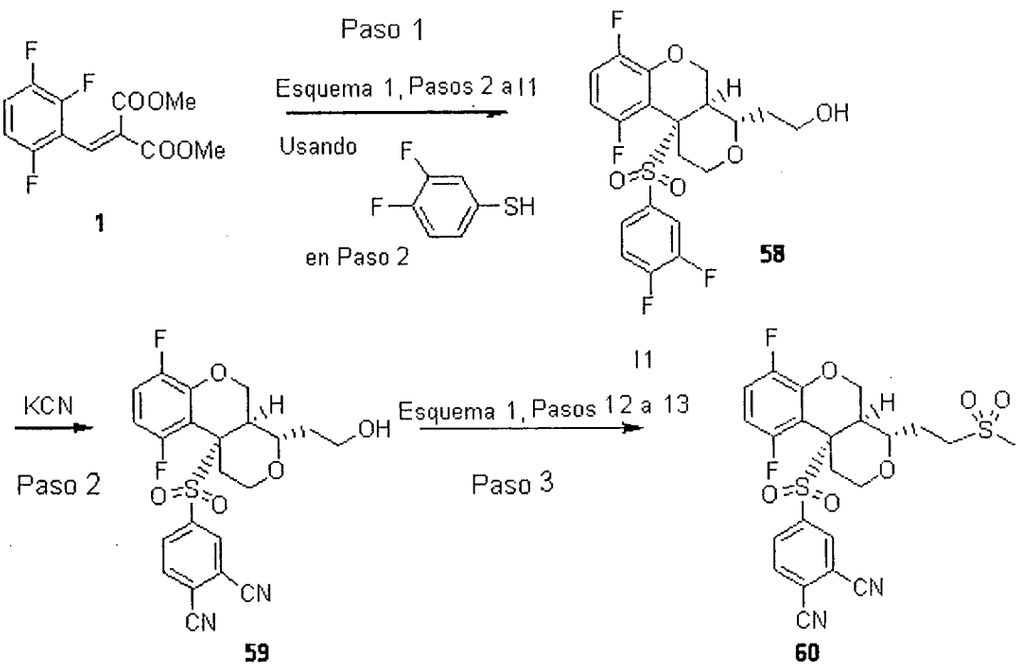
Paso 1

Compuesto **1** se sometió a condiciones análogas a las descriptas en el Esquema 1, Pasos 2 a 13, y usando 3,4–difluorotiofenol en vez de 4–clorotiofenol en el Paso 2, para proporcionar el compuesto **57**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ

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7,54 (m, 1 H), 7,48 (m, 1 H), 7,33 (m, 1 H), 7,11 (m, 1 H), 6,47 (m, 1 H), 5,15 (dd, J = 13, 3 Hz, 1 H), 4,45 (d, J = 12 Hz, 1 H), 3,91 (m, 1 H), 3,35 (m, 1 H), 3,27 (m, 1 H), 3,14 (t, J = 12 Hz, 1 H), 3,01 (m, 1 H), 2,91 (s, 3 H), 2,50–2,60 (m, 2 H), 2,44 (m, 1 H), 2,31 (m, 1 H), 2,04 (m, 1 H). MS: Calculado para $C_{21}H_{21}F_4O_6S_2$ (MH+), m/z = 509,1; experimental 509,3. Tiempo de retención: 4,13 min.

Esquema 14:



Paso 1

El Compuesto **1** se sometió a condiciones similares a las descriptas en el Esquema 1 Pasos 2 a 11, y usando 3,4–difluorotiofenol en vez de 4–clorotiofenol en el Paso 2, para proporcionar el compuesto **58**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,40–7,60 (m, 2 H), 7,34 (m, 1 H), 7,12 (m, 1 H), 6,47 (m, 1 H), 5,15 (dd, J = 12, 3 Hz, 1 H), 4,44 (d, J = 12 Hz, 1 H), 3,93 (m, 1 H), 3,80 (m, 2 H), 3,50 (m, 1 H), 3,20 (t, J = 12 Hz, 1 H), 2,67 (m, 1 H), 2,52 (d, J = 10 Hz, 1 H), 2,35 (m, 1 H), 2,26 (m,

1 H), 2,12 (m, 1 H), 1,85 (m, 1 H), 1,55 (s, 1 H), MS: Calculado para $C_{20}H_{19}F_4O_5S$ (MH+), m/z = 447,1; experimental 447,2. Tiempo de retención: 3,93 min.

Paso 2

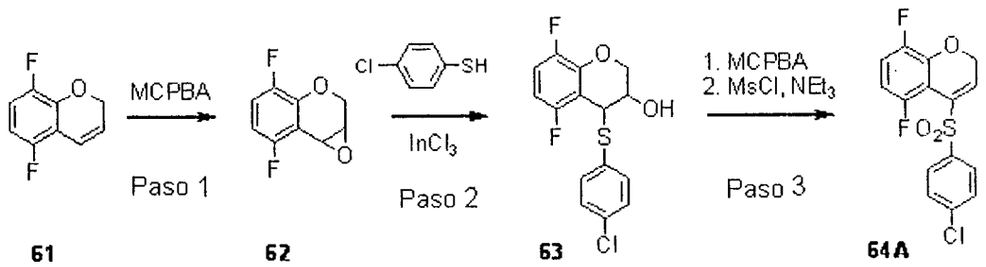
Una solución de 100 mg (0,22 mmol) del compuesto **58** en 2 ml de acetonitrilo se trató con 30 mg (0,44 mmol) de cianuro de potasio y se calentó a reflujo toda la noche. La mezcla se diluyó con agua y diclorometano y se extrajo con diclorometano. Los extractos orgánicos combinados se secaron con sulfato de sodio y se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 1% a 50% de acetato de etilo en hexanos para proporcionar 25 mg del compuesto **59** y 25 mg de **58** inicial. **59**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 8,10 (s, 1 H), 8,05 (d, J = 8 Hz, 1 H), 7,99 (d, J = 8 Hz, 1 H), 7,16 (m, 1 H), 6,49 (m, 1 H), 5,08 (dd, J = 12, 3 Hz, 1 H), 4,48 (d, J = 13 Hz, 1 H), 3,93 (m, 1 H), 3,80 (m, 2 H), 3,52 (m, 1 H), 3,18 (m, 1 H), 2,74 (d, J = 10 Hz, 1 H), 2,68 (m, 1 H), 2,38 (m, 1 H), 2,24 (m, 1 H), 2,12 (m, 1 H), 1,86 (m, 1 H), 1,05 (s, 1 H), MS: Calculado para $C_{22}H_{19}F_2N_2O_5S$ (MH+), m/z = 461,1; experimental 461,3. Tiempo de retención: 3,78 min.

Paso 3

El Compuesto **59** se sometió a condiciones similares a las descriptas en el Esquema 1, Pasos 12 a 13 para proporcionar el compuesto **60**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 8,10 (s, 1 H), 8,04 (d, J = 9 Hz, 1 H), 7,99 (d, J = 9 Hz, 1 H), 7,17 (m, 1 H), 6,50 (m, 1 H), 5,11 (dd, J = 12, 2,2 Hz, 1 H), 4,50 (d, J = 12 Hz, 1 H), 3,93 (br d, J = 12 Hz, 1 H), 3,38 (m, 1 H), 3,29 (m, 1 H), 3,14 (m, 1 H), 3,03 (m, 1 H), 2,93 (s, 3 H), 2,67 (d, J = 9 Hz, 1 H), 2,45–2,55 (m, 2 H), 2,08 (m, 1 H); MS Calculado para $C_{23}H_{21}F_2N_2O_6S_2$ (MH+), m/z = 523,1; experimental 523,3. Tiempo de retención: 3,92 min.

Esquema 15:

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Paso 1:*Óxido de 5,8–difluoro–2H–cromeno óxido*

5,8–Difluoro–2H–cromeno **61** (35g, 0,21 mol) se disolvió en 500 ml de diclorometano y se agregaron 93 g de MCPBA (77%, 0,42 mol). La reacción se agitó a temperatura ambiente durante 30 minutes. La reacción se inactivó con una solución de 50 g $Na_2S_2O_3$ en 500 ml agua. La fase orgánica se lavó con dos porciones de 500 ml de solución de NaOH 2N, 200 ml de salmuera, se secó con Na_2SO_4 y se concentró. El residuo se recristalizó en solución de EtOAc/Hexano para dar origen a 21,6 g de producto puro **62**. El residuo del agua madre se purificó por cromatografía en columna eluyendo con un gradiente de hexanos a 25% EtOAc/hexanos durante 55 minutos para obtener 1,4 g adicionales de **62**. Rendimiento total: 23 g, 60%. ^{1}H RMN ($CDCl_3$ 400 MHz δ 7,00 (m, 1H), 6,63 (m, 1H), 4,67 (d, J = 12,4 Hz, 1H), 4,27 (m, 2H), 3,84 (d, J = 4,4Hz, 1H).

Paso 2: *4–(4–Cloro–fenilsulfanil)–5,8–difluoro–croman–3–ol*

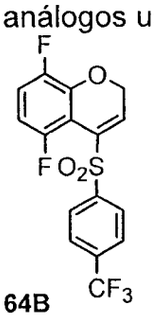
Se disolvieron óxido de 5,8–difluoro–2H–cromeno **62** (23 g, 0,125 mol) y 4–cloro–bencenotiol (18,1 g, 0,125 mmol) en n 500 ml de diclorometano y se agregaron 2,9 g de $InCl_3$ (0,013 mol). La reacción se agitó a temperatura ambiente toda la noche. La reacción se dividió entre 200 ml de diclorometano y 200 ml de agua. La fase orgánica se lavó con salmuera, se secó con Na_2SO_4 y se concentró. El producto se purificó por cromatografía en columna eluyendo con un gradiente de hexanos a 50% de EtOAc/hexano durante 55 minutos para dar 23,2 g de alcohol **63** (57%). ^{1}H RMN ($CDCl_3$ 400 MHz δ 7,48 (d, J = 8,8 Hz, 2H), 7,34

(d, J = 8,8 Hz, 2H), 7,01 (m, 1H), 6,64 (m, 1H), 4,63 (d, J = 11,7 Hz, 1H), 4,32–4,41 (m, 2H), 4,12 (m, 1H).

Paso 3: *4–(4–Cloro–bencenosulfonil)–5,8–difluoro–2H–cromeno*

Se disolvió 4–(4–cloro–fenilsulfanil)–5,8–difluoro–chroman–3–ol **63** (23,2 g, 71 mmol) en 200 ml de diclorometano y se agregaron 31,7 g (77%, 142 mmol) de MCPBA. La reacción se agitó a temperatura ambiente durante 3 horas, luego se inactivó con una solución de 10 g de $Na_2S_2O_3$ en 50 ml agua. La fase orgánica se lavó con 2 porciones de 100 ml de una solución de NaOH 1N, 100 ml de salmuera, se secó con Na_2SO_4 y se concentró. El residuo se disolvió en 200 ml de diclorometano, se agregaron 16,1 g de cloruro de mesilo (142 mmol) y 14,3 g de trietilamina (142 mmol). La reacción se agitó a temperatura ambiente durante una hora. La solución de reacción se lavó con 100 ml de salmuera, se secó con Na_2SO_4 y se concentró. El residuo se recristalizó en solución de EtOAc/Hexano para dar 8,4 g de producto de vinilsulfona puro **64**. El residuo del agua madre se purificó por cromatografía en columna eluyendo con un gradiente de hexanos a 25% de EtOAc/hexano durante 55 minutos para dar 7,1 g vinilsulfona adiciona **64A**. Rendimiento total: 15,5 g, 64%. ^{1}H RMN ($CDCl_3$ 400 MHz δ 7,84 (dd, J = 8,8 y 2,2 Hz, 2H), 7,51 (d, J = 8,1 Hz, 2H), 7,30 (t, J = 4,4Hz, 1H), 7,00 (m, 1H), 6,54 (m, 1H), 4,99 (d, J = 4,4 Hz, 2H).

El siguiente compuesto (**64B**) se preparó por medio de una vía de tres pasos análogos usando 4–trifluorometilfenilsulfuro en el Paso 2:

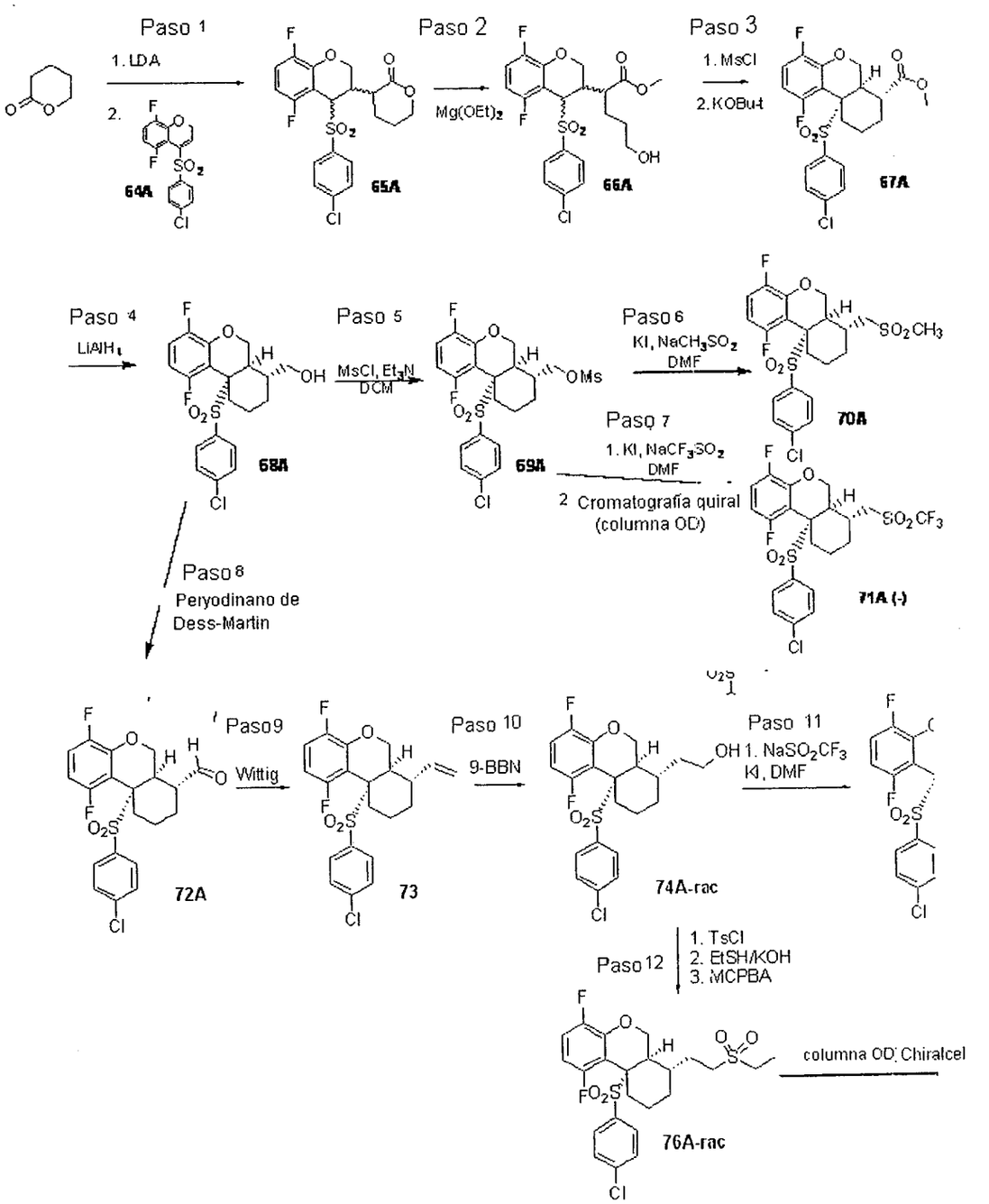


64B

^{1}HRMN (CDCl3)δ: 8,03 (d, 2H), 7,81 (d, 2H), 7,38 (m, 1H), 7,01δ (m, 1H), 6,54 (m, 1H), 5,01 (d, 2H)

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Esquema 16:



Paso 1

A una solución de 8,25 ml (58,3 mmol) de diisopropilamina en 100 ml de THF a –40 °C se agregaron 23,3 ml (58,3 mmol) de una solución 2,5 M de n–butil litio en hexanos. La mezcla se agitó durante 20 min y enfrió a –78°C. Una

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solución de 5,84 g (58,35 mmol) de delta–valerolactona en 10 ml de THF se agregó gota a gota. La mezcla viscosa resultante se agitó a –78°C durante un período de 45 min, seguido por la adición gota a gota de una solución de 10,0 g (29,177 mmol) de alqueno **64A** en 40 ml de THF. La mezcla se agitó en el frío durante 15 min, se inactivó con 50% de NH_4Cl saturado, se extrajo con EtOAc, se lavó con salmuera, se secó con $MgSO_4$, y se concentró. El producto bruto se pasó a través de 120 g de gel de sílice usando un gradiente de 0% a 40% de acetato de etilo en hexanos para suministrar 11,53 g de producto **65A** como una mezcla de diastereómeros. ^1H RMN ($CDCl_3$ 400 MHz) δ 7,91 (d, J = 8,8 Hz, 1 H), 7,78 (d, J = 8,8 Hz, 1 H), 7,75 (d, J = 8,8 Hz, 1 H), 7,53 (d, J = 8,8 Hz, 1 H), 7,10–7,01 (ser. m., 1 H), 6,59–6,47 (ser. m., 1 H), 5,09 (s, 0,5 H), 4,95 (dd, J = 12,3, 8,6 Hz, 0,5 H), 4,81 (dd, J = 12,6, 2,6 Hz, 0,5 H), 4,60 (dt, J = 12,3, 1,8 Hz, 0,5 H), 4,47 (dt, J = 12,6, 1,8 Hz, 0,5 H), 4,46 (s, 0,5 H), 4,29–4,14 (ser. m., 2H), 3,34 (m, 0,5 H), 3,08 (dm, J = 9,8 Hz, 0,5 H), 2,64–2,52 (ser. m, 0,5 H), 2,39–2,29 (m, 0,5 H), 2,28–2,19 (m, 0,5 H), 1,96–1,87 (ser m, 1,5 H), 1,70–1,62 (ser. m., 1,5 H), 1,39–1,28 (m, 0,5 H).

Paso 2

A una mezcla de 11,00 g (24,88 mmol) del compuesto **65A** en 120 ml de metanol se agregaron 3,20 g (29,86 mmol) de etóxido de magnesio. La mezcla resultante se agitó toda la noche y se tomó en 1200 ml de acetato de etilo. La mezcla se lavó sucesivamente con 600 ml de NaOH 1M, dos veces con 1 L de agua, y 600 ml de salmuera. La fase orgánica se secó con $MgSO_4$ y se concentró in vacuo para suministrar 11,0 g de alcohol **66A**. ^1H RMN ($CDCl_3$ 400 MHz) δ 7,77 (d, J = 8,8 Hz, 1 H), 7,74 (d, J = 8,8 Hz, 1 H), 7,54 (d, J = 8,8 Hz, 1 H), 7,52 (d, J = 8,8 Hz, 1 H), 7,10–7,00 (m, 1 H), 6,53–6,40 (ser. m, 1 H), 4,90 (td, J = 12,5, 3,1 Hz, 1H), 4,56–4,46 (ser. m., 1 H), 4,31–4,24 (ser. m., 1 H), 3,65 (s, 1,5 H), 3,67–3,48 (ser. m., 2 H), 3,51 (s, 1,5 H), 3,12 (d, J = 11,5 Hz, 0,5 H), 2,96 (d, J = 9,7 Hz, 0,5 H), 2,43–2,28 (ser. m., 1 H), 1,97–1,29 (ser. m., 5 H).

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Paso 3

Una mezcla de alcohol **66A** obtenida en el paso previo y trietilamina (10,49 ml, 74,65 mmol) en 120 ml de diclorometano se enfrió con hielo/agua y trató gota a gota con 2,89 ml (37,23 mmol) de cloruro de metansulfonilo. La mezcla de reacción se agitó durante 1 h, se lavó con un volumen igual de HCl 1M, se secó con Na_2SO_4, se concentró y bombeó en alto vacío toda la noche para suministrar 12,16 g de mesilato bruto que se usó sin purificación posterior. A una solución de 11,16 g (20,18 mmol) de este material en 200 ml de THF se agregó en porciones 2,94 g (20,18 mmol) de ter-butóxido de potasio. La mezcla de reacción se agitó durante 40 min y se inactivó con volúmenes iguales de 50% de NH_4Cl saturado y acetato de etilo. La fase orgánica se separó, se secó con $MgSO_4$, y se concentró. El producto se purificó por cromatografía en columna en gel de sílice usando un gradiente de 0–30% de acetato de etilo en hexanos como solvente para suministrar 6,0 g de éster **67A**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,61 (d, J = 8,7 Hz, 2 H), 7,50 (d, J = 8,7 Hz, 2 H), 7,12–7,04 (m, 1 H), 6,47–6,40 (m, 1 H), 5,19 (dd, J = 12,5, 2,7 Hz, 1 H), 4,20 (d, J = 12,2 Hz, 1 H), 3,72 (s, 3 H), 2,98 (d, J = 9,9 Hz, 1 H), 2,64 (d, J = 11,2 Hz, 1 H), 2,46 (td, J = 11,9, 4,2 Hz, 1 H), 1,98–1,87 (m, 2 H), 1,81–1,74 (m, 1 H), 1,58–1,49 (m, 2 H), 1,17–1,06 (m, 1 H).

Paso 4

A una solución de 2,70 g (5,91 mmol) de éster **67A** en 59 ml de THF a 0°C se agregaron 6,50 ml (6,50 mmol) de una solución 1M de hidruro de aluminio y litio en THF. La mezcla de reacción se agitó durante 15 min y se inactivó por la adición cuidadosa gota a gota de HCl 1M, hasta que no hubo más desarrollo de gas. La mezcla se dividió entre HCl 1M y acetato de etilo. La fase acuosa se separó y se extrajo con acetato de etilo. La fase orgánica combinada se lavó con salmuera, se secó con $MgSO_4$, y se concentró para suministrar 2,40 g de alcohol **68A** que se usó sin purificación posterior. δ 7,62 (d, J = 8,6 Hz, 2 H), 7,49 (d, J =

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8,6 Hz, 2 H), 7,09–7,02 (m, 1 H), 6,46–6,39 (m, 1 H), 5,17 (dd, J = 12,1, 2,5 Hz, 1 H), 4,63 (d, J = 12,6 Hz, 1 H), 3,88 (dd, J = 11,0, 4,4 Hz, 1 H), 3,71 (dd, J = 11,2, 2,9 Hz, 1 H), 2,70 (d, J = 11,0 Hz, 1 H), 2,57 (d, J = 14,6 Hz, 1 H), 1,94–1,83 (m, 1 H), 1,78–1,66 (m, 2 H), 1,57–1,41 (m, 3 H), 1,17–1,04 (m, 1 H).

Paso 5

Al alcohol **68A** (1,794 g, 4,18 mmol) en diclorometano (50 ml) se agregaron Et_3N (1,17 ml, 0,846 g, 8,36 mmol,) y MsCl (0,48 ml, 0,719 g, 6,27 mmol,) respectivamente, la mezcla se agitó a 0°C durante 30 minutos y se inactivó con agua. Se lavó con HCl 1N, y se extrajo con diclorometano. Las fases orgánicas combinadas se lavaron con $NaHCO_3$ saturado y salmuera, se secaron con $MgSO_4$, filtraron y evaporaron al vacío. El **69A** bruto (2,257 g, cuantitativo) se usó durante el próximo paso en forma directa. ^{1}H–RMN (CDCl3 400 MHz) δ: 7,61 (d, *J* = 9,0 Hz, 2H), 7,50 (d, *J* = 8,7 Hz, 2H), 7,12–7,03 (m, 1H), 6,50–6,40 (m, 1H), 5,21 (d, *J* = 13,0 Hz, 1H), 4,55–4,46 (m, 2H), 4,20 (dd, *J* = 2,4, 10,4 Hz, 1H), 3,06 (s, 3H), 2,68 (d, *J* = 11,6 Hz, 1H), 2,57 (d, *J* = 13,2 Hz, 1H), 1,96–1,84 (m, 1H), 1,82–1,66 (m, 3H), 1,58–1,46 (m, 1H), 1,18–1,04 (m, 1H).

Paso 6:

Al compuesto **69A** (0,131 g, 0,26 mmol) en DMF se agregaron 0,129 g de KI (0,78 mmol) y 0,079 g de metansulfinato de sodio (0,78 mmol), la mezcla estuvo a 120 °C durante 1 hora, y se inactivó con agua. Se extrajo con diclorometano, se secó con $MgSO_4$, filtró y evaporó al vacío. El **70A** bruto se purificó por TLC preparativa, seguido por HPLC en fase reversa. ^{1}H–RMN (CDCl3 400 MHz) δ: 7,62 (d, *J* = 8,5 Hz, 2H), 7,50 (d, *J* = 8,7 Hz, 2H), 7,15–7,03 (m, 1H), 6,54–6,41 (m, 1H), 5,27 (d, *J* = 12,4 Hz, 1H), 4,44 (d, *J* = 12,2 Hz, 1H), 3,36 (d, *J* = 14,7 Hz, 1H), 3,02–2,88 (m, 1H), 2,95 (s, 3H), 2,57 (d, *J* = 11,6 Hz, 2H), 2,27 (d, *J* = 12,4 Hz, 1H), 2,10–1,95 (m, 1H), 1,96–1,81 (m, 1H), 1,79–1,66 (m, 1H), 1,48–1,33 (m, 1H), 1,17–1,02 (m, 1H). LCMS $[M+H]^+$: 491,3 (4,44 min)

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Paso 7: Lasulfona **71A** se obtuvo por un procedimiento análogo al descripto en el procedimiento general de preparación de la sulfona **70A** (Paso 6 anterior, usando trifluorometilsulfinato de sodio). La forma racémica de **71A** se separó por cromatografía preparativa en columna Chiracel OD para dar dos enantiómeros: **71A (–)** $[\alpha]_D = -122,6^\circ$ (c = 1,00, diclorometano) y **71A (+)** $[\alpha]_D = +132,5$ (c = 1,00, diclorometano). ^{1}H–RMN (CDCl3 400 MHz) δ: 7,62 (d, *J* = 9,2 Hz, 2H), 7,51 (d, *J* = 8,8 Hz, 2H), 7,15–7,05 (m, 1H), 6,53–6,44 (m, 1H), 5,27 (d, *J* = 13,2 Hz, 1H), 4,44–4,40 (d, *J* = 13,0 Hz, 1H), 3,50 (d, *J* = 14,0 Hz, 1H), 3,23 (dd, *J* = 8,2, 14,4 Hz, 1H), 2,72–2,52 (m, 2H), 2,28–2,10 (m, 2H), 1,98–1,85 (m, 1H), 1,78 (d, *J* = 14,8 Hz, 1H), 1,60–1,48 (m, 1H), 1,20–1,04 (m, 1H). LCMS $[M+H]^+$: 545,3 (5,08 min).

Paso 8

El alcohol **68A** se disolvió en 60 ml de diclorometano y se trató con 2,50 g (5,91 mmol) de reactivo de Dess–Martin. Después de 30 min, se confirmó la finalización de la reacción por TLC (se usó 30% de acetato de etilo en hexanos como solvente). La reacción se inactivó con una solución de 1 g de tiosulafato de sodio en 10 ml de agua, seguido por 10 ml de $NaHCO_3$ sat. La mezcla bifásica se agitó vigorosamente durante 30 min, y se extrajo con diclorometano. La fase orgánica se secó con Na_2SO_4, se concentró, y el residuo se cromatografió en gel de sílice eluyendo con 0–20% acetato de etilo en hexanos como solvente para suministrar 2,356 g de aldehído **72A**. ^{1}H–RMN (CDCl3 400 MHz) δ 9,67 (s, 1 H), 7,62 (d, J = 8,6 Hz, 2 H), 7,50 (d, J = 8,6 Hz, 2 H), 7,12–7,05 (m, 1 H), 6,49–6,41 (m, 1 H), 5,17 (dd, J = 12,3, 2,7 Hz, 1 H), 4,33 (d, J = 12,1 Hz, 1 H), 3,02 (d, J = 11,7 Hz, 1 H), 2,68 (d, 11,7 Hz, 1 H), 2,53 (m, 1 H), 1,96 (m, 1 H), 1,92–1,81 (m, 2 H), 1,33–1,09 (ser. m., 2 H).

Paso 9

A una suspensión agitada de 14,42 g (40,36 mmol) de bromuro de metiltrifenilfosfonio en 200 ml de THF a –40°C se agregó gota a gota 15,52 ml

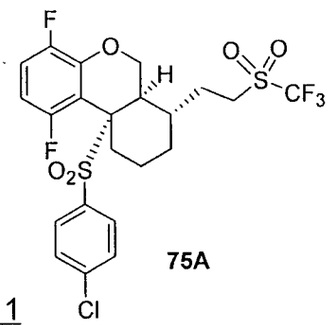
(38,8 mmol) de una solución 2,5 M de n–butil litio en hexanos, después de lo cual la reacción se agitó en un baño de hielo durante 45 min. A esta mezcla amarilla de reactivo de Wittig se agregó una solución de 6,62 g (15,52 mmol) de aldehído **72A** en 75,0 ml de THF. La mezcla se agitó 1 hora a 0°C, luego se retiró el enfriamiento y continuó la agitación durante 2 horas adicionales. La reacción se inactivó con agua y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó con $MgSO_4$ y se concentró. El producto se purificó por cromatografía en columna en gel de sílice eluyendo con un gradiente de 0–20% acetato de etilo en hexanos como solvente para suministrar 5,560 g de alqueno **73A**. ^{1}H–RMN (CDCl3 400 MHz) δ 7,60 (d, J = 8,6 Hz, 2 H), 7,48 (d, J = 8,6 Hz, 2 H), 7,10–7,03 (m, 1 H), 6,44–6,37 (m, 1 H), 5,62 (dt, J = 18,0, 8,9 Hz, 1 H), 5,18 (s, 1 H), 5,15 (d, J = 5,8 Hz, 1 H), 5,06 (dd, J = 11,8, 2,8 Hz, 1 H), 4,52 (d, J = 11,7 Hz, 1 H), 2,59 (d, J = 13,2 Hz, 1 H), 2,38 (d, J = 12,2 Hz, 1 H), 2,09–1,97 (m, 1 H), 1,96–1,87 (m, 1 H), 1,75–1,64 (m, 2 H), 1,38–1,25 (m, 1 H), 1,17–1,04 (m, 1 H)

Paso 10

A una solución de 1,90 g (4,47 mmol) de alqueno **73A** en 10 ml de THF bajo nitrógeno se agregaron 17,88 ml (8,94 mmol) de una solución 0,5 M de 9–BBN–THF. El matraz estaba equipado con un condensador de reflujo y se colocó en un baño de aceite precaletnado a 80°C durante 1 hora. La mezcla de reacción se enfrió a 0°C y se trató gota a gota con 7,96 g de 35% de solución acuosa de peróxido de hidrógeno y luego gota a gota con 13,4 ml de NaOH 2M. La mezcla lechosa se agitó durante 1 hora temperatura ambiente. Se agregó agua (50 ml) d y la mezcla se extrajo con porciones 3x100 ml de acetato de etilo. La fase orgánica combinada se lavó con salmuera, se secó con $MgSO_4$, y se concentró in vacuo, en un baño de temperatura que no excede 40 °C. El residuo se purificó por cromatografía en columna en gel de sílice eluyendo con un gradiente de 0–40 acetato de etilo en hexanos para suministrar 1,8 g de alcohol **74A–rac**. ^{1}H–RMN

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(CDCl3 400 MHz) δ 7,61 (d, J = 8,4 Hz, 2 H), 7,48 (d, J = 8,6 Hz, 2 H), 7,09–7,02 (m, 1 H), 6,45–6,38 (m, 1 H), 5,17 (dd, J = 12,5, 2,3 Hz, 1 H), 4,61 (d, J = 12,5 Hz, 1 H), 3,80–3,71 (m, 1 H), 3,71–3,63 (m, 1 H), 2,56 (d, J = 13,7 Hz, 1 H), 2,41 (d, J = 10,0 Hz, 1 H), 2,04–1,67 (ser. m., 4 H), 1,19–1,00 (ser. m., 5 H).



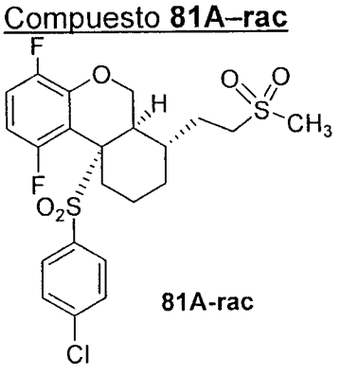
75A

Paso 11

A partir de alcohol **74A–rac** y usando un procedimiento análogo al descripto en el Paso 7 anterior, se obtuvo la sulfona **75A–rac**. MS: Calculado para $C_{22}H_{21}ClF_5O_5S_2$ (MH^+), m/z = 559,04.; experimental 559,3. Tiempo de retención: 5,08 min.

Los siguientes compuestos se prepararon de modo análogo:

Compuesto **81A–rac**

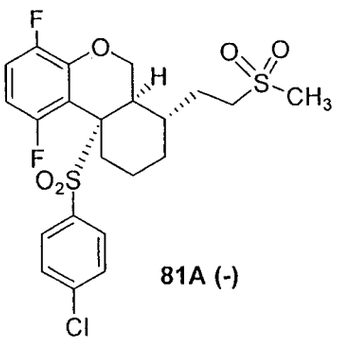


81A-rac

MS: Calculado para $C_{22}H_{23}ClF_2O_5S_2$ (MH^+), m/z = 505,1.; experimental 505,3. Tiempo de retención: 4,47 min. La resolución del compuesto usando cromatografía Chiralcel OD produjo:

Compuesto **81A(–)**

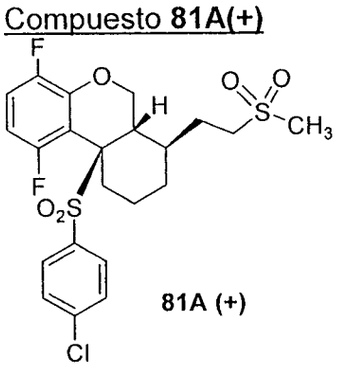
593



81A (-)

MS: Calculado para $C_{22}H_{23}ClF_2O_5S_2$ (MH^+), m/z = 505,1.; experimental 505,3. Tiempo de retención: 4,47 min.

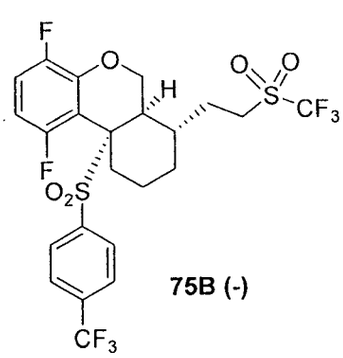
Compuesto **81A(+)**



81A (+)

MS: Calculado para $C_{22}H_{24}ClF_2O_5S_2$ (MH^+), m/z = 505,1.; experimental 505,3. Tiempo de retención: 4,47 min.

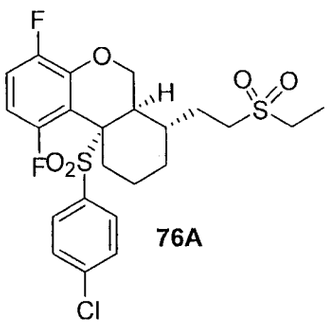
Compuesto **75B(–)**



75B (-)

^{1}H RMN ($CDCl_3$) δ 7,83 (d, 2H), 7,78 (d, 2H), 7,06–7,12 (m, 1H), 6,41–6,47 (m, 1H), 5,17 (dd, 1H), 4,58 (d, 1H), 3,63 (m, 1H), 3,47–3,54 (m, 1H), 2,52 (d, 1H),

2,44 (d, 1H), 2,21–2,29 (m, 1H), 1,92 (tt, 1H), 1,67–1,84 (m, 3H), 1,55–1,63 (m, 1H), 1,02 (m, 2H).



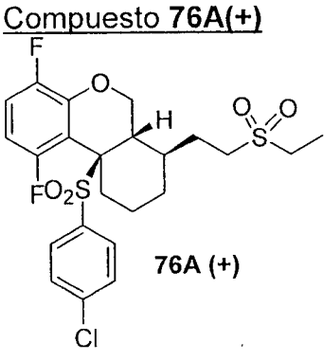
76A

Paso 12

El alcohol **74A–rac** se tosiló usando un procedimiento análogo al descripto en el Esquema 1, Paso 12 y se convirtió a la sulfona **76A** usando un procedimiento análogo al que se describe en el Esquema 1, Paso 14. **76A–rac:** MS: Calculado para $C_{23}H_{26}ClF_2O_5S_2$ $(M+1)^+$,m/z = 519,09; experimental 519,3. Tiempo de retención: 4,58 min. Usando cromaografía quiral en una columna Chiralcel OD, **76A (–)** se aisló $[\alpha]_D^{20}$ –163,18° (c=1, diclorometano).

Los siguientes compuestos se prepararon de modo análogo:

Compuesto **76A(+)**

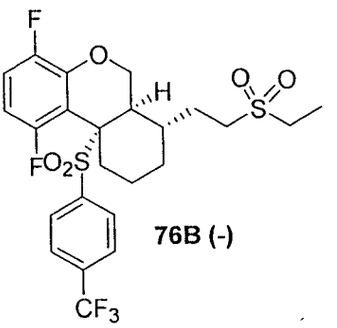


76A (+)

MS: Calculado para $C_{23}H_{26}ClF_2O_5S_2$ $(M+1)^+$,m/z = 519,09; experimental 519,3. Tiempo de retención: 4,58 min.

Compuesto **76B(–)**

595



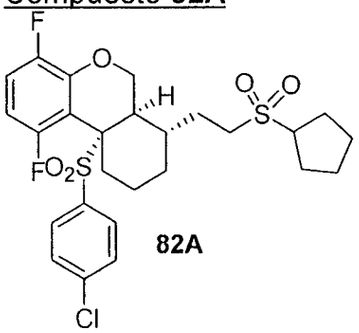
76B (-)

MS: Calculado para $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$,m/z = 553,1; experimental 553,3.

Tiempo de retención: 4,64 min.

596

Compuesto **82A**

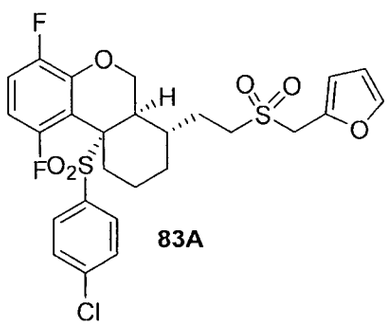


82A

MS: Calculado para $C_{26}H_{30}ClF_2O_5S_2$ $(M+1)^+$,m/z = 559,1; experimental 559,3.

Tiempo de retención: 4,92 min.

Compuesto **83A**

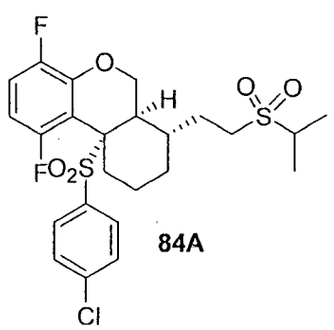


83A

MS: Calculado para $C_{26}H_{26}ClF_2O_6S_2$ $(M+1)^+$,m/z = 571,1; experimental 571,3.

Tiempo de retención: 4,81 min.

Compuesto **84A**



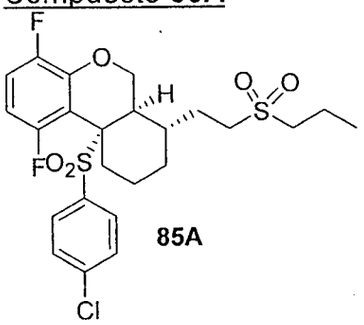
84A

MS: Calculado para $C_{24}H_{28}ClF_2O_5S_2$ $(M+1)^+$,m/z = 533,1; experimental 533,1.

Tiempo de retención: 4,70 min.

597

Compuesto **85A**

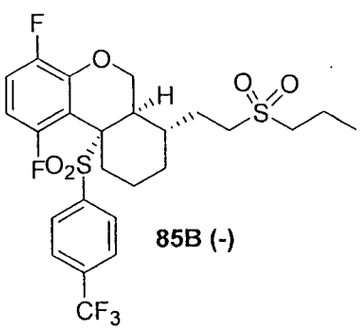


85A

MS: Calculado para $C_{24}H_{28}ClF_2O_5S_2$ $(M+1)^+$,m/z = 533,1; experimental 533,3.

Tiempo de retención: 4,76 min.

Compuesto **85B**

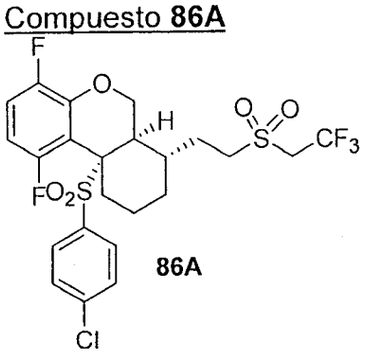


85B (-)

MS: Calculado para $C_{25}H_{28}F_5O_5S_2$ $(M+1)^+$,m/z = 567,1; experimental 567,3.

Tiempo de retención: 4,79 min.

Compuesto **86A**



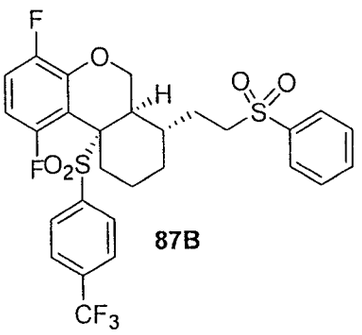
86A

MS: Calculado para $C_{23}H_{23}ClF_5O_5S_2$ $(M+1)^+$,m/z = 573,1; experimental 573,3.

Tiempo de retención: 4,86 min.

598

Compuesto **87B**

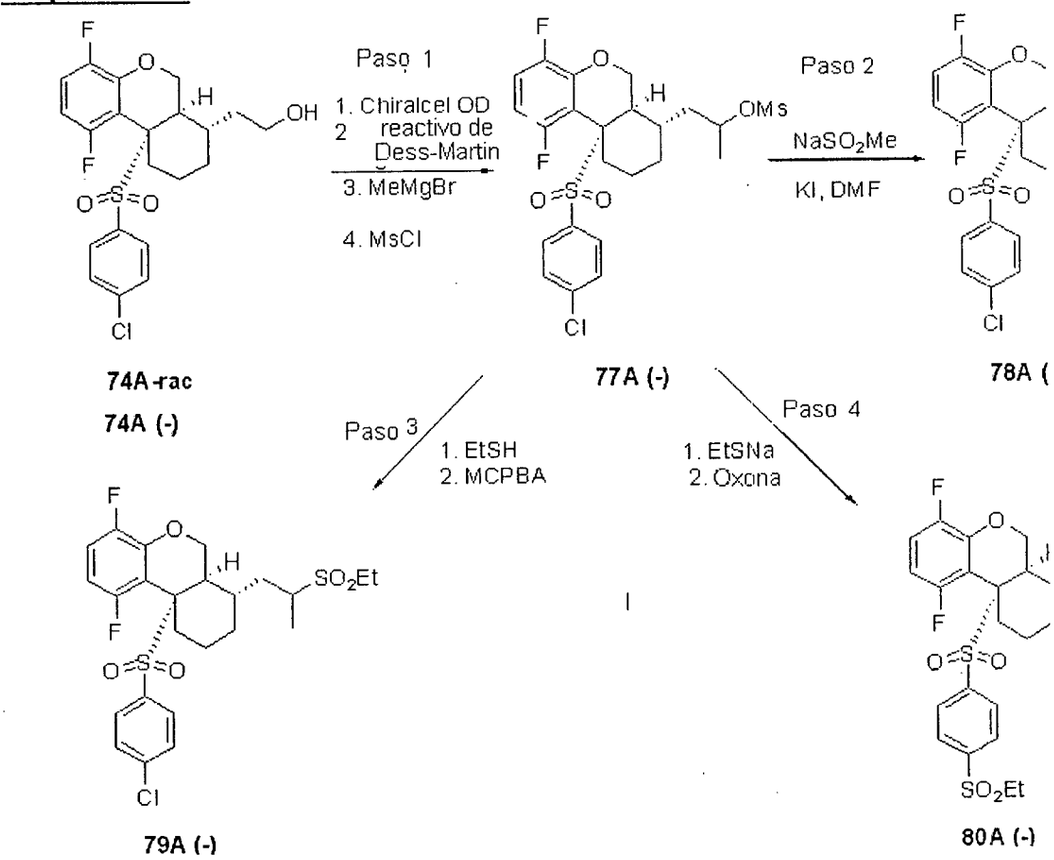


87B

MS: Calculado para $C_{28}H_{26}F_5O_5S_2$ $(M+1)^+$,m/z = 601,1; experimental 601,3.

Tiempo de retención: 4,95 min.

Esquema 17:



Paso 1

599

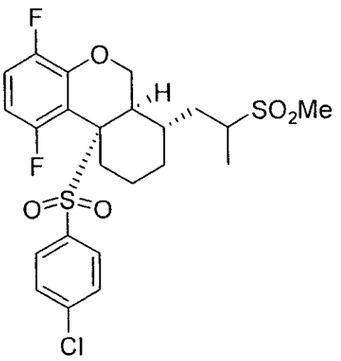
El alcohol 10 se resolvió mediante una columna Chiracel OD eluyendo con 30% de alcohol isopropílico en hexanos. El primer pico de elución **74A (+)** tiene rotación óptica positiva, $[\alpha]_D^{20}$ +1,71° (c=0,6, diclorometano). El segundo pico de elución **74A (–)** tiene rotación óptica negativa $[\alpha]_D^{20}$ –1,69° (c=0,5, diclorometano). Se usó **74 (–)** en las reacciones químicas posteriores.

El alcohol **74 (–)** se oxidó a un aldehído usando un procedimiento análogo al del Esquema 16, Paso 8. ^{1}H–RMN (CDCl3 400 MHz) δ 9,76 (dd, J = 2,5, 1,1 Hz, 1 H), 7,61 (d, J = 8,6 Hz, 2 H), 7,49 (d, J = 8,6 Hz, 2 H), 7,13–7,05 (m, 1 H), 6,49–6,41 (m, 1 H), 5,21 (dd, J = 12,6, 2,5 Hz, 1 H), 4,43 (d, J = 12,5 Hz, 1H), 2,79 (dd, J = 16,8, 2,5 Hz, 1 H), 2,57 (d, J = 12,6 Hz, 1 H), 2,50 (d, J = 11,5 Hz, 1 H), 2,40 (ddd, J = 17,0, 8,8, 2,7 Hz, 1 H), 2,02–1,67 (ser. m., 4 H), 1,19–1,07 (m, 2 H).

El aldehído resultante (100 mg, 0,227 mmol) se disolvió en 2,0 ml de THF, enfriado a 0°C y se trató con 0,113 ml (0,34 mmol) de una solución 3M de bromuro de metilmagnesio en éter. Después de 10 min de agitación, la mezcla se inactivó con agua y se extrajo con acetato de etilo para suministrar 40 mg del alcohol secundario. ^{1}H–RMN (CDCl3 400 MHz) δ 7,61 (d, J = 8,6 Hz, 2 H), 7,49 (d, J = 8,6 Hz, 2 H), 7,10–7,01 (m, 1 H), 6,46–6,39 (m, 1 H), 5,16 (dd, J = 12,6, 2,5 Hz, 1 H), 4,61 (d, J = 13,0 Hz, 1H), 3,89 (m, 1 H), 2,57 (d, J = 14,8 Hz, 1 H), 2,34 (d, J = 12,8 Hz, 1 H), 1,94–1,68 (ser. m., 3 H), 1,30–1,19 (ser. M., 2 H), 1,23 (d, J = 6,0 Hz, 3 H), 1,14–1,05 (ser. m., 2 H).

El alcohol secundario se mesiló de acuerdo con el procedimiento del Esquema 16, Paso 5 para dar el intermediario mesilato **77A (–)**: ^{1}H–RMN (CDCl3 400 MHz) δ 7,61 (d, J = 8,6 Hz, 2 H), 7,49 (d, J = 8,6 Hz, 2 H), 7,10–7,01 (m, 1 H), 6,46–6,39 (m, 1 H), 5,16 (dd, J = 12,5, 2,5 Hz, 1 H), 4,87 (m, 1 H), 4,55 (d, J = 12,1 Hz, 1H), 2,97 (s, 3 H), 2,57 (d, J = 13,3 Hz, 1 H), 2,34 (d, J = 12,1 Hz, 1 H), 2,09 (m, 1 H), 2,00–1,83 (ser. m., 2 H), 1,74–1,65 (m, 1 H), 1,46 (d, J = 6,2 Hz, 3 H), 1,40–1,31 (ser. m., 2 H), 1,13–1,02 (m, 2 H).

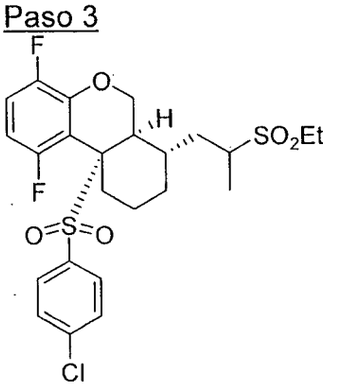
Paso 2



78A (-)

El mesilato **77A (–)** se convirtió en sulfona **78A (–)** usando un procedimiento análogo al usado en el Esquema 16, Paso 6. MS: Calculado para $C_{23}H_{26}ClF_2O_5S_2$ $(M+1)^+$, m/z = 519,09.; experimental 519,3. Tiempo de retención: 4,38 min.

Paso 3

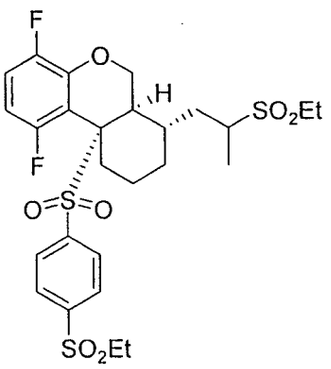


79A (-)

El mesilato **77A (–)** se convirtió en sulfona **79A (–)** usando un procedimiento análogo al usado en el Esquema 16, Paso 12. MS: Calculado para $C_{24}H_{28}ClF_2O_5S_2$ $(M+1)^+$, m/z = 533,10; experimental 533,3. Tiempo de retención: 4,66 min.

Paso 4

601

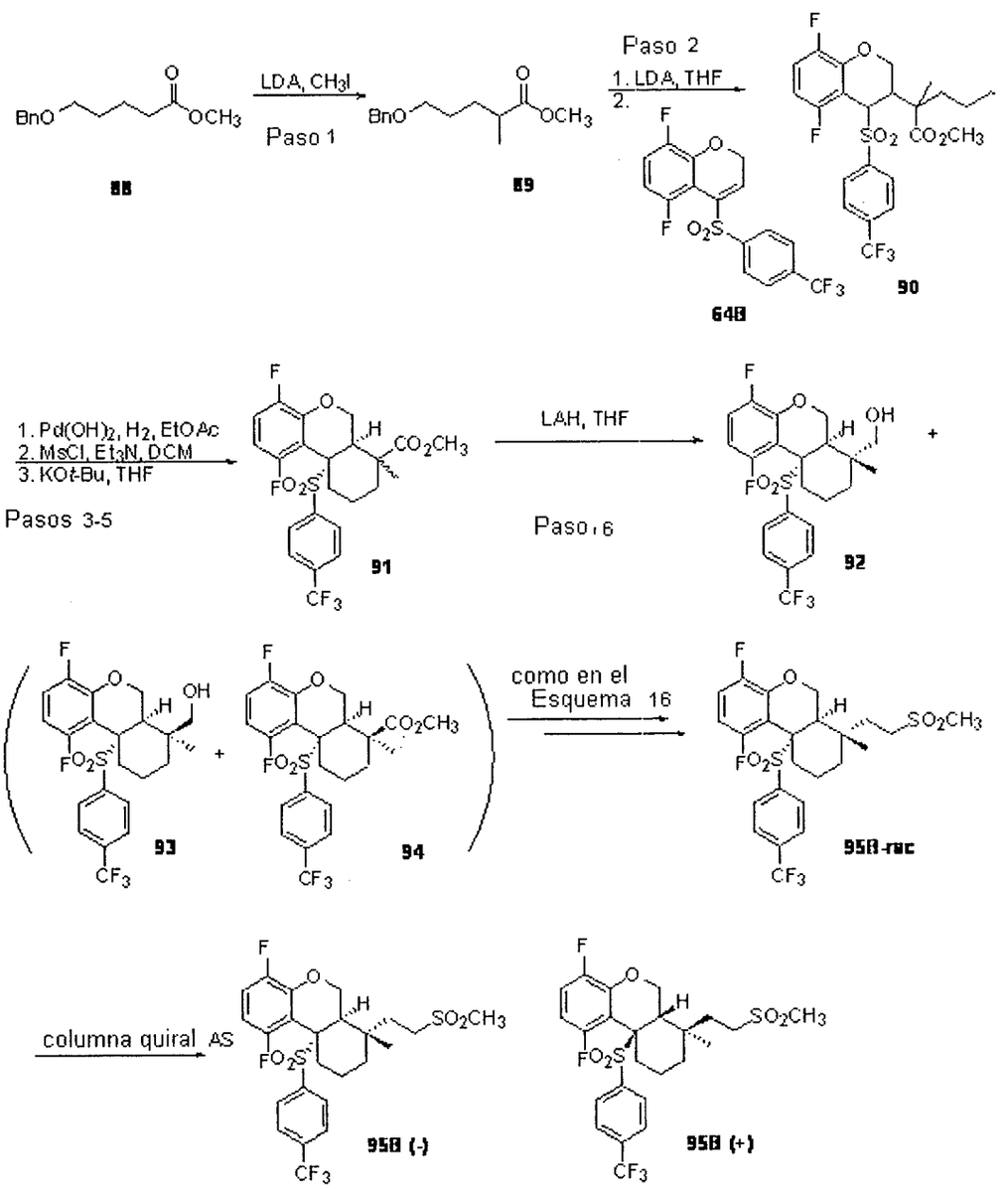


80A (-)

Una solución de 0,088 mmol del mesilato **77A (–)** en una mezcla de 1,0 ml de THF y 1,0 ml de DMF se trató con 100 mg (1,19 mmol) de etiltiolato de sodio. Después de 1 hora de agitación la mezcla de reacción se elaboró usando agua y acetato de etilo. La fase orgánica se secó con $MgSO_4$ y se concentró. El producto se redisolvió en una mezcla 0,88 ml de acetona y 0,22 ml de agua y se trató con 215 mg (0,35 mmol) de oxona. Después de 2 horas de agitación los sólidos se filtraron y el producto se colocó en una placa de TLC preparativa y se eluyó con una mezcla de 80% de acetato de etilo y 20% de hexanos para suministrar 9,0 mg de sulfona **80A (–)**. MS: Calculado para $C_{26}H_{33}F_2O_7S_3$ $(M+1)^+$, m/z = 591,14; experimental 591,3. Tiempo de retención: 4,11 min.

Esquema 18:

602



Paso 1

A 0°C, a diisopropilamina (15 g, 1,1 equiv.) en 300 ml de THF se agregaron 60 ml de *n*–BuLi (2,5 M en tolueno, 0,15 mol, 1,1 equiv.) gota a gota dentro de 10 minutos, y la mezcla de reacción se agitó durante 10 minutos adicionales. La reacción se enfrió a –78 °C y se agregó éster de metilo **88** en 100 ml de THF dentro de 20 minutos. La reacción se agitó durante 30 minutos, seguido por la adición de 21 g de yodometano (0,15 mol, 1,1 equiv.) en 100 ml de THF gota a

603

gota durante 30 minutos. La mezcla de reacción se agitó durante una hora con temperatura que aumentó lentamente a r.t. La reacción se inactivó con 500 ml de salmuera, y se diluyó con 1 L de EtOAc. La fase orgánica se separó, se lavó con 200 ml de salmuera, se secó con Na_2SO_4 y se concentró. La mezcla de reacción bruta se purificó por la cromatografía en columna en gel de sílice eluyendo con un gradiente de 100% de hexanos a 25% EtOAc/Hexano durante 45 minutos para dar 20,0 g del compuesto **89** (63% de rendimiento). ^{1}H–RMN (CDCl3 400 MHz) δ: 7,40–7,20 (m, 5H), 4,49 (s, 2H), 3,66 (s, 3H), 3,46 (t, *J* = 6,59, 2H), 2,52–2,40 (m, 1H), 1,78–1,46 (m, 4H), 1,16 (d, *J* = 6,4 Hz, 2H).

Paso 2

A 0 °C, a diisopropilamina (6,1g, 60 mmol, 3,0 equiv.) en 200 ml de THF se agregaron gota a gota 37,5 ml de 1,6 N de *n*–BuLi en hexanos (60,0 mmol, 3,0 equiv.). La reacción se agitó durante 10 minutos, seguida por la adición de 14,1 g de **89** (60 mmol, 3,0 equiv.) en 60 ml de THF anhidro. La reacción se agitó a 0°C durante otros 30 minutes antes de enfriar a –78°C. La vinilsulfona **64B** (6,9 g, 20 mmol, 1,0 equiv.) en 70 ml de THF se enfrió a –78 °C, y se agregó a la mezcla de reacción anterior. Se retiró el baño de enfriamiento y la mezcla se agitó durante 20 minutos, se inactivó con 400 ml de agua, y se diluyó con 300 ml de EtOAc. La fase orgánica se lavó con 2 porciones de 200–ml de solución de HCl 1N, 100 ml de salmuera, se secó con Na_2SO_4 y se concentró. La mezcla de reacción bruta se purificó por la cromatografía en columna en gel de sílice eluyendo con un gradiente de hexanos a 20% EtOAc/Hexano durante 45 minutos para dar 9,7 g del compuesto **90** (78% de rendimiento) como una mezcla de diastereómeros. Este material se usó directamente en la próxima reacción.

Pasos 3–5

A 9,7 g de **90** (16 mmol, 1,0 equiv.) en 200 ml de EtOAc se agregó 1 g de $Pd(OH)_2$ y la mezcla se agitó a 1 atm de H_2 a r.t. durante 30 minutos. El catalizador se filtró a través de un lecho de celite, y el solvente se eliminó al vacío.

La mezcla de reacción bruta se disolvió en 200 ml de diclorometano, seguido por la adición de 8 ml Et_3N y 5 ml de cloruro de metansulfonilo. La reacción se agitó a r.t. durante 10 minutos, y se inactivó con 200 ml de agua y se diluyó con 100 ml de diclorometano. La fase orgánica se separó, se lavó con 200 ml de una solución de HCl 1N, 200 ml de salmuera, se secó con Na_2SO_4, y se concentró in vacuo. El residuo se disolvió en 200 ml de anhidro THF, seguido por la adición de 40 ml de KO*t*–Bu (1M en *t*–BuOH). La mezcla se agitó a r.t. durante 10 minutos y se agregaron 300 ml de EtOAc. La fase orgánica se lavó con 2 porciones de 100 ml de salmuera, se secó con Na_2SO_4 y se concentró. La mezcla de reacción bruta se purificó por cromatografía en columna en gel de sílice eluyendo con un gradiente de hexanos a 25% EtOAc/Hexano durante 45 minutos, para dar 7,3 g de una mezcla de dos diastereómeros **91** (14,4 mmol, 90% de rendimiento durante tres pasos). MS: Calculado para $C_{23}H_{22}F_5O_5S$ $[M–HSO_2C_6H_4CF_3+H]^+$: m/z = 295,2 (5,01 min), 295,2 (5,12 min).

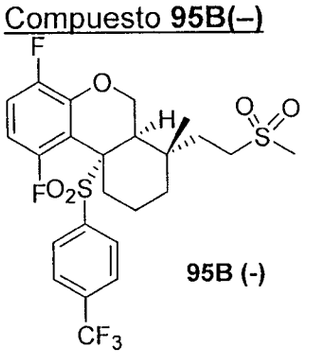
Paso 6

A 7,3 g de la mezcla **91** (14,4 mmol, 1,0 equiv.) en 200 ml de THF se agregaron 0,7 g de LAH (18,4 mmol, 1,3 equiv.). La reacción se agitó a r.t. durante 35 minutos y la TLC mostró el material de partida y dos nuevas manchas. La reacción se inactivó con 100 ml de HCl 1N y se diluyó con 300 ml de EtOAc. La fase orgánica se separó, se lavó con 200 ml de HCl 1N, 100 ml de salmuera, se secó con $MgSO_4$ y se concentró. La mezcla de reacción bruta se purificó por cromatografía en columna en gel de sílice tres veces eluyendo con un gradiente de hexanos a 40% EtOAc/Hexano durante 30 minutos para dar tres compuestos diferentes: isómero *trans* recuperado **94**, isómero *trans* **93** y 3,5 g de alcohol **92** (7,3 mmol). Alcohol **92:** ^{1}H–RMN ($CDCl_3$ 400 MHz) δ: 7,82–7,66 (m, 4H), 7,10–7,03 (m, 1H), 6,42–6,32 (m, 1H), 5,14 (dd, *J* = 4,8, 12,8 Hz, 1H), 4,71 (d, *J* = 12,4 Hz, 1H), 3,68 (d, *J* = 10,8 Hz, 1H), 3,29 (d, *J* = 12,0 Hz, 1H), 3,00 (d, *J* = 4,8 Hz, 1H), 2,59 (d, *J* = 13,2 Hz, 1H), 2,01–1,90 (m, 1H), 1,79–1,62 (m, 2H), 1,39–1,18

(m, 2H), 0,65 (s, 3H). MS: Calculado para $C_{22}H_{22}F_5O_4S$ $(M+1)^+$ m/z = 477,1, experimental 477,3, Rt = 4,69 min

Mediante procedimientos análogos a los del Esquema 16, se preparó el compuesto **95B–rac**. MS: Calculado para $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$ m/z = 553,1, experimental 533,3, Rt = 4,60 min. Este compuesto se resolvió en una columna Chiralpak AS para dar los siguientes enantiómeros:

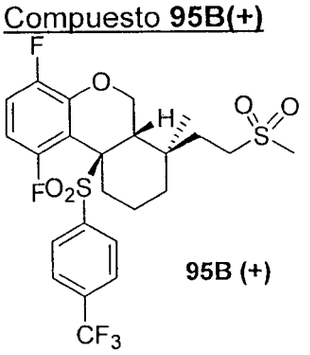
Compuesto **95B(–)**



95B (-)

MS: Calculado para $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$ m/z = 553,1, experimental 533,3, Rt = 4,65 min.

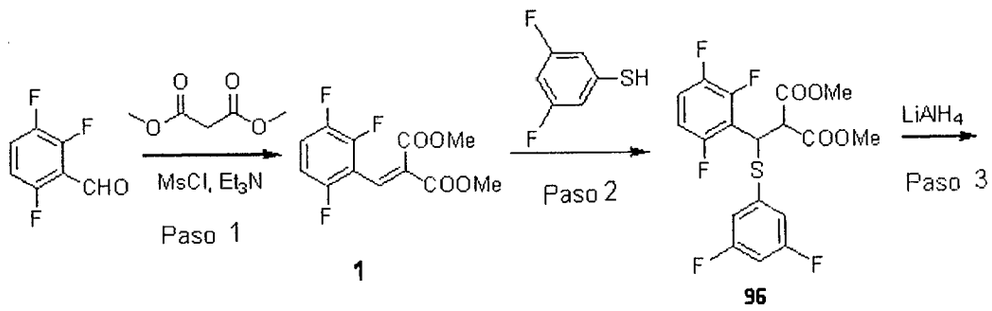
Compuesto **95B(+)**



95B (+)

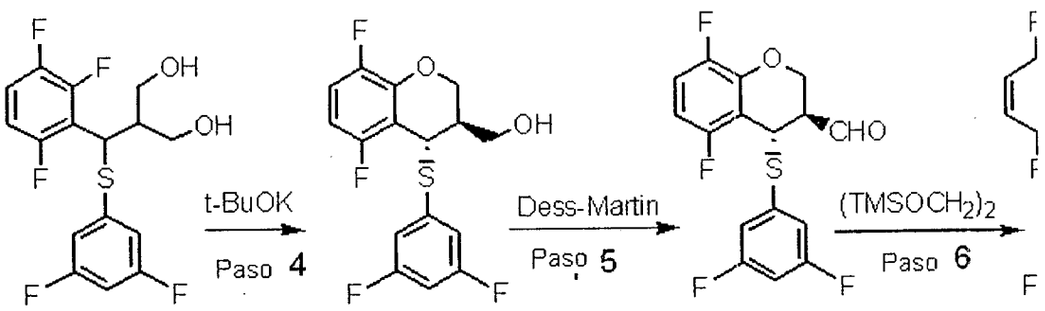
MS: Calculado para $C_{24}H_{26}F_5O_5S_2$ $(M+1)^+$ m/z = 553,1, experimental 533,3, Rt = 4,65 min.

Esquema 19:



1

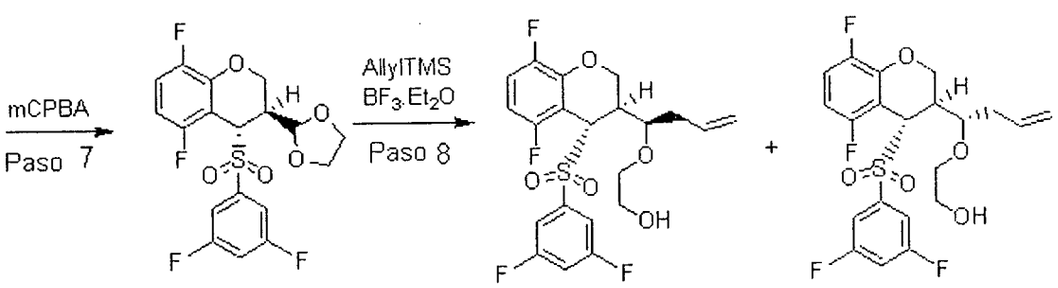
96



97

98

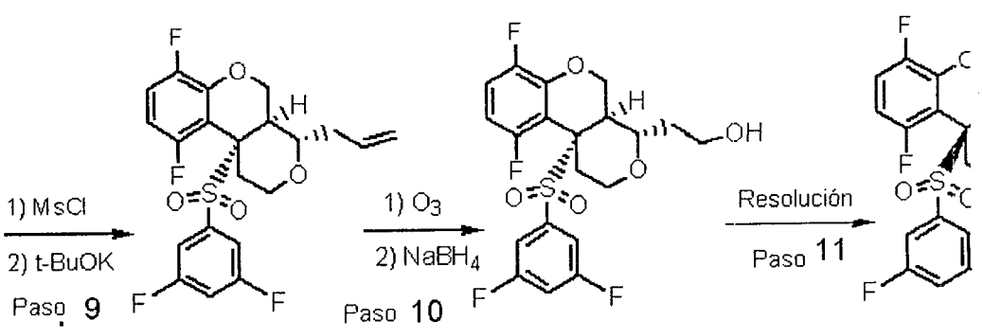
99



101

102B

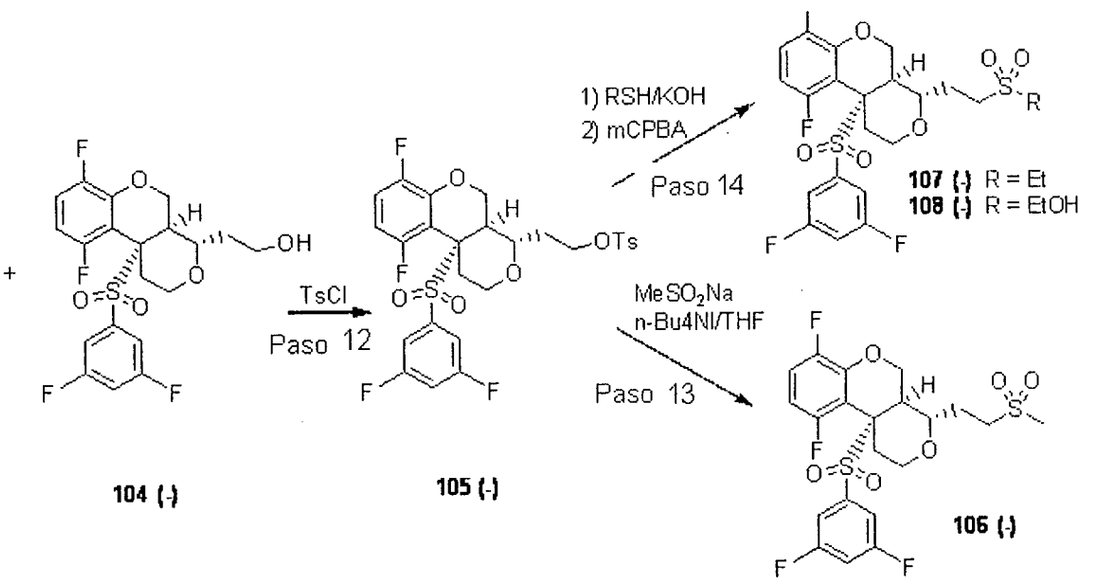
102A



103

104-rac

10



Paso 1

Ver siguiente Ejemplo del proceso 2.

Paso 2

A una solución de 20 g (72,9 mmol) del compuesto **1** y 10,7 g (72,9 mmol) de 3,5–difluorotiofenol en 500 ml de tetrahidrofurano se agregaron 10,1 g (72,9 mmol) de carbonato de potasio. Después de 5 h, se inactivó con 300 ml de agua, se extrajo con dos porciones de 300 ml de acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se concentró y filtraron. El filtrado se concentró para dar 31 g del compuesto bruto **96**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,03 (m, 1 H), 6,93 (m, 2 H), 6,79 (m, 2 H), 5,15 (d, J = 12 Hz, 1 H), 4,35 (d, J = 12 Hz, 1 H), 3,84 (s, 3 H), 3,57 (s, 3 H).

Paso 3

A una suspensión agitada de 6,5 g (170 mmol) de hidruro de aluminio y litio en 600 ml de tetrahidrofurano se agregó a 0°C una solución de 34 g (80,8 mmol)

del compuesto **96** en 100 ml de tetrahidrofurano durante un período de 1 h. Se agitó a temperatura ambiente durante 2 h y se inactivó con 15 ml de agua (enfriada con baño de hielo-agua). Tras la adición de 500 ml de HCl 6N, se extrajo con dos 500 ml porciones de éter etílico seguido por dos 500 ml porciones de acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se concentró, y el residuo se purificó por cromatografía eluyendo con un gradiente de 8% a 90% de acetato de etilo en hexanos para dar 9,1 g del compuesto **97**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,05 (m, 1 H), 6,90 (m, 2H), 6,80 (m, 1 H), 6,66 (m, 1 H), 4,99 (d, J = 12 Hz, 1 H), 4,33 (m, 1 H), 4,21 (d, J = 11 Hz, 1 H), 3,85 (dd, J = 11, 2.,4 Hz, 1 H), 3,50 (m, 1 H), 2,46 (m, 1 H), 2,20 (br s, 2 H).

Paso 4

A una solución agitada de 9,1 g (25 mmol) del compuesto **97** en 50 ml de tetrahidrofurano enfriado a 0°C se agregó una solución de 27,5 ml (27,5 mmol) de ter-butóxido de potasio (1,0M en THF). Se agitó a temperatura ambiente durante 1,5 h y se inactivó con 100 ml de 1 N HCl. La mezcla de reacción se extrajo con tres porciones de 100 ml de diclorometano. Los extractos orgánicos combinados se concentraron, y el residuo se purificó por cromatografía eluyendo con un gradiente de 5% a 40% de acetato de etilo en hexanos para dar 6,0 g del compuesto **98**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,04 (m, 3 H), 6,71 (m, 1H), 6,59 (m, 1 H), 4,68 (s, 1 H), 4,57 (dd, J = 11, 2,2 Hz, 1 H), 4,44 (d, J = 11,7 Hz, 1 H), 3,76 (m, 1 H), 3,58 (m, 1 H), 2,32 (m, 1 H), 1,62 (s, 1 H).

Paso 5

A una solución agitada de 6 g (17,4 mmol) del compuesto **98** en 100 ml de diclorometano se agregaron 8,9 g (21 mmol) de peryodinano de Dess–Martin. La mezcla se agitó a temperatura ambiente durante 2 h, se concentró en vacuo y se diluyó con 100 ml de éter etílico. Se agitó con 100 ml de bicarbonato de sodio saturado y 100 ml de solución de tiosulfato de sodio 10% y se extrajo dos veces con éter etílico. Los extractos orgánicos combinados se lavaron tres veces con

bicarbonato de sodio saturado, se secaron con sulfato de magnesio y se filtraron. El filtrado se concentró para dar 6,0 g de aldehído **99**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 9,74 (d, J = 1,5 Hz, 1 H), 7,02 (m, 3 H), 6,78 (m, 1 H), 6,64 (m, 1 H), 5,00 (s, 1 H), 4,94 (d, J = 11,7 Hz, 1 H), 4,74 (d, J = 11,7 Hz, 1 H), 2,88 (s, 1 H).

Paso 6

A una solución agitada de 6,0 g (17,4 mmol) del compuesto **99** en 90 ml de diclorometano se agregaron 4,31 g (20,9 mmol) de 1,2–bis(trimetilsiloxi)etano y 0,39 g (1,75 mmol) de trifluorometansulfonato de trimetilsililo a –78°C. Después de 30 min, se calentó a temperatura ambiente y se agitó durante 12 h. La reacción se diluyó con diclorometano y se lavó con tres porciones de 100 ml de bicarbonato de sodio saturado, y agua. La fase orgánica se concentró para dar 6,1 g del compuesto **100**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,01 (m, 3 H), 6,68 (m, 1 H), 6,59 (m, 1 H), 4,83 (s, 1H), 4,81 (dd, J = 7,3, 2,2 Hz, 1 H), 4,60 (dd, J = 11,7, 2,2 Hz, 1 H), 4,56 (dd, J = 11,7, 2,2 Hz, 1 H), 3,94 (m, 5 H), 2,18 (d, J = 7,3 Hz, 1 H).

Paso 7

A una solución agitada de 6,1 g (15,8 mmol) del compuesto **100** en 150 ml de diclorometano se agregaron 7,9 g (32 mmol) de ácido 3–cloroperoxibenzoico. Después de 2 h, la mezcla de reacción se diluyó con 200 ml de diclorometano y se lavó con cuatro porciones de 200 ml de bicarbonato de sodio saturado. Se filtró, se concentró y el residuo se purificó por cromatografía eluyendo con un gradiente de 12% a 100% de diclorometano en hexanos para dar 4,7 g del compuesto **101**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,39 (m, 2 H), 7,14 (m, 1 H), 7,02 (m, 1 H), 6,41 (m, 1 H), 4,86 (dd, J = 11,7, 3,7 Hz, 1 H), 4,73 (m, 2 H), 4,66 (dd, J = 11,7, 1,5 Hz, 1 H), 3,99–3,79 (m, 3 H), 2,89 (m, 1 H).

Paso 8

Una solución de 4,7 g (11,2 mmol) del compuesto **101**, 6,4 g (56 mmol) de aliltrimetilsilano y 7,9 g (56 mmol) de eterato de trifluoruro de boro en 75 ml de

diclorometano se agitó a temperatura ambiente durante 1 día. Se agregaron al 3,2 g (28 mmol) de aliltrimetilsilano adicional y 4,0 g (28 mmol) de eterato de trifluoruro de boro y la mezcla se agitó a reflujo durante otro día. Se agregaron 3,2 g (28 mmol) adicionales de aliltrimetilsilano y 4,0 g (28 mmol) de eterato de trifluoruro de boro, y la mezcla se agitó a reflujo durante otros dos días. La reacción se enfrió (baño de hielo) y se inactivó gota a gota con 50 ml de bicarbonato de sodio saturado, y se extrajo con dos porciones de 100 ml de diclorometano seguido por dos porciones de 100 ml de acetato de etilo. Los extractos orgánicos combinados se concentraron y el residuo se purificó por cromatografía eluyendo con un gradiente de 8% a 66% de acetato de etilo en hexanos para dar 2,3 g del compuesto **102A** y 1,3 g de **102B**. **102A**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,39 (m, 2 H), 7,14 (m, 1 H), 7,07 (m, 1 H), 6,49 (m, 1 H), 5,82 (m, 1 H), 5,20 (d, J = 11,7 Hz, 1 H), 4,97 (s, 1 H), 4,86 (dd, J = 12,4, 2,9 Hz, 1 H), 4,53 (s, 1 H), 4,43 (dd, J = 12,4, 1,5 Hz, 1 H), 3,67 (m, 3 H), 3,22 (m, 1 H), 3,13 (m, 1 H), 2,90 (m, 1 H), 2,54 (m, 1 H), 1,57 (m, 1 H). **102B**: ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,35 (m, 2 H), 7,14 (m, 1 H), 7,06 (m, 1 H), 6,48 (m, 1 H), 5,72 (m, 1 H), 5,11 (d, J = 10,3 Hz, 1 H), 5,07 (d, J = 16,8 Hz, 1 H), 4,80 (dd, J = 12,4, 2,9 Hz, 1 H), 4,67 (d, J = 11,7 Hz, 1 H), 4,53 (s, 1 H), 3,67 (m, 3 H), 3,50 (m, 1 H), 3,30 (m, 1 H), 2,92 (m, 1 H), 2,35 (m, 1 H), 1,85 (m, 1 H).

Paso 9

A una solución de 2,3 g (5,37 mmol) del compuesto **102A** en 50 ml de diclorometano se agregaron 1,04 g (10,2 mmol) de trietilamina y 0,92 g (8,06 mmol) de cloruro de metansulfonilo. La mezcla se agitó a temperatura ambiente durante 1 h. Se inactivó con 80 ml de HCl 1N y se extrajo con dos porciones de 100 ml de diclorometano. Los extractos orgánicos combinados se lavaron con bicarbonato de sodio saturado, se concentraron y el residuo se disolvió en 50 ml de tetrahidrofurano y se enfrió a 0°C. A esta solución se agregaron 12 ml (12 mmol) de ter-butóxido de potasio 1 N en THF. La mezcla se agitó a temperatura

ambiente durante 15 min., se inactivó con 100 ml de cloruro de amonio saturado y se extrajo con dos porciones de 100 ml de acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se concentró y el residuo se purificó por cromatografía eluyendo con un gradiente de 2% a 20% de acetato de etilo en hexanos para dar 0,90 g del compuesto **103**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,24 (m, 2 H), 7,11 (m, 2 H), 6,47 (m, 1 H), 5,85 (m, 1 H), 5,11 (m, 3 H), 4,46 (d, J = 13,2 Hz, 1 H), 3,93 (m, 1 H), 3,37 (m, 1 H), 3,15 (dd, J = 11,6, 11,6 Hz, 1 H), 2,65 (m, 3 H), 2,40 (m, 1 H), 2,31 (m, 1 H).

Paso 10

A una solución agitada de 900 mg (2,03 mmol) del compuesto **103** en 20 ml de 1:1 diclorometano/metanol a –78°C se burbujeó con O_3 hasta color azul sostenido. Se burbujeó con N_2 para eliminar el exceso de O_3. A esta solución se agregaron 230 mg (6,0 mmol) de borohidruro de sodio y se calentó a 0°C. La mezcla se agitó a temperatura ambiente. Después de 30 min, se agregaron 300 mg (7,94 mmol) adicionales de borohidruro de sodio. Después de 14 h, la mezcla de reacción se inactivó con 20 ml cloruro de amonio saturado y se concentró. El residuo se extrajo con dos porciones de 100 ml de diclorometano y los extractos combinados se lavaron con bicarbonato de sodio saturado y se secó con sulfato de magnesio para dar 800 mg del compuesto **104–rac**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,25 (m, 2 H), 7,16 (m, 2 H), 6,49 (m, 1 H), 5,11 (dd, J = 12,4, 2,2 Hz, 1 H), 4,46 (d, J = 12,4 Hz, 1 H), 3,93 (m, 1 H), 3,79 (t, J = 5,9 Hz, 2 H), 3,50 (ddd, J = 12,4, 9,5, 2,9 Hz, 1 H), 3,20 (dd, J = 11,7, 11,7 Hz, 1 H), 2,68 (d, J = 11 Hz, 1 H), 2,55 (d, J = 13,2 Hz, 1 H), 2,34 (m, 3 H), 2,11 (m, 1 H), 1,83 (m, 2 H).

Paso 11

El compuesto **104–rac** (800 mg) se resolvió en una columna Chiral OD eluyendo con 20% de isopropanol en hexanos y 40 ml /min de velocidad de flujo para dar dos enantiómeros **104 (+)** (310 mg, tiempo de retención 49–68 min, $[\alpha]_D^{20}$ +95,5°) y **104 (–)** (310 mg, tiempo de retención 71–88 min., $[\alpha]_D^{20}$ –89,9°).

Paso 12

Una solución de 305 mg (0,683 mmol) del compuesto **104 (–)**, 195 mg (1,02 mmol) de cloruro de *p*–toluensulfonilo y 138 mg (1,4 mmol) de trietilamina en 7 ml de diclorometano se agitó a temperatura ambiente durante 6 h. Se agregó dimetilaminopiridina (10 mg) y la reacción se agitó durante 14 h. Se inactivó con 80 ml de cloruro de amonio saturado y se extrajo con dos porciones de 80 ml de diclorometano. Los extractos orgánicos combinados se lavaron con bicarbonato de sodio saturado, se concentró y el residuo se purificó por cromatografía eluyendo con un gradiente de 8% a 66% de acetato de etilo en hexanos para dar 348 mg del compuesto **105 (–)**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,73 (dd, J = 8,8, 2,2 Hz, 2 H), 7,31 (dd, J = 8,8, 1,5 Hz, 2 H), 7,23 (m, 2 H), 7,14 (m, 2 H), 6,51 (m, 1 H), 5,05 (dd, J = 13,2, 2,9 Hz, 1 H), 4,31 (d, J = 12,4 Hz, 1 H), 4,18 (m, 2 H), 3,78 (m, 1 H), 3,27 (m, 1 H), 2,97 (dd, J = 12,4, 11,7 Hz, 1 H), 2,51 (d, J = 11,7 Hz, 1 H), 2,42 (s, 3 H), 2,26 (m, 1 H), 2,18 (m, 1 H), 1,79 (m, 1 H).

Paso 13

Una mezcla de 75 mg (0,124 mmol) del compuesto **105 (–)** y 138 mg (0,375 mmol) de yoduro de tetrabutilamonio en 4 ml de tetrahidrofurano se agitó a reflujo durante 1,5 h. Tras la adición de 50 mg (0,50 mmol) de metansulfinato de sodio, la mezcla se agitó a reflujo durante 18 h y se diluyó con 80 ml de cloruro de amonio saturado. Se extrajo con 80 ml de acetato de etilo, y el extracto orgánico se lavó con bicarbonato de sodio saturado, salmuera, se concentró y el residuo se purificó por cromatografía eluyendo con un gradiente de 8% a 66% de acetato de etilo en hexanos para dar 54 mg del compuesto **106 (–)**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,24 (m, 2 H), 7,13 (m, 2 H), 6,50 (m, 1 H), 5,13 (dd, J = 12,4, 2,9 Hz, 1 H), 4,48 (d, J = 12,4 Hz, 1 H), 3,94 (m, 1 H), 3,36 (m, 1 H), 3,28 (m, 1 H), 3,15 (dd, J = 12,4, 11,7 Hz, 1 H), 3,01 (m, 1 H), 2,91 (s, 3 H), 2,57 (m, 2 H), 2,44 (m, 1 H),

613

2,32 (m, 1 H), 2,04 (m, 1 H). MS: Calculado para $C_{21}H_{21}F_4O_6S_2$ (MH^+), 509,6; experimental 509,3. Tiempo de retención: 4,20 min.

Paso 14

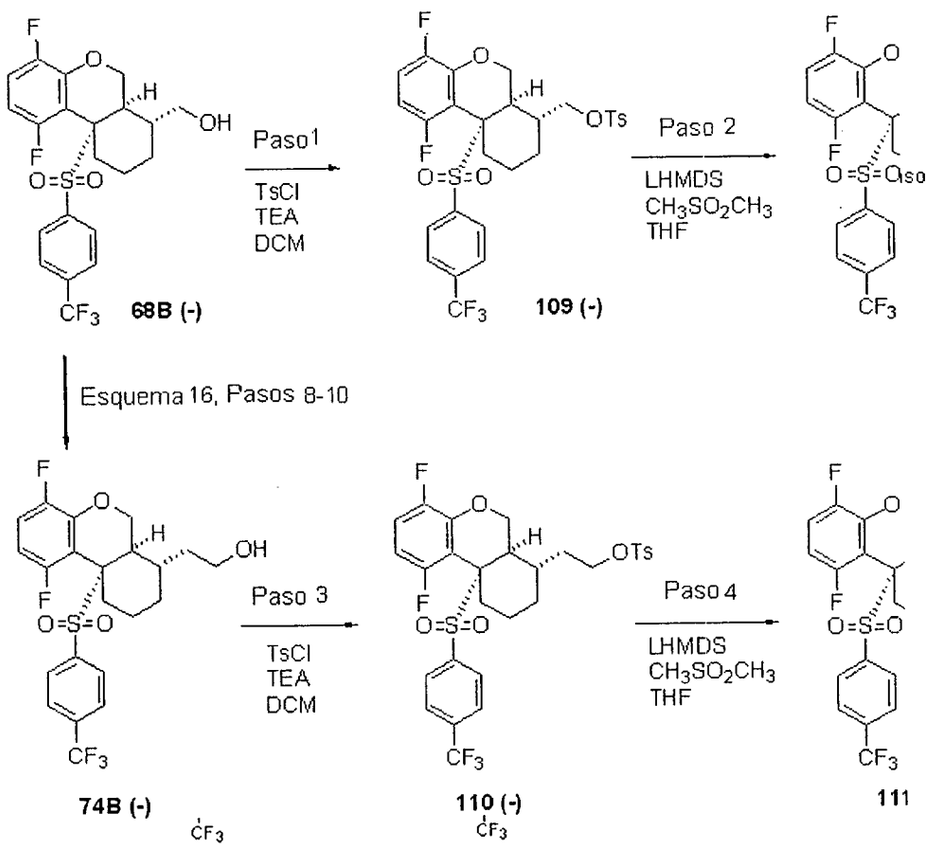
Una mezcla de 50 mg (0,08 mmol) del compuesto **105 (–)** y 10,6 mg (0,17 mmol) de etanotiol y 8 mg (0,15 mmol) de hidróxido de potasio se agitó a 50°C durante 1 h y se diluyó con cloruro de amonio saturado. La mezcla de reacción se extrajo con tres porciones de 20 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el producto sulfuro bruto se disolvió en 1 ml de diclorometano. A esta solución se agregaron 50 mg (0,29 mmol) de 70% ácido 3–cloroperoxibenzoico. Tras agitar a temperatura ambiente durante 14 h, se diluyó con 20 ml de carbonato de sodio saturado y se extrajo con tres porciones de 20 ml de acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera y se concentraron. El residuo se purificó por cromatografía preparativa en capa delgada eluyendo con 33% de acetato de etilo en hexanos para dar 35,8 mg del compuesto **107 (–)**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,26 (m, 2 H), 7,16 (m, 2 H), 6,50 (m, 1 H), 5,16 (d, J = 13,2, Hz, 1 H), 4,48 (d, J = 12,4 Hz, 1 H), 3,91 (m, 1 H), 3,36 (m, 1 H), 3,22 (m, 1 H), 3,15 (dd, J = 12,4, 11,7 Hz, 1 H), 3,01 (m, 3 H), 2,59 (d, J = 13,2 Hz, 2 H), 2,45 (m, 1 H), 2,32 (m, 1 H), 2,02 (m, 1 H), 1,40 (t, J = 7,3 Hz, 3 H). MS: Calculado para $C_{22}H_{23}F_4O_6S_2$ (MH^+), 523,1; experimental 523,3. Tiempo de retención: 4,29 min.

Paso 14 (alternativo)

Una mezcla de 50 mg (0,08 mmol) del compuesto **105 (–)** y 105 mg (0,280 mmol) de yoduro de tetrabutilamonio en 2 ml de tetrahidrofurano se agitó a reflujo durante 3,5 h. La mezcla de reacción se diluyó con 50 ml de éter etílico, se lavó con HCl 1N, bicarbonato de sodio saturado, se secó y se concentró. El residuo se disolvió en 1 ml de etanol y 26 µL (0,37 mmol) de β–mercaptoetanol y 10 mg (0,18 mmol) de hidróxido de potasio se agitó a 50°C durante 1 h y se diluyó con cloruro de amonio saturado. La mezcla de reacción se extrajo con tres porciones

de 20 ml de diclorometano. Los extractos orgánicos combinados se concentraron y el producto sulfuro bruto se disolvió en 1 ml de diclorometano. A esta solución se agregaron 60 mg (0,35 mmol) de 70% ácido 3–cloroperoxibenzoico. Tras agitar a temperatura ambiente durante 14 h, se diluyó con 20 ml de carbonato de sodio saturado y se extrajo con tres porciones de 20 ml de diclorometano. Los extractos orgánicos combinados se concentraron. El residuo se purificó por cromatografía preparativa en capa delgada eluyendo con 67% de acetato de etilo en hexanos para dar 39,4 mg del compuesto **108 (–)**. ^{1}H RMN ($CDCl_3$ 400 MHz) δ 7,24 (m, 2 H), 7,14 (m, 2 H), 6,50 (m, 1 H), 5,11 (d, J = 12,4, Hz, 1 H), 4,49 (d, J = 12,4 Hz, 1 H), 4,11 (m, 2 H), 3,90 (d, J = 11,7 Hz, 1 H), 3,36 (m, 2 H), 3,21 (m, 2 H), 3,14 (m, 2 H), 2,57 (m, 2 H), 2,45 (m, 1 H), 2,31 (m, 1 H), 2,06 (m, 1 H). MS: Calculado para $C_{22}H_{23}F_4O_7S_2$ (MH^+), 539,1; experimental 539,3. Tiempo de retención: 3,88 min.

Esquema 20:



El Compuesto **68B (–)** se preparó similar al Esquema 16, Pasos 1–4 a partir de vinilsulfona **64B** y se resolvió en una columna Chiralcel OD.

Paso 1

A una solución de 0,165 g de alcohol **68B (–)** (0,357 mmol) en diclorometano (10 ml) se agregaron 0,15 ml de Et_3N (0,1 mmol,) y 0,137 g de TsCl (0,718 mmol,) respectivamente. La mezcla se agitó a temperatura ambiente toda la noche. Se agregó cloruro de tosilo (0,14 g) y se agitó a temperatura ambiente toda la noche. El solvente se eliminó al vacío y el producto se aisló por cromatografía en gel de sílice eluyendo con un gradiente de hexanos a 40% acetato de etilo/hexano para suministrar 0,21 g del compuesto **109 (–)**. ^{1}H–RMN ($CDCl_3$ 400 MHz) δ 7,80 (m, 6H), 7,39 (d, 2H), 7,08 (m, 1H), 6,42 (m, 1H), 5,03 (d, 1H), 4,24 (d, 1H), 4,18 (d,

1H), 4,01 (d, 1H), 2,65 (d, 1H), 2,47 (s, 3H), 1,86 (m, 1H), 1,71 (m, 1H), 1,51 (m, 4H), 1,05 (m, 1H).

Paso 2

A una solución de 0,18 g de dimetil sulfona (1,9 mmol) en 20 ml de THF a –78°C se agregaron 1,9 ml de LHMDS (solución 1M en THF, 1,9 mmol) y la reacción se agitó durante 20 minutes. Se agregó una solución de 0,12 g de **109 (–)** (0,19 mmol) en 5 ml de THF. La mezcla de reacción se calentó lentamente a temperatura ambiente y se agitó toda la noche. La reacción se inactivó por la adición de 50 ml de una solución de HCl 1N y se extrajo con diclorometano. El solvente se eliminó al vacío y el producto se aisló por cromatografía en gel de sílice eluyendo con un gradiente de hexanos a 50% de acetato de etilo/hexano para suministrar 0,029 g del compuesto **81B (–)**. ^{1}H–RMN ($CDCl_3$ 400 MHz) δ 7,79 (m, 4H), 7,07 (m, 1H), 6,44 (m, 1H), 5,20 (d, 1H), 4,48 (d, 1H), 3,07 (m, 1H), 2,98 (m, 1H), 2,96 (s, 3H), 2,55 (d, 1H), 2,44 (d, 1H), 2,25 (m, 1H), 1,89 (m, 3H), 1,60 (m, 2H), 1,16 (m, 2H). MS: Calculado para $C_{23}H_{24}F_5O_5S_2$ (MH^+),

m/z = 539,10; experimental 539,3. Tiempo de retención: 4,56 min.

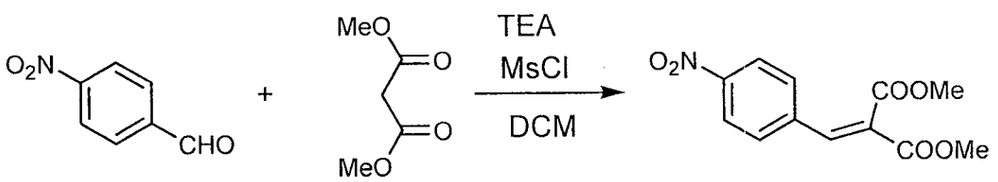
El alcohol primario **74B (–)** se preparó de modo análogo a las reacciones del Esquema 16, Pasos 8–10 a partir del compuesto **68B (–)**. Se tosiló de acuerdo con el procedimiento del Esquema 20 (este esquema), Paso 1 para dar tosilato **110 (–)**: ^{1}H–RMN ($CDCl_3$ 400 MHz) δ 7,83 (m, 6H), 7,40 (d, 2H), 7,08 (m, 1H), 6,46 (m, 1H), 5,05 (d, 1H), 4,34 (d, 1H), 4,28 (d, 1H), 4,11 (d, 1H), 2,65 (d, 1H), 2,48 (s, 3H), 1,9 (m, 3H), 1,71 (m, 1H), 1,51 (m, 4H), 1,15 (m, 1H).

El tosilato **110 (–)** se convirtió en sulfona **111** (–) de acuerdo con el procedimiento del Paso 2 (anterior). ^{1}H–RMN ($CDCl_3$ 400 MHz) δ 7,79 (m, 4H), 7,08 (m, 1H), 6,43 (m, 1H), 5,18 (d, 1H), 4,58 (d, 1H), 3,00 (m, 2H), 2,98 (s, 3H), 2,52 (d, 1H), 2,43 (d, 1H), 1,78 (m, 6H), 1,45 (s, 1H), 1,40 (m, 1H), 1,05 (m, 2H).

MS: Calculado para $C_{24}H_{26}F_5O_5S_2$ (MH^+), m/z = 553,11; experimental 553,3. Tiempo de retención: 4,62 min.

Los siguientes ejemplos ilustran los procesos de esta invención.

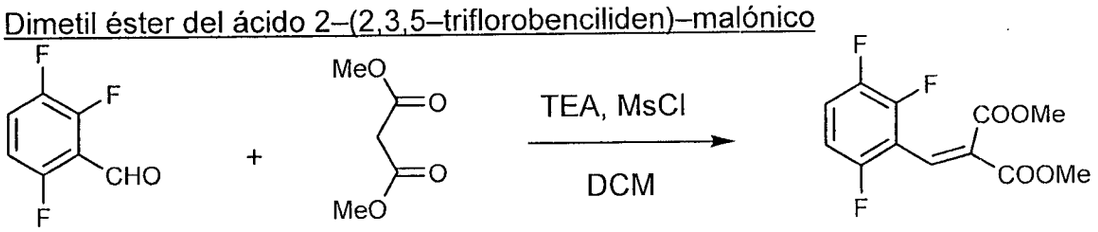
Ejemplo del Proceso 1



A una solución de 4–nitrobenzaldehído (3,02g, 20mmol) y dimetilmalonato (2,77 g, 21 mmol) en diclorometano anhidro (30 ml) bajo N_2 a 5°C en baño de hielo y agua, se agregó trietilamina (4,86 g, 48 mmol) durante 5 min. La reacción se agitó durante 20 min. Se agrego cloruro de metansulfonilo (2,75 g, 24 mmol) durante 4 horas a 5°C. La reacción se agitó durante 30 min. Se agregó agua (20 ml), se separaron las fases. La fase acuosa se extrajo con diclorometano (20 ml). La fase de diclorometano combinada se lavó con agua y se secó con sulfato de sodio anhidro. Se concentró a sólido (5,7 g) y se identificó como dimetil éster del ácido 2–(4–nitrobenciliden)–malónico. ^1H RMN ($CDCl_3$): δ 8,25 (d, 2H), 7,80 (s, 1H), 7,58 (d, 2H), 3,88 (s, 3H), 3,84 (s, 3H). Mass: [M+1] 266.

Ejemplo del Proceso 2

Dimetil éster del ácido 2–(2,3,5–triflorobenciliden)–malónico

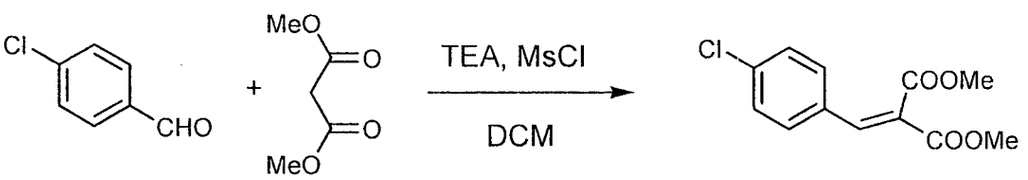


A una solución de 2,3,5–triflorobenzaldehído (1,6 g, 10 mmol) y dimetilmalonato (1,2 ml, 10,5mmol) en diclorometano anhidro (20 ml) bajo N_2 a temperatura ambiente en un baño de agua, se agregó trietilamina (2,1 ml, 15,4

mmol). Se agregó cloruro de metansulfonilo (1,0 ml, 12,8 mmol) a temperatura ambiente. La reacción se agitó durante 1 hora. Se agregó trietilamina adicional (2,1 ml, 15,4 mmol). Después de la mezcla se agitó durante 3 horas a temperatura ambiente, se agregaron cloruro de metansulfonilo adicional (0,5 ml, 6,4 mmol) y trietilamina (1,5 ml, 10 mmol). La mezcla se agitó durante 1 hora. Se agregaron agua (50 ml) y acetato de etilo (50 ml), se separaron las fases. La fase acuosa se extrajo con acetato de etilo (50 ml). La fase orgánica combinada se lavó con salmuera y se secó con anhidro sulfato de sodio. Se concentró a aceite (3,5 g) y se identificó como diemtil éster del ácido 2–(2,3,5–triflorobenciliden)–malónico. ^{1}H RMN ($CDCl_3$): δ 7,20 (m, 1H), 6,85 (m, 1H), 3,88 (s, 3H), 3,84 (s, 3H). Mass: [M+1] 243.

Ejemplo del Proceso 3

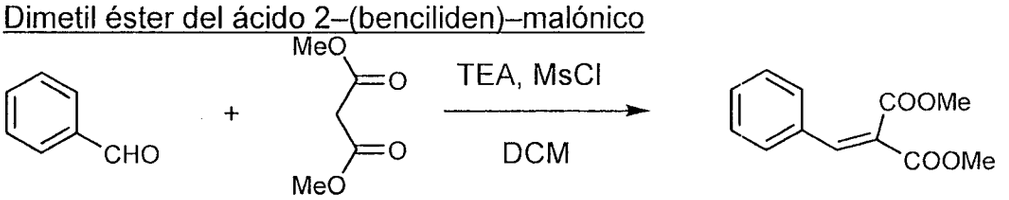
Dimetil éster del ácido 2–(4–clorobenziliden)–malónico



Siguiendo un proceso similar al del Ejemplo del Proceso 1, 4–clorobenzaldehído reacciona con dimetilmalonato bajo trietilamina y cloruro de metansulfonilo en diclorometano anhidro para producir el dimetil éster del ácido 2–(4–clorobenciliden)–malónico.

Ejemplo del Proceso 4

Dimetil éster del ácido 2–(benciliden)–malónico



Siguiendo un proceso similar al del Ejemplo del Proceso 1, benzaldehído reacciona con dimetilmalonato bajo trietilamina y cloruro de metansulfonilo en diclorometano anhidro para producir dimetil éster del ácido 2–(benciliden)–malónico.

Ensayo

Las propiedades farmacológicas de los compuestos de esta invención se pueden evaluar por varios ensayo farmacológicos. Se puede determinar la actividad de secretasa se puede determinar por el ensayo que se describe a continuación.

Se determinó la actividad de gamma secretasa como se describe en Zhang et al. (Biochemistry, 40 (16), 5049 –5055, 2001), que está incorporado en la presente como referencia. La actividad se expresa como porcentaje de inhibición o como la concentración del compuesto que produce 50% de inhibición de la actividad enzimática.

Reactivos

LOs anticuerpos W02, G2–10, y G2–11 se obtuvieron de Dr. Konrad Beyreuther (University de Heidelberg, Heidelberg, Alemania). W02 reconoce residuos 5–8 del péptido Aβ, mientras que G2–10 y G2–11 reconocen la estructura C–terminal específica de Aβ 40 y Aβ 42, respectivamente. La biotina–4G8 se compró en Senetec (St. Louis, MO). Todos los reactivos del cultivo de tejido usados en este trabajo provinieron de Life Technologies, Inc., a menos que se especifique lo contrario. La pepstatina A se compró en Roche Molecular Biochemicals; DFK167 provino de Enzyme Systems Products (Livermore, CA).

cDNA Constructs, Tissue Culture, y Cell Line Construction.

La construcción de SPC99–Ion, que contiene los primeros 18 residuos y los 99 aminoácidos de C–terminal de APP que portan la mutación London han sido descriptos (Zhang, L., Song, L., y Parker, E. (1999) J. Biol. Chem. 274, 8966–8972). Tras la inserción en la membrana, el péptido señal de 17 aminoácidos se procesa, dejando una leucina adicional en el extremo N–terminal de Aβ. Se clonó

SPC99–lon en el vector pcDNA4/TO (Invitrogen) y se transfectó en 293 células transfectadas en forma estable con pcDNA6/TR, que se proporcionó en el sistema T–REx (Invitrogen). Las células transfectadas se seleccionaron en medio Eagle modificado de Dulbecco (DMEM) suplementado con 10% de suero bovino fetal, 100 unidades/ml penicilina, 100 g/ml de estreptomicina, 250 g/ml de zeocina, y 5 g/ml de blasticidina (Invitrogen). Las colonias se analizaron rescpecto de la producción de Aβ por la inducción de la expresión de C99 con 0,1 g/ml de tetraciclina durante 16–20 h y se analizó el medio acondicionado con un ensayo sándwich (ver más adelante). Uno de los clones, designados como pTRE,15, se usó en estos estudios.

Preparación de membrana.

La expresión de las células C99 se indujo con 0,1 g/ml de tetraclicina durante 20 h. Las células se pretrataron con 12–miristato 13–acetato de phorbol 1M (PMA) y brefeldina A 1 M (BFA) durante 5–6 h a 37C antes de la recolección. Las células se lavaron 3 veces con solución salina bufereada con fosfato frío (PBS) y se recolectó en buffer A que contiene 20 mM de Hepes (pH 7,5), 250 mM de sacarosa, 50 mM de KCl, 2 mM de EDTA, 2 mM de EGTA, y comprimidos de inhibidor de proteasa completa (Roche Molecular Biochemicals). Los pellet de células se congelaron rápidamente en nitrógeno líquido y se conservaron a –70°C antes de usar.

Para preparar membranas, las células se resuspendieron en buffer A y se lisaron en una bomba de nitrógeno a 600 psi. El lisado de células se centrifugó a 1500 g durante 10 min para eliminar los núcleos y desechos celulares grandes. El sobrenadante se centrifugó a 100000 g durante 1 h. El pellet de membrana se resuspendió en buffer A más NaCl 0,5 M, y las membranas se recogieron por centrifugación a 200000 g durante 1 h. El pellet de membrana lavado con sal se lavó otra vez con buffer A y se centrifugó a 100000 g durante 1 h. El pellet de membrana final se resuspendió en un pequeño volumen de buffer A usando un

homogenizador de vidrio-Teflon. Se determinó la concentración de proteína, y las alícuotas de membrana se congelaron en nitrógeno líquido y se conservaron a –70°C.

Reacción de γ–Secretasa y análisis de Aβ.

Para medir la actividad de γ-secretasa, las membranas se incubaron a 37°C durante 1 h en 50 μL de buffer que contiene 20 mM de Hepes (pH 7,0) y 2 mM de EDTA. Al fin de la incubación, se midieron Aβ 40 y Aβ 42 usando un inmunoensayo basado en electroquimioluminiscencia (ECL). Aβ 40 fue identificado con pares de anticuerpos TAG–G2–10 y biotina–W02, mientras que Aβ 42 se identificó con TAG–G2–11 y biotina–4G8. La señal ECL se midió usando un instrumento ECL–M8 (IGEN International, Inc.) de acuerdo con las instrucciones del fabricante. Los datos presentados fueron mediciones por duplicado o triplicado para cada experimento. Las características de actividad de γ-secretasa descriptas se confirmaron mediante más de cinco preparaciones de membrana independientes.

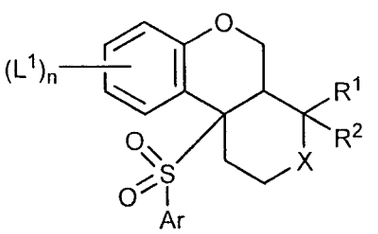
Los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–) tenían una IC_{50} de $A\beta_{40}$ en el rango de aproximadamente 6 μM a aproximadamente 1 nM.

Si bien la presente invención se ha descripto en conjunto con las realizaciones específicas expuestas anteriormente, muchas alternativas, modificaciones y otras variaciones de estas será evidente para los expertos en el arte. Todas estas alternativas, modificaciones y variaciones se incluyen en el espíritu y alcance de la presente invención.

REIVINDICACIONES

Habiendo así descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto de la fórmula:



(I)

o una de sus sales, solvatos o ésteres aceptables para uso farmacéutico, en donde:

X se selecciona del grupo que consiste en N y CH_2;

R^1 se selecciona del grupo que consiste en: (1) –alquilen–$S(O)_2$–alquilo(C_1–C_6), (2) –alquilen–$S(O)_2$–haloalquilo(C_1–C_6); (3) –alquilen–$S(O)_2$–R^6, (4) –alquilen–$S(O)_2$–R^8, (5) –alquilen–$S(O)_2$–alquilo(C_1–C_6) sustituido, (6) –alquilen–(1,1–dióxido de tetrahidrotiofeno), (7) –alquenil–$S(O)_2$–alquilo(C_1–C_6), y (8) –cicloalquil–$S(O)_2$–alquilo(C_1–C_6);

en donde dicho grupo R^1 –alquilen–$S(O)_2$–alquilo(C_1–C_6) sustituido está sustituido con uno o más sustituyentes seleccionados de modo independiente del grupo que consiste en: –OH, halo, –CN, $–CF_3$, –O–alquilo(C_1–C_6), y –O–(haloalquilo(C_1–C_6));

R^2 se selecciona del grupo que consiste en: H y alquilo;

R^6 se selecciona del grupo que consiste en: (1) arilo (C_6–C_{14}) no sustituido, (2) arilo (C_6–C_{14}) sustituido con uno o más grupos L^{1A}, (3) heteroarilo (C_5–C_{14}) no sustituido, (4) heteroarilo (C_5–C_{14}) sustituido con uno o más grupos L^{1A}, (5) heteroarilalquilo(C_5–C_{14}) no sustituido, y (5) heteroarilalquilo (C_5–C_{14}) sustituido con uno o más grupos L^{1A};

R^8 se selecciona del grupo que consiste en cicloalquilo no sustituido y cicloalquilo sustituido con uno o más grupos L^3 (en donde los ejemplos de dichos grupos cicloalquilo (no sustituido o sustituido) incluyen anillos cicloalquilo C_3–C_{10});

cada L^3 se selecciona de modo independiente del grupo que consiste en: (1) –CN, (2) =O, (3) $-CH_2OH$, (4) amino, (5) halo, (6) $-CH_2NH_2$, (7) $-CH_2NH$alquilo, (8) –C(O)OH, (9) –alquilen–C(O)NH alquilo (C_1 a C_6), (10) –alquilen–C(O)N(alquilo (C_1 a C_6))$_2$ en donde cada alquilo se selecciona de modo independiente, (11) –alquilen–C(O)NH haloalquilo (C_1 a C_6), y (12) –alquilen–C(O)N(haloalquilo (C_1 a C_6))$_2$ en donde cada alquilo se selecciona de modo independiente);

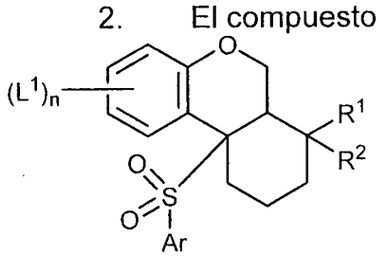
Ar se selecciona del grupo que consiste en: (1) arilo no sustituido, (2) arilo sustituido con uno o más grupos L^{1A}, (3) heteroarilo no sustituido, y (4) heteroarilo sustituido con uno o más grupos L^{1A};

cada L^1 se selecciona de modo independiente del grupo que consiste en: halógeno, alquilo (por ej., alquilo C_1–C_6), –CN, $-CF_3$, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, alcoxialcoxi–, y $-S(O)_2$alquilo(C_1–C_6);

cada L^{1A} se selecciona de modo independiente del grupo que consiste en: halógeno, alquilo, –CN, $-CF_3$, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, alcoxialcoxi–, y $-S(O)_2$alquilo(C_1–C_6); y

n es 0, 1, 2 o 3.

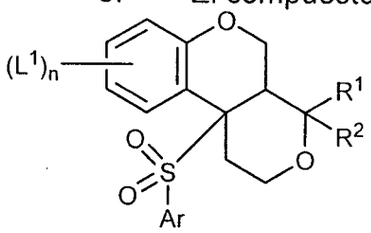
2. El compuesto de la reivindicación 1 que tiene la fórmula:



(I.A1)

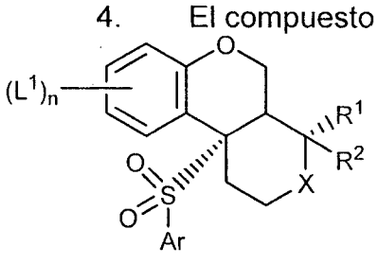
624

3. El compuesto de la reivindicación 1 que tiene la fórmula:



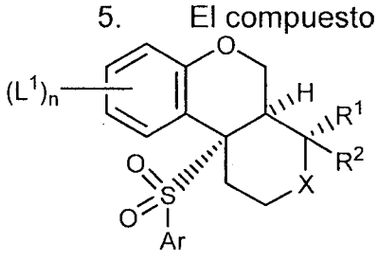
(I.A2)

4. El compuesto de la reivindicación 1 que tiene la fórmula:



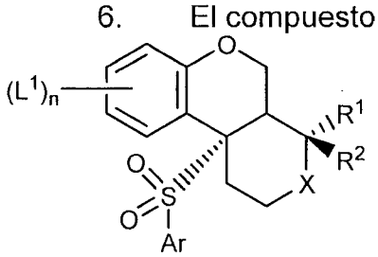
(Ii)

5. El compuesto de la reivindicación 1 que tiene la fórmula:



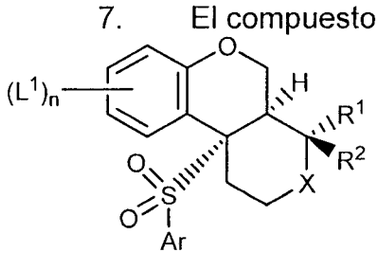
(Iii)

6. El compuesto de la reivindicación 1 que tiene la fórmula:



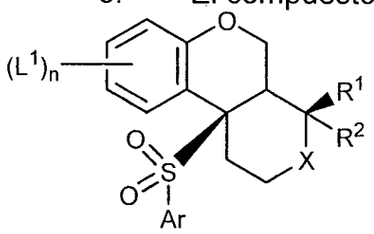
(Iiii)

7. El compuesto de la reivindicación 1 que tiene la fórmula:



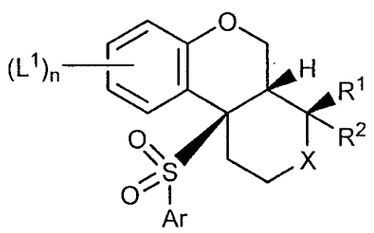
(Iiv)

8. El compuesto de la reivindicación 1 que tiene la fórmula:



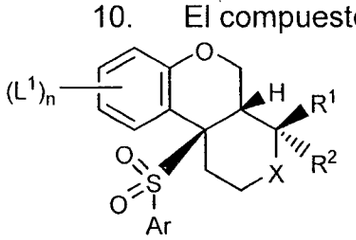
(Iv)

9. El compuesto de la reivindicación 1 que tiene la fórmula:



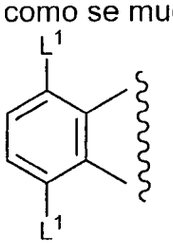
(Ivi)

10. El compuesto de la reivindicación 1 que tiene la fórmula:



(Ivii)

11. El compuesto de la reivindicación 1 seleccionado del grupo que consiste en los compuestos de las fórmulas (Ii) a (Ivii) en donde n es 2, cada L^1 es el mismo o diferente halo, y dichos grupos L^1 están unidos al grupo fenilo como se muestra en la fórmula (IIA):

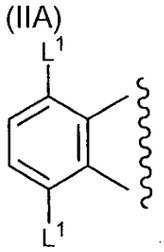


(IIA)

12. El compuesto de la reivindicación 11 en donde cada L^1 es F.

626

13. El compuesto de la reivindicación 1 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos de las fórmulas (Ii) a (Ivii) en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA)



(IIA)

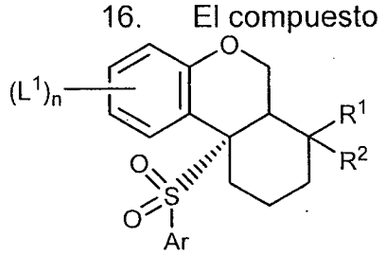
,

y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo, y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo, –CN, –CF_3, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, y alcoxialcoxi–.

14. El compuesto de la reivindicación 13 en donde cada L^1 es el mismo o diferente halo.

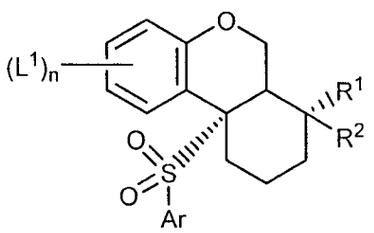
15. El compuesto de la reivindicación 14 en donde dichos grupos L^1 son F.

16. El compuesto de la reivindicación 1 que tiene la fórmula:



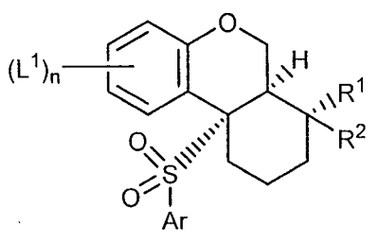
(I.A1a)

17. El compuesto de la reivindicación 1 que tiene la fórmula:



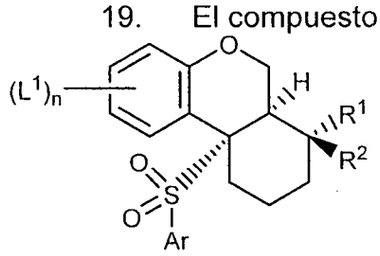
(I.A1b)

18. El compuesto de la reivindicación 1 que tiene la fórmula:



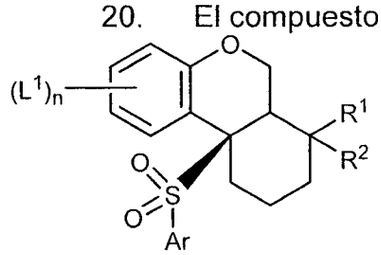
(I.A1c)

19. El compuesto de la reivindicación 1 que tiene la fórmula:



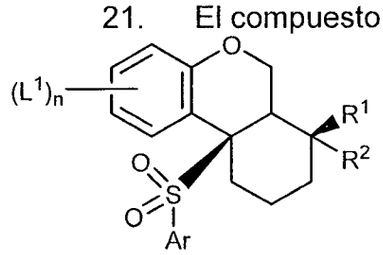
(I.A1d)

20. El compuesto de la reivindicación 1 que tiene la fórmula:



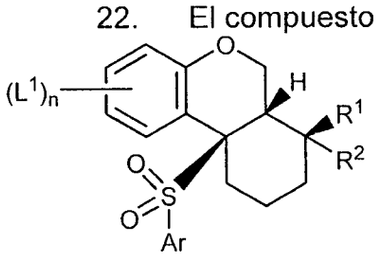
(I.A1e)

21. El compuesto de la reivindicación 1 que tiene la fórmula:



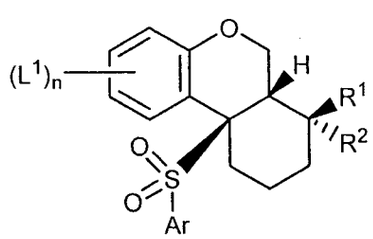
(I.A1f)

22. El compuesto de la reivindicación 1 que tiene la fórmula:



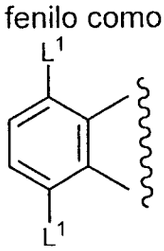
(I.A1g)

23. El compuesto de la reivindicación 1 que tiene la fórmula:



(I.A1h)

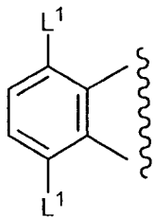
24. El compuesto de la reivindicación 1 seleccionado del grupo que consiste en los compuestos de las fórmulas (I.A1a) a (I.A1h) en donde n es 2, cada L^1 es el mismo o diferente halo, y dichos grupos L^1 están unidos al grupo fenilo como se muestra en formula (IIA):



(IIA)

25. El compuesto de la reivindicación 24 en donde cada L^1 es F.

26. El compuesto de la reivindicación 1 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos de las fórmulas (I.A1a) a (I.A1h) en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA)


(IIA)

y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo, –CN, –CF_3, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, y alcoxialcoxi–.

27. El compuesto de la reivindicación 26 en donde cada L^1 es el mismo o diferente halo.

28. El compuesto de la reivindicación 27 en donde dichos grupos L^1 son F.

29. El compuesto de la reivindicación 28 en donde Ar es p–Cl–fenilo–.

30. El compuesto de la reivindicación 28 en donde Ar es p–CN–fenilo–.

31. El compuesto de la reivindicación 28 en donde Ar es p–CF_3–fenilo.

32. El compuesto de la reivindicación 28 en donde Ar es p–$CH_3CH_2SO_2$fenilo.

33. El compuesto de la reivindicación 28 en donde Ar es p–Br–fenilo.

34. El compuesto de la reivindicación 28 en donde Ar es m,p–di–F–fenilo.

35. El compuesto de la reivindicación 28 en donde Ar es m,p–di–CN–fenilo.

36. El compuesto de la reivindicación 28 en donde Ar es p–CH_3O–fenilo.

37. El compuesto de la reivindicación 28 en donde Ar es p–CF_3CH_2Ofenilo.

38. El compuesto de la reivindicación 24 en donde R^2 es H.

39. El compuesto de la reivindicación 24 en donde R^2 es alquilo.

40. El compuesto de la reivindicación 24 en donde R^2 es metilo.

41. El compuesto de la reivindicación 25 en donde R^2 es H.

42. El compuesto de la reivindicación 25 en donde R^2 es alquilo.

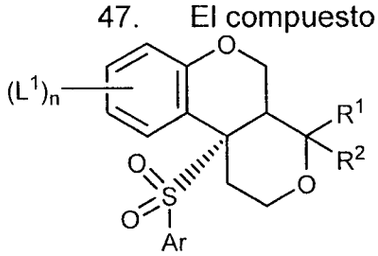
43. El compuesto de la reivindicación 25 en donde R^2 es metilo.

44. El compuesto de la reivindicación 28 en donde R^2 es H.

45. El compuesto de la reivindicación 28 en donde R^2 es alquilo.

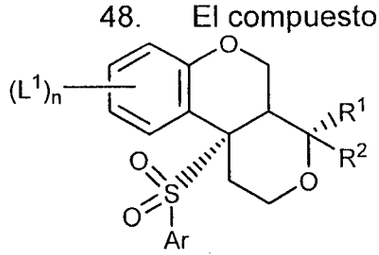
46. El compuesto de la reivindicación 28 en donde R^2 es metilo.

47. El compuesto de la reivindicación 1 que tiene la fórmula:



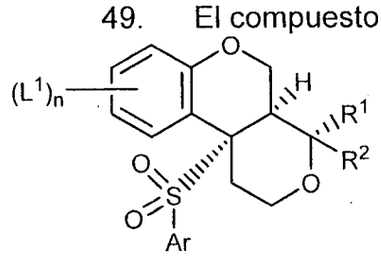
(I.A2a)

48. El compuesto de la reivindicación 1 que tiene la fórmula:



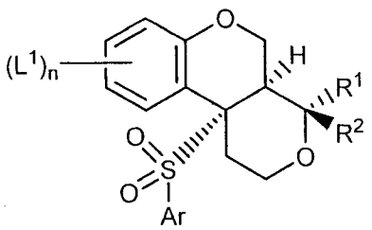
(I.A2b)

49. El compuesto de la reivindicación 1 que tiene la fórmula:



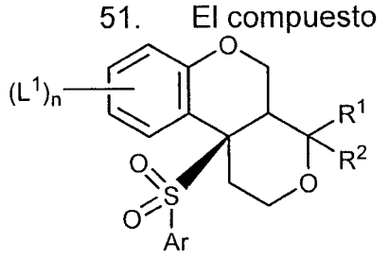
(I.A2c)

50. El compuesto de la reivindicación 1 que tiene la fórmula:



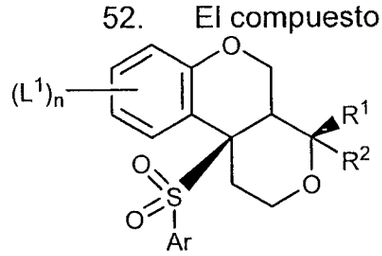
(I.A2d)

51. El compuesto de la reivindicación 1 que tiene la fórmula:



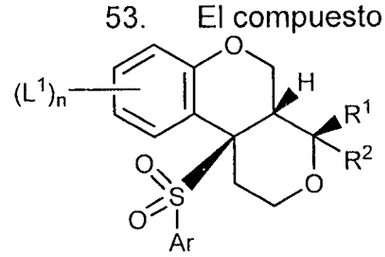
(I.A2e)

52. El compuesto de la reivindicación 1 que tiene la fórmula:



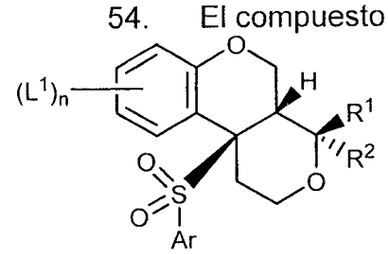
(I.A2f)

53. El compuesto de la reivindicación 1 que tiene la fórmula:



(I.A2g)

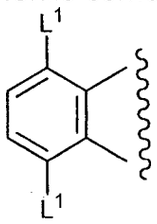
54. El compuesto de la reivindicación 1 que tiene la fórmula:



(I.A2h)

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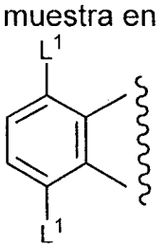
55. El compuesto de la reivindicación 1 seleccionado del grupo que consiste en los compuestos de las fórmulas (I.A2a) a (I.A2h) en donde n es 2, cada L^1 es el mismo o diferente halo, y dichos grupos L^1 están unidos al grupo fenilo como se muestra en formula (IIA):



(IIA)

56. El compuesto de la reivindicación 55 en donde cada L^1 es F.

57. El compuesto de la reivindicación 1 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos de las fórmulas (I.A2a) a (I.A2h) en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA)



(IIA)

y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo, –CN, –CF_3, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, y alcoxialcoxi–.

58. El compuesto de la reivindicación 57 en donde cada L^1 es el mismo o diferente halo.

59. El compuesto de la reivindicación 58 en donde dichos grupos L^1 son F.

60. El compuesto de la reivindicación 59 en donde Ar es p–Cl–fenilo–.

61. El compuesto de la reivindicación 59 en donde Ar es p–CN–fenilo–.

62. El compuesto de la reivindicación 59 en donde Ar es p–CF_3–fenilo.

63. El compuesto de la reivindicación 59 en donde Ar es p–$CH_3CH_2SO_2$fenilo.

64. El compuesto de la reivindicación 59 en donde Ar es p–Br–fenilo.

65. El compuesto de la reivindicación 59 en donde Ar es m,p–di–F–fenilo.

66. El compuesto de la reivindicación 59 en donde Ar es m,p–di–CN–fenilo.

67. El compuesto de la reivindicación 59 en donde Ar es p–CH_3O–fenilo.

68. El compuesto de la reivindicación 59 en donde Ar es p–CF_3CH_2Ofenilo.

69. El compuesto de la reivindicación 55 en donde R^2 es H.

70. El compuesto de la reivindicación 55 en donde R^2 es alquilo.

71. El compuesto de la reivindicación 55 en donde R^2 es metilo.

72. El compuesto de la reivindicación 56 en donde R^2 es H.

73. El compuesto de la reivindicación 56 en donde R^2 es alquilo.

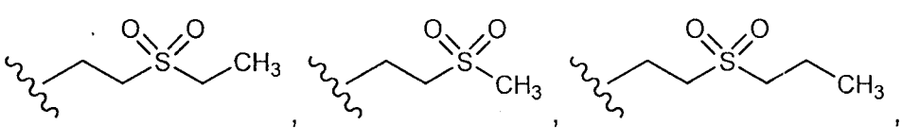
74. El compuesto de la reivindicación 56 en donde R^2 es metilo.

75. El compuesto de la reivindicación 59 en donde R^2 es H.

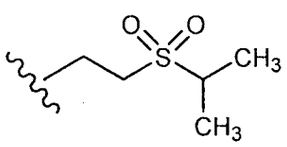
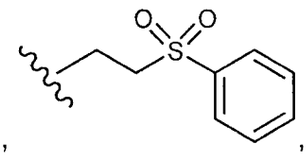
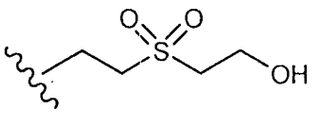
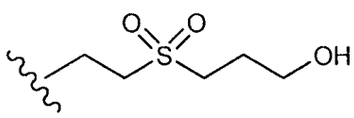
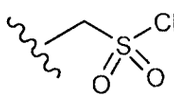
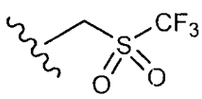
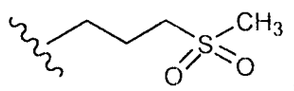
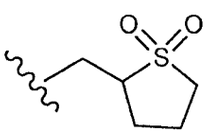
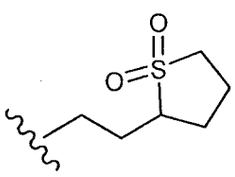
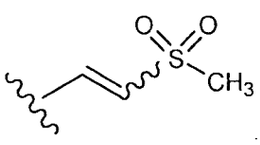
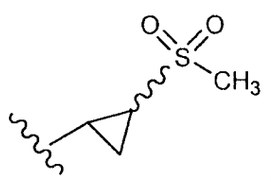
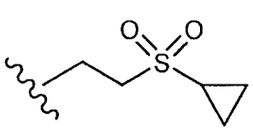
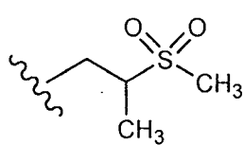
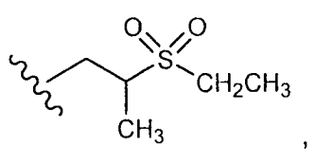
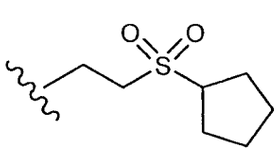
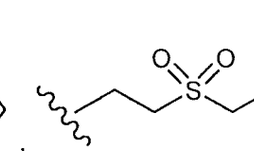
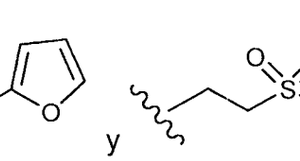
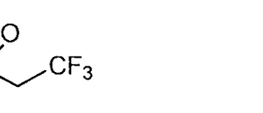
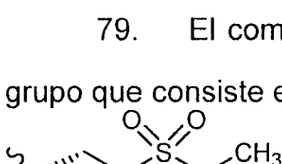
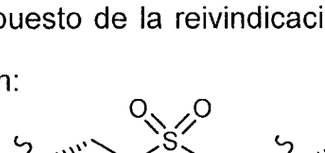
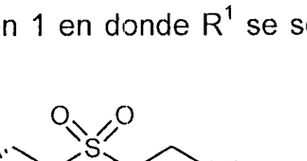
76. El compuesto de la reivindicación 59 en donde R^2 es alquilo.

77. El compuesto de la reivindicación 59 en donde R^2 es metilo.

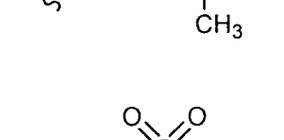
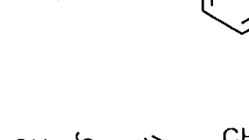
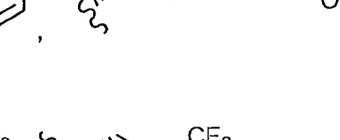
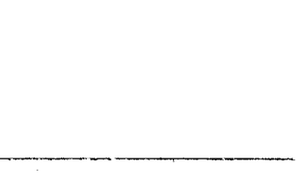
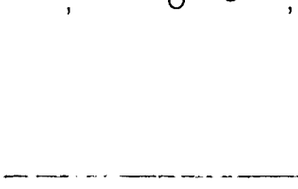
78. El compuesto de la reivindicación 1 en donde R^1 se selecciona del grupo que consiste en:



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79. El compuesto de la reivindicación 1 en donde R^1 se selecciona del grupo que consiste en:


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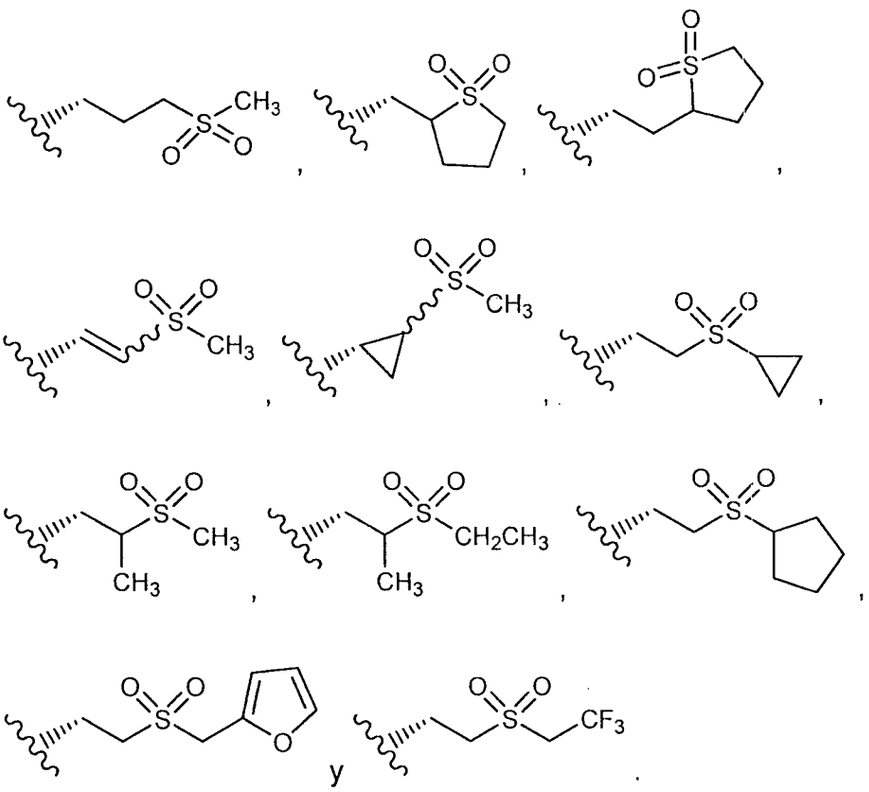
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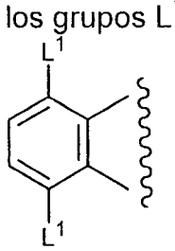
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80. El compuesto de la reivindicación 79 en donde el compuesto de fórmula (I) es un compuesto seleccionado del grupo que consiste en los compuestos de las fórmulas (Ii), (Iii), (Iiii), (Iiv), (I.A1b), (I.A1c), (I.A1d), (I.A2b), (I.A2c), o (I.A1d).

81. El compuesto de la reivindicación 80 en donde en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA)



(IIA)

y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno,

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alquilo, –CN, $–CF_3$, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, y alcoxialcoxi–.

82. El compuesto de la reivindicación 81 en donde cada L^1 es el mismo o diferente halo.

83. El compuesto de la reivindicación 82 en donde dichos grupos L^1 son F.

84. El compuesto de la reivindicación 83 en donde R^2 es H.

85. El compuesto de la reivindicación 83 en donde R^2 es alquilo.

86. El compuesto de la reivindicación 83 en donde R^2 es metilo.

87. El compuesto de la reivindicación 84 en donde Ar es p–Cl–fenilo–.

88. El compuesto de la reivindicación 84 en donde Ar es p–CN–fenilo–.

89. El compuesto de la reivindicación 84 en donde Ar es p–CF_3–fenilo.

90. El compuesto de la reivindicación 84 en donde Ar es p–$CH_3CH_2SO_2$fenilo.

91. El compuesto de la reivindicación 84 en donde Ar es p–Br–fenilo.

92. El compuesto de la reivindicación 84 en donde Ar es m,p–di–F–fenilo.

93. El compuesto de la reivindicación 84 en donde Ar es m,p–di–CN–fenilo.

94. El compuesto de la reivindicación 84 en donde Ar es p–CH_3O–fenilo.

95. El compuesto de la reivindicación 84 en donde Ar es p–CF_3CH_2Ofenilo.

96. El compuesto de la reivindicación 86 en donde Ar es p–Cl–fenilo–.

97. El compuesto de la reivindicación 86 en donde Ar es p–CN–fenilo–.

98. El compuesto de la reivindicación 86 en donde Ar es p–CF_3–fenilo.

99. El compuesto de la reivindicación 86 en donde Ar es p–$S(O)_2CH_2CH_3$.

100. El compuesto de la reivindicación 86 en donde Ar es p–Br–fenilo.

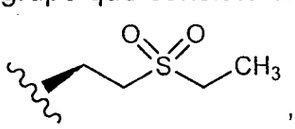
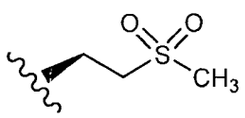
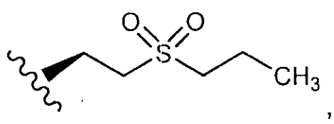
101. El compuesto de la reivindicación 86 en donde Ar es m,p–di–F–fenilo.

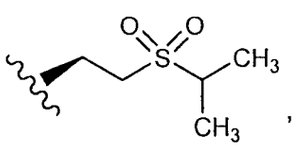
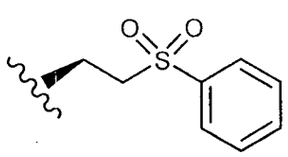
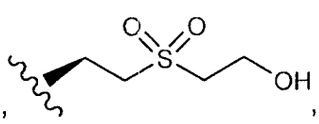
102. El compuesto de la reivindicación 86 en donde Ar es m,p–di–CN–fenilo.

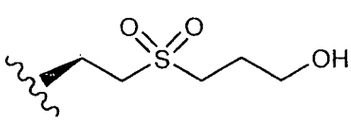
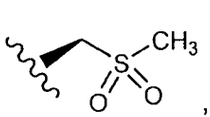
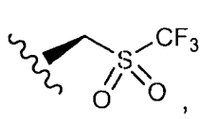
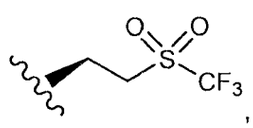
103. El compuesto de la reivindicación 86 en donde Ar es p–CH_3O–fenilo.

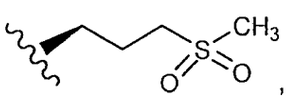
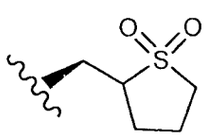
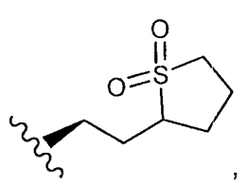
104. El compuesto de la reivindicación 86 en donde Ar es p–CF_3CH_2Ofenilo.

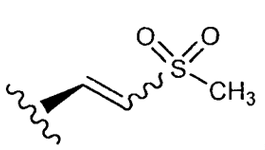
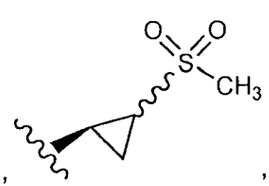
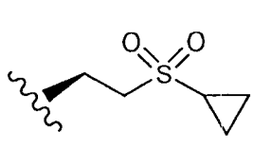
105. El compuesto de la reivindicación 1 en donde R^1 se selecciona del grupo que consiste en:

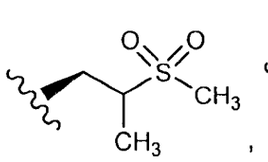
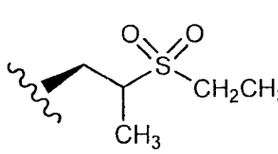
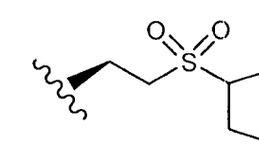

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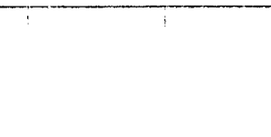

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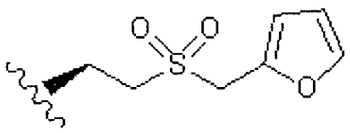
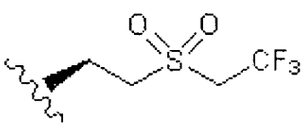

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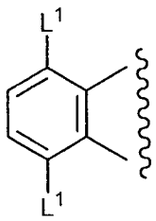
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106. El compuesto de la reivindicación 105 en donde el compuesto de fórmula (I) se selecciona del grupo que consiste en los compuestos de las fórmulas (Iv), (Ivi), (Ivii), (I.A1f), (I.A1g), (I.A1h), (I.A2f), (I.A2g) y (I.A2h).

107. El compuesto de la reivindicación 106 en donde en donde n es 2, y los grupos L^1 están unidos al grupo fenilo como se muestra en (IIA)

 (IIA)

y Ar se selecciona del grupo que consiste en p–Cl–fenilo–, p–CN–fenilo–, p–CF_3–fenilo, p–$CH_3CH_2SO_2$fenilo, p–Br–fenilo, m,p–di–F–fenilo, m,p–di–CN–fenilo, p–CH_3O–fenilo, p–CF_3CH_2Ofenilo, piridilo y piridilo sustituido con 1 o 2 sustituyentes seleccionados de modo independiente del grupo que consiste en: halógeno, alquilo, –CN, –CF_3, –O–alquilo(C_1–C_6), –O–(haloalquilo(C_1–C_6)), –C(O)–O–alquilo(C_1–C_6), –alquilen–OH, haloalquilo(C_1–C_6), hidroxialcoxi–, y alcoxialcoxi–.

108. El compuesto de la reivindicación 107 en donde cada L^1 es el mismo o diferente halo.

109. El compuesto de la reivindicación 108 en donde dichos grupos L^1 son F.

110. El compuesto de la reivindicación 109 en donde R^2 es H.

111. El compuesto de la reivindicación 109 en donde R^2 es alquilo.

112. El compuesto de la reivindicación 109 en donde R^2 es metilo.

113. El compuesto de la reivindicación 110 en donde Ar es p–Cl–fenilo–.

114. El compuesto de la reivindicación 110 en donde Ar es p–CN–fenilo–.

115. El compuesto de la reivindicación 110 en donde Ar es p–CF_3–fenilo.

116. El compuesto de la reivindicación 110 en donde Ar es p–$CH_3CH_2SO_2$fenilo.

117. El compuesto de la reivindicación 110 en donde Ar es p–Br–fenilo.

118. El compuesto de la reivindicación 110 en donde Ar es m,p–di–F–fenilo.

119. El compuesto de la reivindicación 110 en donde Ar es m,p–di–CN–fenilo.

120. El compuesto de la reivindicación 110 en donde Ar es p–CH_3O–fenilo.

121. El compuesto de la reivindicación 110 en donde Ar es p–CF_3CH_2Ofenilo.

122. El compuesto de la reivindicación 112 en donde Ar es p–Cl–fenilo–.

123. El compuesto de la reivindicación 112 en donde Ar es p–CN–fenilo–.

124. El compuesto de la reivindicación 112 en donde Ar es p–CF_3–fenilo.

125. El compuesto de la reivindicación 112 en donde Ar es p–$CH_3CH_2SO_2$fenilo.

126. El compuesto de la reivindicación 112 en donde Ar es p–Br–fenilo.

127. El compuesto de la reivindicación 112 en donde Ar es m,p–di–F–fenilo.

128. El compuesto de la reivindicación 112 en donde Ar es m,p–di–CN–fenilo.

129. El compuesto de la reivindicación 112 en donde Ar es p–CH_3O–fenilo.

130. El compuesto de la reivindicación 112 en donde Ar es p–CF_3CH_2Ofenilo.

131. El compuesto de la reivindicación 1 seleccionado del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31,

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33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

132. El compuesto de la reivindicación 1 seleccionado de un solvato de un compuesto seleccionado del grupo que consiste en 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

133. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 12.

134. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 13.

135. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22A.

136. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22B.

137. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22B–RAC.

138. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22C.

139. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22D.

140. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22E.

141. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22F.

142. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22G.

143. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22H.

144. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22I.

145. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22J.

146. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22K.

147. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22L.

148. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22M.

149. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 22N.

150. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 26A.

151. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 26B.

152. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 27.

153. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 28.

154. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 31.

155. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 33(–).

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156. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 36.

157. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 37.

158. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 39.

159. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 44A.

160. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 44B.

161. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 55.

162. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 56.

163. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 57.

164. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 60.

165. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 70A.

166. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 71A(–).

167. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 75A–rac.

168. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 75B(–).

169. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 76A(–).

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170. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 76A(+).

171. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 76B(–).

172. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 78A(–).

173. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 79A(–).

174. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 80A(+).

175. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 81A–rac.

176. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 81A(–).

177. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 81A(+).

178. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 81B(–).

179. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 82A.

180. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 83A.

181. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 84A.

182. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 85A.

183. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 85B(–).

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184. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 86A.

185. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 87B.

186. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 95B–rac.

187. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 95B(–).

188. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 95B(+).

189. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 106(–).

190. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 107(–).

191. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 108(–).

192. El compuesto de la reivindicación 1 en donde dicho compuesto es el compuesto 111(–).

193. Una composición farmacéutica que comprende una cantidad efectiva de al menos un compuesto de la reivindicación 1 y al menos un vehículo aceptable para uso farmacéutico.

194. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto de la reivindicación 1 y un vehículo aceptable para uso farmacéutico.

195. La composición farmacéutica de la reivindicación 194 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–),

79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

196. la composición farmacéutica de la reivindicación 194 en donde dicho compuesto es un solvato de un compuesto seleccionado del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

197. Un método de inhibir gamma-secretasa en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1.

198. Un método de inhibir gamma-secretasa en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

199. Un método de tratar una o más enfermedades neurodegenerativas en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1.

200. Un método de tratar una o más enfermedades neurodegenerativas en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A,

71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

201. Un método de inhibir el depósito de proteína beta amiloide en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1.

202. Un método de inhibir el depósito de proteína beta amiloide en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

203. Un método de tratar enfermedad de Alzheimer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1.

204. Un método de tratar enfermedad de Alzheimer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos seleccionados del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+), 76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

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205. Un método de inhibir gammá secretasa en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más diferentes drogas seleccionadas del grupo que consiste en: (a) drogas para el tratamiento de enfermedad de Alzheimer, (b) drogas para inhibir el depósito de proteína amiloide en, sobre o alrededor del tejido neurológico, (c) drogas para tratar enfermedades neurodegenerativas, y (d) drogas para inhibir la gamma-secretasa.

206. Un método de inhibir gamma secretasa en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: inhibidores de BACE, antagonistas muscarínicos, inhibidores de colinesterasa; inhibidores de gamma secretasa; moduladores de gamma secretasa; inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa; inhibidores de PDE–10 e inhibidores de absorción de colesterol.

207. Un método de inhibir gamma secretasa en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de uno o más inhibidores de BACE.

208. El método de la reivindicación 205 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

209. El método de la reivindicación 206 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

210. El método de la reivindicación 207 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

211. Un método de tratar una o más enfermedades neurodegenerativas en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: (a) drogas para el tratamiento de enfermedad de Alzheimer, (b) drogas para inhibir el depósito de proteína amiloide en, sobre o alrededor del tejido neurológico, (c) drogas para tratar enfermedades neurodegenerativas, y (d) drogas para inhibir la gamma-secretasa.

212. Un método de tratar una o más enfermedades neurodegenerativas en un paciente que necesita dicho tratamiento que comprende administrar a dicho

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paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: inhibidores de BACE, antagonistas muscarínicos, inhibidores de colinesterasa; inhibidores de gamma secretasa; moduladores de gamma secretasa; inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa; inhibidores de PDE–10 e inhibidores de absorción de colesterol.

213. Un método de tratar una o más enfermedades neurodegenerativas en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de uno o más inhibidores de BACE.

214. El método de la reivindicación 211 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

215. El método de la reivindicación 212 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac,

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81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

216. El método de la reivindicación 213 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

217. Un método de inhibir el depósito de proteína amiloide en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: (a) drogas para el tratamiento de enfermedad de Alzheimer, (b) drogas para inhibir el depósito de proteína amiloide en, sobre o alrededor del tejido neurológico, (c) drogas para tratar enfermedades neurodegenerativas, y (d) drogas para inhibir la gamma-secretasa.

218. Un método de inhibir el depósito de proteína amiloide en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: inhibidores de BACE, antagonistas muscarínicos, inhibidores de colinesterasa; inhibidores de gamma secretasa; moduladores de gamma secretasa; inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4;

agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa; inhibidores de PDE–10 e inhibidores de absorción de colesterol.

219. Un método de inhibir el depósito de proteína amiloide en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de uno o más inhibidores de BACE.

220. El método de la reivindicación 217 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

221. El método de la reivindicación 218 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

222. El método de la reivindicación 219 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

223. Un método de tratar enfermedad de Alzheimer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una

cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: (a) drogas para el tratamiento de enfermedad de Alzheimer, (b) drogas para inhibir el depósito de proteína amiloide en, sobre o alrededor del tejido neurológico, (c) drogas para tratar enfermedades neurodegenerativas, y (d) drogas para inhibir la gamma-secretasa.

224. Un método de tratar enfermedad de Alzheimer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de una o más drogas diferentes seleccionadas del grupo que consiste en: inhibidores de BACE, antagonistas muscarínicos, inhibidores de colinesterasa; inhibidores de gamma secretasa; moduladores de gamma secretasa; inhibidores de HMG–CoA reductasa; agentes antiinflamatorios no esteroides; antagonistas del receptor N–metil–D–aspartato; anticuerpos anti-amiloideos; vitamina E; agonistas del receptor nicotínico de acetilcolina; agonistas inversos del receptor de CB1 o antagonistas del receptor de CB1; un antibiótico; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de agregación amiloide; inhibidores de beta glicógeno sintasa quinasa; promotores de la actividad alfa secretasa; inhibidores de PDE–10 e inhibidores de absorción de colesterol.

225. Un método de tratar enfermedad de Alzheimer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 1, y una cantidad terapéuticamente efectiva de uno o más inhibidores de BACE.

226. El método de la reivindicación 223 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 22B–

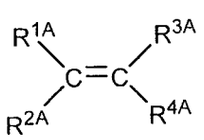
RAC, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

227. El método de la reivindicación 224 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

228. El método de la reivindicación 225 en donde dicho compuesto se selecciona del grupo que consiste en los compuestos 12, 13, 22A a 22N, 26A, 26B, 27, 28, 31, 33(–), 36, 37, 39, 44A, 44B, 55 a 57, 60, 70A, 71A(–), 75A–rac, 75B(–), 76A(–), 76A(+),76B(–), 78A(–), 79A(–), 80A(+), 81A–rac, 81A(–), 81A(+), 81B(–), 82A, 83A, 84A, 85A, 85B(–), 86A, 87B, 95B–rac, 95B(–), 95B(+), 106(–), 107(–), 108(–), y 111(–).

229. El compuesto de la reivindicación 1 en forma purificada.

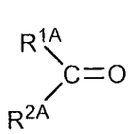
230. Un proceso para preparar un compuesto de la fórmula:



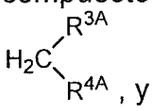
dicho proceso que comprende hacer reaccionar:

(1) una mezcla que comprende:

(a) un compuesto de la fórmula:


, y

(b) un compuesto de la fórmula:

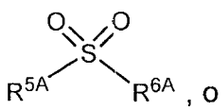


, y

(c) un solvente orgánico adecuado; con

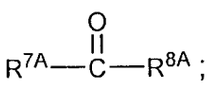
(2) cualquiera de:

(a) una amina básica, y un compuesto de la fórmula



, o

(b) una amina básica, y un compuesto de la fórmula



;

en donde:

cada uno de R^{1A} y R^{2A} se seleccionan de modo independiente del grupo que consiste en: H, alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, heteroalquilo, arilo, heteroarilo, alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido; en donde dichos grupos sustituidos están sustituidos con uno o más sustituyentes, cada uno seleccionado de modo independiente del grupo que consiste en: $-NO_2$, –NO, $-SO_2R^{7B}$, $-SO_2-$arilo, $-SO_2-$heteroarilo, $-SO_2OR^{7B}$, –CN, –COOH, halo, $-CF_3$, –Oarilo, –Oheteroarilo, $-COOR^{7B}$, $-CONH_2$, $-CONHR^{7B}$, $CON(R^{7B})_2$, –CHO, $-OR^{7B}$, $-COR^{7B}$, –SH, $-SR^{7B}$, –OH, arilo, y heteroarilo;

Cada R^{3A} y R^{4A} se seleccionan de modo independiente del grupo que consiste en: $-NO_2$, –NO, $-SO_2R^{7B}$, $-SO_2-$arilo, $-SO_2-$heteroarilo, $-SO_2OR^{7B}$, –CN, –COOH, halo, $-CF_3$, –Oarilo, –Oheteroarilo, $-COOR^{7B}$, $-CONH_2$,

$-CONHR^{7B}$, $CON(R^{7B})_2$, $-CHO$, $-OR^{7B}$, $-COR^{7B}$, $-SH$, $-SR^{7B}$, $-OH$, arilo, y heteroarilo;

R^{5A} se selecciona del grupo que consiste en: H, alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, heteroalquilo, arilo, heteroarilo, alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido; y en donde:

dichos grupos alquilo sustituidos están sustituidos con uno o más sustituyentes, cada uno seleccionado de modo independiente del grupo que consiste en: halo, $-NO_2$, $-CN$, y $-OR^{12A}$; y

dichos grupos alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido están sustituidos con uno o más sustituyentes, cada uno seleccionado de modo independiente del grupo que consiste en: halo, $-NO_2$, $-CN$, y $-OR^{12A}$, alquilo y haloalquilo sustituido (por ej., alquilo sustituido con F, tal como, por ejemplo, $-CF_3$);

R^{6A} se selecciona del grupo que consiste en: halo, y $-OSO_2R^{5A}$;

R^{7A} se selecciona del grupo que consiste en: arilo no sustituido, arilo sustituido con al menos un grupo atrayente de electrones, heteroarilo, y heteroarilo sustituido con al menos un grupo atrayente de electrones;

Cada R^{7B} se selecciona de modo independiente del grupo que consiste en: alquilo, cicloalquilo y heteroalquilo;

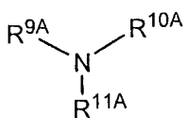
R^{8A} se selecciona del grupo que consiste en: halo, y $-OC(O)R^{7A}$;

R^{12A} es alquilo; y

R^{13A} se selecciona del grupo que consiste en: alquilo, alcoxialquilo, hidroxialquilo, alcanoílo, arilo, heteroarilo, aroílo, y carbamoílo, y con preferencia alquilo.

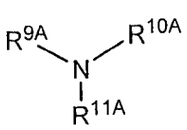
456

231. El proceso de la reivindicación 230 en donde dicha amina básica es un compuesto de la fórmula:



en donde cada R^{9A}, R^{10A}, y R^{11A} se selecciona de modo independiente del grupo que consiste en: alquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, heteroalquilo, arilo, heteroarilo, alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, heterocicloalquilo sustituido, heteroalquilo sustituido, arilo sustituido, y heteroarilo sustituido; en donde dichos grupos sustituidos están sustituidos con uno o más sustituyentes, cada uno seleccionado de modo independiente del grupo que consiste en: halo, alquilo y alcoxi.

232. El proceso de la reivindicación 230 en donde dicha amina básica es un compuesto de la fórmula:



en donde R^{9A}, R^{10A}, y R^{11A} son grupos alquilo, en donde cada grupo alquilo se selecciona de modo independiente.

233. El proceso de la reivindicación 232 en donde dicha amina básica es trietilamina.

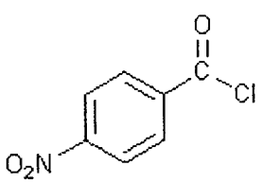
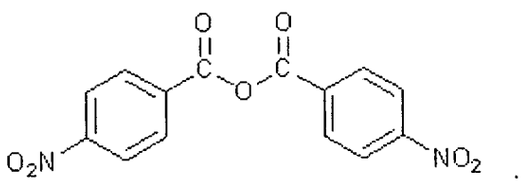
234. El proceso de la reivindicación 233 en donde dicha amina básica es diisopropiletilamina.

235. El proceso de la reivindicación 230 en donde dicho solvente orgánico se selecciona del grupo que consiste en: (1) haloalcanos, (2) arilhaluros, (3) DMSO, (4) DMF, (5) THF, (6) éteres, y (7) sus mezclas.

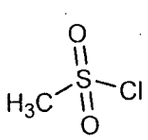
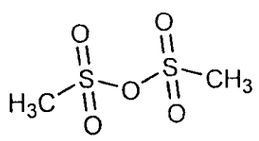
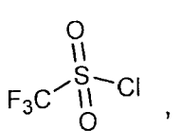
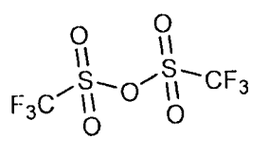
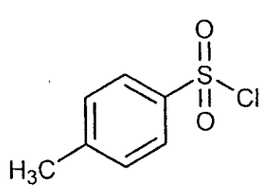
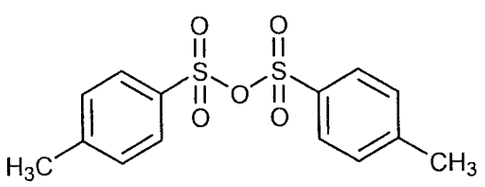
236. El proceso de la reivindicación 230 en donde dicho solvente se selecciona del grupo que consiste en: diclorometano anhidro, dicloroetano anhidro, clorobenceno anhidro, DMSO anhidro, DMF anhidro, THF anhidro y dietiléter anhidro.

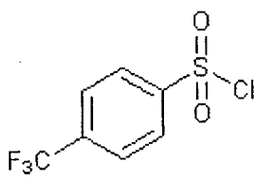
237. El proceso de la reivindicación 236 en donde dicho solvente orgánico es diclorometano anhidro.

238. El proceso de la reivindicación 230 en donde dicho compuesto $R^{7A}C(O)R^{8A}$ se selecciona del grupo que consiste en:

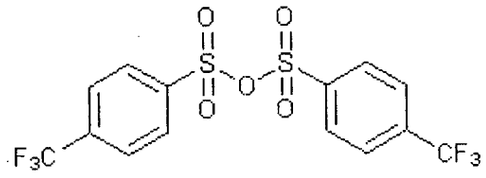



239. El proceso de la reivindicación 230 en donde dicho compuesto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:

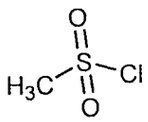









y



240. El proceso de la reivindicación 239 en donde el compuesto es:



241. El proceso de la reivindicación 230 en donde el proceso se lleva a cabo a una temperatura en el rango de aproximadamente –40°C a aproximadamente 40°C.

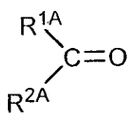
242. El proceso de la reivindicación 230 en donde el proceso se lleva a cabo a una temperatura en el rango de aproximadamente 0°C a aproximadamente 30°C.

243. El proceso de la reivindicación 230 en donde el proceso se lleva a cabo a una temperatura en el rango de aproximadamente 0°C a aproximadamente 10°C.

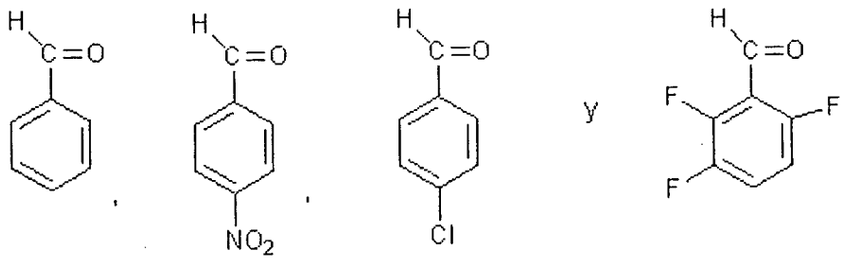
244. El proceso de la reivindicación 230 en donde la mezcla de (1)(a) y (1)(b) reacciona con (2)(a).

245. El proceso de la reivindicación 230 en donde la mezcla de (1)(a) y (1)(b) reacciona con (2)(b).

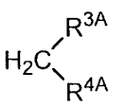
246. El proceso de la reivindicación 230 en donde el compuesto



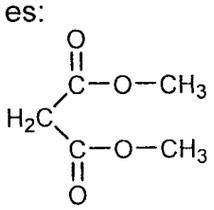
se selecciona del grupo que consiste en:



247. El proceso de la reivindicación 230 en donde el compuesto



es:



248. El proceso de la reivindicación 230 en donde la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{3A}CH_2R^{4A}$ es aproximadamente 1:0,8 a aproximadamente 1:1.2.

249. El proceso de la reivindicación 230 en donde la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{5A}S(O)_2R^{6A}$ es aproximadamente 1:1 a aproximadamente 1:4.

250. El proceso de la reivindicación 230 en donde la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{7A}C(O)R^{8A}$ es aproximadamente 1:1 a aproximadamente 1:4.

251. El proceso de la reivindicación 230 en donde la relación molar de $R^{5A}S(O)_2R^{6A}$ a la amina básica es aproximadamente 1:2 a aproximadamente 1:3.

252. El proceso de la reivindicación 230 en donde la relación molar de $R^{7A}C(O)R^{8A}$ a la amina básica es aproximadamente 1:2 a aproximadamente 1:3.

253. El proceso de la reivindicación 230 en donde la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{3A}CH_2R^{4A}$ es aproximadamente 1:1.

660

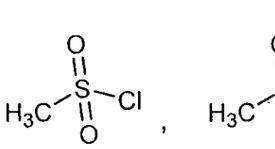
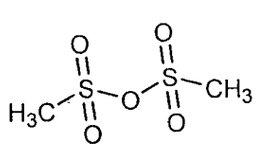
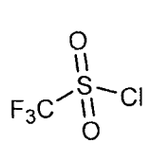
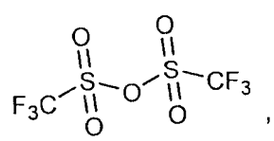
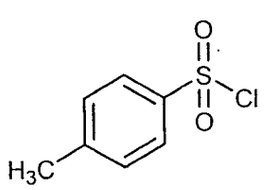
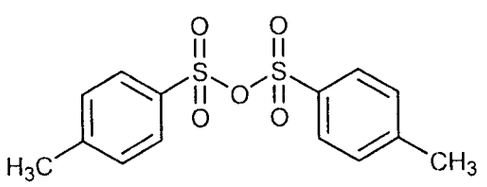
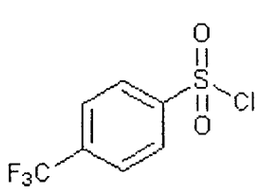
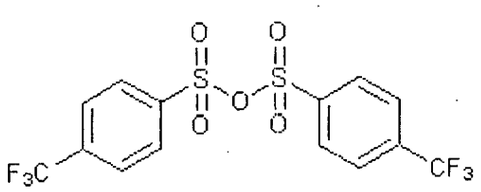
254. El proceso de la reivindicación 230 en donde la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{5A}S(O)_2R^{6A}$ es aproximadamente 1:1.

255. El proceso de la reivindicación 230 en donde la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{7A}C(O)R^{8A}$ es aproximadamente 1:1.

256. El proceso de la reivindicación 230 en donde la relación molar de $R^{5A}S(O)_2R^{6A}$ a la amina básica es aproximadamente 1:2.

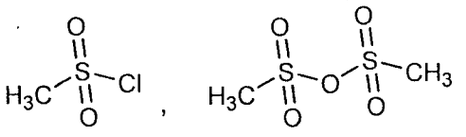
257. El proceso de la reivindicación 230 en donde la relación molar de $R^{7A}C(O)R^{8A}$ a la amina básica es aproximadamente 1:2.

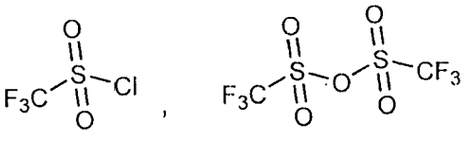
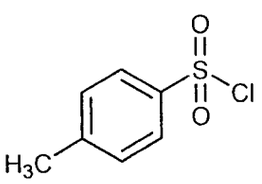
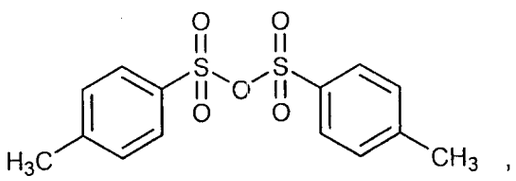
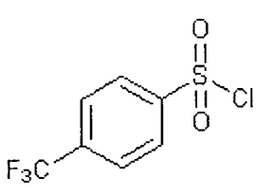
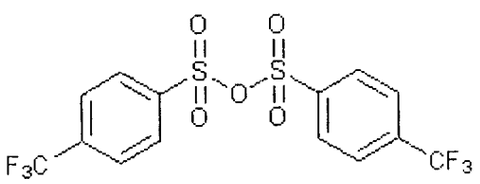
258. El proceso de la reivindicación 230 en donde la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 30°C, la amina básica es una trialquilamina, el solvente orgánico es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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y

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uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo y arilo sustituido, y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son los mismos restos – $C(O)OR^{12A}$, y R^{12A} es alquilo C_1 a C_4.

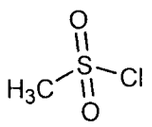
259. El proceso de la reivindicación 230 en donde la mezcla de (1)(a) y (1)(b) reacciona con (2)(a), la reacción se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C, la amina básica es una trialquilamina, el solvente orgánico es diclorometano anhidro, el resto $R^{5A}S(O)_2R^{6A}$ se selecciona del grupo que consiste en:


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y

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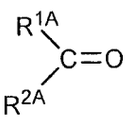
uno de R^{1A} y R^{2A} se selecciona del grupo que consiste en: arilo y arilo sustituido, y el otro de R^{1A} y R^{2A} es H, y R^{3A} y R^{4A} son el mismo resto – $C(O)OR^{12A}$, y R^{12A} es un alquilo C_1 a C_4.

260. El proceso de la reivindicación 230 en donde el resto $R^{5A}S(O)_2R^{6A}$ es

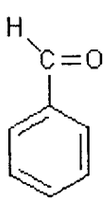
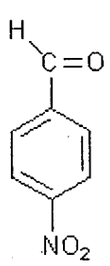
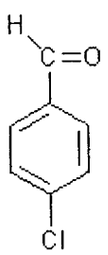
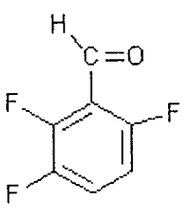


261. El proceso de la reivindicación 260 en donde la amina básica es trietilamina.

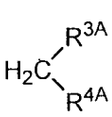
262. El proceso de la reivindicación 261 en donde el resto



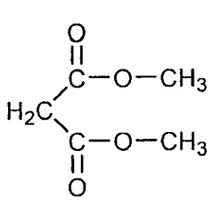
se selecciona del grupo que consiste en:




y

, y

el resto



es



263. El proceso de la reivindicación 262 en donde:

la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{3A}CH_2R^{4A}$ es aproximadamente 1:0.8 a aproximadamente 1:1,2,

la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{5A}S(O)_2R^{6A}$ es aproximadamente 1:1 a aproximadamente 1:4, y

la relación molar de $R^{5A}S(O)_2R^{6A}$ a la amina básica es aproximadamente 1:2 a aproximadamente 1:3,

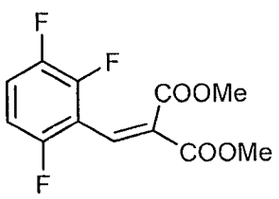
264. El proceso de la reivindicación 263 en donde:

la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{3A}CH_2R^{4A}$ es 1:1,

la relación molar de $R^{1A}C(O)R^{2A}$ a $R^{5A}S(O)_2R^{6A}$ es 1:1, y

la relación molar de $R^{5A}S(O)_2R^{6A}$ a la amina básica es aproximadamente 1:2.

265. Un proceso para preparación un compuesto de la fórmula:



dicho proceso que comprende la reacción:

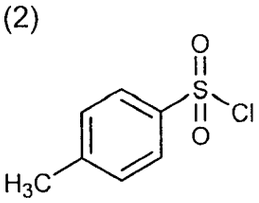
(1) una mezcla que comprende:

(a) 2,3,5–trifluorobenzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano anhidro; con

(2)



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C;

la relación molar de 2,3,5–trifluorobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0,8 a aproximadamente 1:1,2, y con preferencia 1:1;

la relación molar de 2,3,5–trifluorobenzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4, y con preferencia 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3, y con preferencia aproximadamente 1:2.

266. El proceso de la reivindicación 265 en donde:

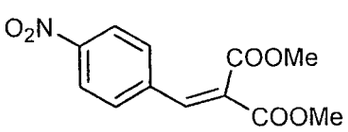
dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C;

la relación molar de 2,3,5–trifluorobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:1;

la relación molar de 2,3,5–trifluorobenzaldehído a cloruro de mesilo es aproximadamente 1 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2.

267. Un proceso para preparar un compuesto de la fórmula:



dicho proceso que comprende reaccionar:

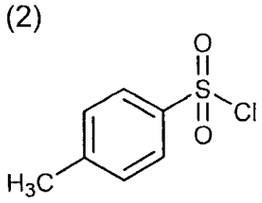
(1) una mezcla que comprende:

(a) 4–nitrobenzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano anhidro; con

(2)



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C;

la relación molar de 4–nitrobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0,8 a aproximadamente 1:1,2;

la relación molar de 4–nitrobenzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3.

268. El proceso de la reivindicación 267 en donde:

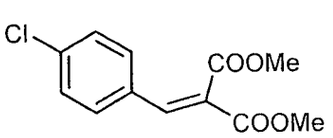
dichos proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C;

la relación molar de 4–nitrobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:1;

la relación molar de 4–nitrobenzaldehído a cloruro de mesilo es aproximadamente 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2.

269. Un proceso para preparación un compuesto de la fórmula:



dicho proceso que comprende hacer reaccionar:

(1) una mezcla que comprende:

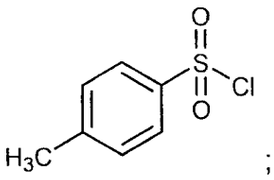
(a) 4–clorobenzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano (con preferencia anhidro); con

166

(2)



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C;

la relación molar de 4–clorobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0,8 a aproximadamente 1:1,2;

la relación molar de 4–clorobenzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3.

270. El proceso de la reivindicación 269 en donde:

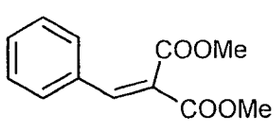
dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C;

la relación molar de 4–clorobenzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:1;

la relación molar de 4–clorobenzaldehído a cloruro de mesilo es aproximadamente 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2.

271. Un proceso para preparación un compuesto de la fórmula:



dicho proceso que comprende hacer reaccionar:

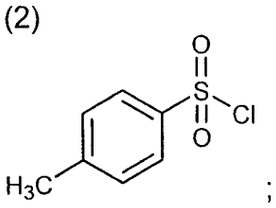
(1) una mezcla que comprende:

(a) benzaldehído, y

(b) $CH_2(C(O)OCH_3)_2$; y

(c) diclorometano (con preferencia anhidro); con

(2)



;

en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente –40°C a aproximadamente 40°C; la relación molar de benzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:0,8 a aproximadamente 1:1,2; la relación molar de benzaldehído a cloruro de mesilo es aproximadamente 1:1 a aproximadamente 1:4; y la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2 a aproximadamente 1:3.

272. El proceso de la reivindicación 271 en donde:

dicho proceso se lleva a cabo a una temperatura dentro del rango de aproximadamente 0°C a aproximadamente 10°C;

la relación molar de benzaldehído a $CH_2(C(O)OCH_3)_2$ es aproximadamente 1:1;

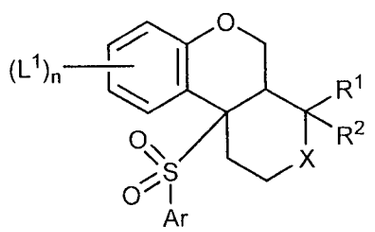
la relación molar de benzaldehído a cloruro de mesilo es aproximadamente 1:1; y

la relación molar de cloruro de mesilo a TEA es aproximadamente 1:2.

p. de: SCHERING CORPORATION

RESUMEN

Se describen nuevos inhibidores de gamma secretasa de la fórmula:



(I)

También se describen métodos de inhibir la gamma-secretasa, métodos de tratar enfermedades neurodegenerativas, y métodos de tratar enfermedad de Alzheimer. También se describen procesos para preparar alquenos en un paso de reacción usando una mezcla de un aldehído (o cetona) y un alquilo sustituido con dos grupos atrayentes de electrones y la reacción de la mezcla con: (a) un haluro de sulfonilo (por ej., un cloruro de sulfonilo) y una amina terciaria básica, o, (b) un anhídrido de sulfonilo y una amina básica, o (c) un aril–C(O)–haluro y una amina terciaria básica, o (d) un aril–C(O)–O–C(O)–arilo y una amina terciaria básica, o (e) un heteroaril–C(O)–haluro y una amina terciaria básica, o (f) un heteroaril–C(O)–O–C(O)–heteroarilo y una amina terciaria básica.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2009 (15.01.2009)

PCT

(10) International Publication Number
WO 2009/008980 A3

(51) International Patent Classification:
C07D 311/78 (2006.01) *A61K 31/35* (2006.01)
C07D 407/12 (2006.01) *A61K 31/352* (2006.01)
C07D 493/04 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/US2008/008192

(22) International Filing Date: 1 July 2008 (01.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/948,033 5 July 2007 (05.07.2007) US

(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **WU, Wen-lian** [US/US]; 5 Roney Road, Edison, New Jesrey 08820 (US). **BARA, Thomas, A.** [US/US]; 15 West Henry Street, Linden, New Jersey 07036 (US). **BURNETT, Duane, A.** [US/US]; 9 Chestnut Avenue, Bernardsville, New Jersey 07924 (US). **CLADER, John, W.** [US/US]; 428 North Union Avenue, Cranford, New Jersey 07016 (US). **DOMALSKI, Martin S.** [US/US]; 23 East Lincoln Street, Verona, New Jersey 07044 (US). **JIN, Yan** [CN/US]; 402 Berkshire Drive, Princeton, New Jersey 08540 (US). **JOSIEN, Hubert, B.** [US/US]; 293 Pavonia Avenue, Jersey City, New Jersey 07302 (US). **LI, Hongmei** [CN/US]; 16 Hemlock Circle, Warren, New Jersey 07059 (US). **LIANG, Xian** [US/US]; 31 Lexington Road, Monmouth Junction, New Jersey 08852 (US). **PISSARNITSKI, Dmitri, A.** [RU/US]; 22 Blue Ridge Circle, Scotch Plains, New Jersey 07076 (US). **SASIKUMAR, Thavalakulamgara, K.** [IN/US]; 21 Canterbury Lane, Edison, New Jersey 08820 (US). **WONG, Jesse, K.** [US/US]; 2 Hampshire Place, Monroe Township, New Jersey 08831 (US). **XU, Ruo** [US/US]; 66 Dogwood Lane, Watchung, New Jersey 07060 (US). **ZHAO, Zhiqiang** [CN/US]; 413 Henry Street, Scotch Plains, New Jersey 07076 (US). **MCNAMARA, Paul** [US/US]; 1261 Christine Circle, Scotch Plains, New Jersey 07076 (US).

(74) Agent: **JEANETTE, Henry, C.**; SCHERING CORPORATION, 2000 Galloping Hill Road, Patent Dept. K-6-1 1990, Kenilworth, NJ 07033 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, 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, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

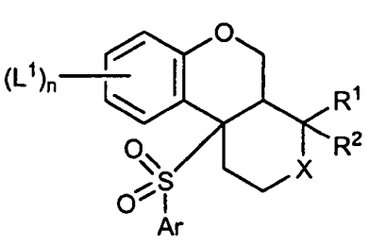
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
19 March 2009

(54) Title: TETRAHYDROPYRANOCHROMENE GAMMA SECRETASE INHIBITORS



(I)

(57) Abstract: Disclosed are novel gamma secretase inhibitors of the formula. Also disclosed are methods of inhibiting gamma-secretase, methods of treating neurodegenerative diseases, and methods of treating Alzheimer's Disease. Also disclosed are processes for preparing alkenes in one reaction step using a mixture of an aldehyde (or ketone) and an alkyl substituted with two electron withdrawing groups, and reacting the mixture with: (a) a sulfonyl halide (e.g., a sulfonyl chloride) and a basic tertiary amine, or, (b) a sulfonyl anhydride and a basic amine, or (c) an aryl-C(O)-halide and a basic tertiary amine, or (d) an aryl-C(O)-O-C(O)-aryl and a basic tertiary amine, or (e) an heteroaryl-C(O)-halide and a basic tertiary amine, or (f) a heteroaryl-C(O)-O-C(O)-heteroaryl and a basic tertiary amine.

WO 2009/008980 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/008192

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/78 C07D407/12 C07D493/04 A61K31/35 A61K31/352
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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, BEILSTEIN 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 2004/031137 A (MERCK SHARP & DOHME [GB]; CHURCHER IAN [GB]; HARRISON TIMOTHY [GB]; KE) 15 April 2004 (2004-04-15) page 1, line 29 - page 2, line 5	1-229
A	WO 03/014075 A (SCHERING CORP [US]) 20 February 2003 (2003-02-20) page 1, line 18 - line 23	1-229
A	WO 2004/101539 A (MERCK SHARP & DOHME [GB]; DINNELL KEVIN [GB]; HARRISON TIMOTHY [GB]; N) 25 November 2004 (2004-11-25) page 1, line 30 - page 2, line 5	1-229
P,A	WO 2007/143523 A (ELAN PHARM INC [US]; NEITZEL MARTIN L [US]; AUBELE DANNIELLE L [US]; H) 13 December 2007 (2007-12-13) page 1, second paragraph,claim 1	1-229

-/--

[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
17 October 2008	28/01/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/008192

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/084595 A (SCHERING CORP [US]; ASBEROM THEODROS [US]; BARA THOMAS [US]; BENNETT C) 26 July 2007 (2007-07-26) examples 337,338	1-229

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/008192

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

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

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-229

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-229

   The provision of compounds of formula I and their use as gamma secretase inhibitors

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2. claims: 230-264

   A process for preparing a compound as described in claim 230

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3. claims: 265, 266

   A process for preparing a compound as described in claim 265

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4. claims: claims 267, 268

   A process for preparing a compound as described in claim 267

---

5. claims: 269, 270

   A process for preparing a compound as described in claim 269

---

6. claims: 271, 272

   A process for preparing a compound as described in claim 271

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/008192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004031137 A	15-04-2004	AT 354562 T	15-03-2007
		AU 2003267614 A1	23-04-2004
		CA 2500964 A1	15-04-2004
		DE 60312016 T2	31-10-2007
		EP 1551797 A1	13-07-2005
		ES 2280774 T3	16-09-2007
		JP 2006501292 T	12-01-2006
		US 2004122050 A1	24-06-2004
WO 03014075 A	20-02-2003	BR 0211698 A	09-11-2004
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		EP 1492765 A2	05-01-2005
		JP 2005504760 T	17-02-2005
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		TW 242555 B	01-11-2005
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		BR PI0409969 A	25-04-2006
		CA 2525841 A1	25-11-2004
		EP 1638951 A1	29-03-2006
		EP 1644346 A1	12-04-2006
		WO 2004101538 A1	25-11-2004
		IS 8058 A	30-09-2005
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-149364- -00000-0000

Fecha: 2009-12-30 17:40:03 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 674

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que p· solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño Industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	9 149364
	Solicitud internacional	PCT/US2008/008192
	Fecha inicio fase nacional	05/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2599

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, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 26 FEB. 2010
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	9 149364
	Solicitud internacional	PCT/US2008/008192
	Fecha inicio fase nacional	05/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2690

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 26 FEB. 2010
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