SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-056873- -00000-0000

Fecha: 2012-04-04 15:16:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 254

Act 411 PRESENTACION ~~Folios: 255~~

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS DE DIÓXIDO DE IMINOTIADIAZINA COMO INHIBIDORES DE BACE, COMPOSICIONES, Y SU USO

SOLICITANTE: SCHERING CORPORATION

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 04 de Abril de 2012

P2012/000032

OLAR
OLARTE MOU

Industria y Comercio
SUPERINTENDENCIA

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PETITORIO - FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2012/000032**

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
Nacionalidad o Domicilio: Estados Unidos
Lugar de Constitución: Estado Unidos

Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03 Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747
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/US2010/051553 Fecha Octubre 6, 2010

Publicación Internacional No. WO 2011/044181 Fecha Abril 14, 2011

(6) **Título (54)** **COMPUESTOS DE DIÓXIDO DE IMINOTIADIAZINA COMO INHIBIDORES DE BACE, COMPOSICIONES, Y SU USO**

Clasificación Internacional (51) A61K 31/54

Prioridad

SI [X] **NO** [ ]

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US	Octubre 8, 2009	61/249.685

(9) **Comprobante de pago No.** 12-009883 **Fecha** Febrero 1, 2012

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. 09-014.463
- [x] Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la regla 4.17 (ii) del PCT.
- [x] 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

LISTA DE INVENTORES PCT/US2010/051553

SCOTT, Jack, D.
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: Estadounidense

STAMFORD, Andrew, W.
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: Australiana

GILBERT, Eric, J.
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: Estadounidense

CUMMING, Jared, N.
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: Estadounidense

ISERLOH, Ulrich
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: Estadounidense

MISIASZEK, Jeffrey, A.
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: Estadounidense

LI, Guoqing
2000 Galloping Hill Road,
Kenilworth, NJ 07033-0530
Estados Unidos de América
Nacionalidad: China

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 12 - 009883

Bogotá D.C., Febrero 01 de 2012 - 11:04:46

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	408377384	31/01/2012	2.360.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	590.000.00	590.000.00
				$590.000.00

SON: **QUINIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-********-

Recibo de Caja Aplicado al Expediente No. _____

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Act. 411 PRESENTACION Folios: 255

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



6

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

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
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

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):

BLIC (Signature):

Marguerite LaCorte

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

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application SCHERING CORPORATION is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from SCOTT, Jack, D. to SCHERING CORPORATION, dated 20 August 2010 (20.08.2010)
VIII-2-1(iv)		an assignment from STAMFORD, Andrew, W. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from GILBERT, Eric, J. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from CUMMING, Jared, N. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from ISERLOH, Ulrich to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from MISIASZEK, Jeffrey, A. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from LI, Guoqing to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application SCHERING CORPORATION is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from SCOTT, Jack, D. to SCHERING CORPORATION, dated 20 August 2010 (20.08.2010)
VIII-2-1(iv)		an assignment from STAMFORD, Andrew, W. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from GILBERT, Eric, J. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from CUMMING, Jared, N. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
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VIII-2-1(iv)		an assignment from MISIASZEK, Jeffrey, A. to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)
VIII-2-1(iv)		an assignment from LI, Guoqing to SCHERING CORPORATION, dated 08 September 2010 (08.09.2010)

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

(19) World Intellectual Property Organization
International Bureau

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PCT

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(22) International Filing Date:
6 October 2010 (06.10.2010)

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(26) Publication Language: English

(30) Priority Data:
61/249,685 8 October 2009 (08.10.2009) 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)*: **SCOTT, Jack, D.** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US). **STAMFORD, Andrew, W.** [AU/US]; 2000 Galloping Hill Road, Kenilworth, New Hampshire 07033 (US). **GILBERT, Eric, J.** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US). **CUMMING, Jared, N.** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US). **ISER-LOH, Ulrich** [DE/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US). **MISIASZEK, Jeffrey, A.** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US). **LI, Guoqing** [CN/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US).

(74) Agents: **Sylvia A. Ayler** et al.; Merck Co., Inc., 126 East Lincoln Avenue, MS:RY60-30, Rahway, NJ 07065 (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, CL, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

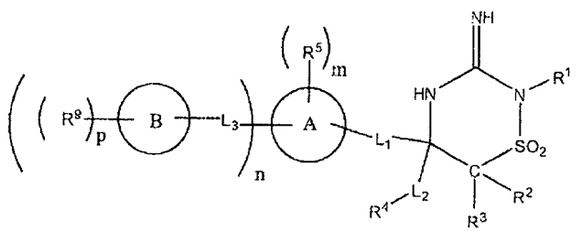
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

Published:

— *with international search report (Art. 21(3))*

(54) Title: IMINOTHIADIAZINE DIOXIDE COMPOUNDS AS BACE INHIBITORS, COMPOSITIONS, AND THEIR USE



(I)

(57) Abstract: In its many embodiments, the present invention provides certain iminothiadiazine dioxide compounds, including compounds Formula (I): (I) and include stereoisomers thereof, and pharmaceutically acceptable salts of said compounds stereoisomers, wherein each of R^1, R^2, R^3, R^4, R^5, R^9, ring A, ring B, m, n, p, -L_1-,L_2-, and L_3- is selected independently and as defined herein. The novel iminothiadiazine dioxide compounds of the invention have surprisingly been found to exhibit properties which are expected to render them advantageous as BACE inhibitors and/or for the treatment and prevention of various pathologies related to β-amyloid (Aβ) production. Pharmaceutical compositions comprising one or more such compounds (alone and in combination with one or more other active agents), and methods for their preparation and use in treating pathologies associated with amyloid beta (Aβ) protein, including Alzheimers disease, are also disclosed.

WO 2011/044181 A1

IMINOTHIADIAZINE DIOXIDE COMPOUNDS AS BACE INHIBITORS, COMPOSITIONS, AND THEIR USE

RELATED APPLICATIONS

This application claims priority to provisional application U.S. Serial No. 61/249,685, filed October 08, 2009, incorporated herein by reference.

FIELD OF THE INVENTION

This invention provides certain iminothiadiazine dioxide compounds and compositions comprising these compounds. The novel iminothiadiazine dioxide compounds of the invention have surprisingly been found to exhibit properties which are expected to render them advantageous as BACE inhibitors and/or for the treatment and prevention of various pathologies related to β-amyloid ("Aβ") production.

BACKGROUND

Amyloid beta peptide ("Aβ") is a primary component of β amyloid fibrils and plaques, which are regarded as having a role in an increasing number of pathologies. Examples of such pathologies include, but are not limited to, Alzheimer's disease, Down's syndrome, Parkinson's disease, memory loss (including memory loss associated with Alzheimer's disease and Parkinson's disease), attention deficit symptoms (including attention deficit symptoms associated with Alzheimer's disease ("AD"), Parkinson's disease, and Down's syndrome), dementia (including pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and Down's syndrome), progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment (including olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and Down's syndrome), β-amyloid angiopathy (including cerebral amyloid angiopathy), hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes, hemodialysis (β2 microglobulins and complications arising therefrom), neurodegenerative diseases such as scrapie, bovine spongiform encephalitis, Creutzfeld-Jakob disease, traumatic brain injury and the like.

Aβ peptides are short peptides which are made from the proteolytic break-down of the transmembrane protein called amyloid precursor protein ("APP"). Aβ peptides are made from the cleavage of APP by β-secretase activity near the position near the N-terminus of Aβ, and by gamma-secretase activity at a position near the C-terminus of Aβ. (APP is also cleaved by α-secretase activity, resulting in the secreted, non-amyloidogenic fragment known as soluble APPα.) Beta site APP Cleaving Enzyme ("BACE-1") is regarded as the primary aspartyl protease responsible for the production of Aβ by β-secretase activity. The inhibition of BACE-1 has been shown to inhibit the production of Aβ.

AD is estimated to afflict more than 20 million people worldwide and is believed to be the most common cause of dementia. AD is a disease characterized by degeneration and loss of neurons and also by the formation of senile plaques and neurofibrillary tangles. Presently, treatment of Alzheimer's disease is limited to the treatment of its symptoms rather than the underlying causes. Symptom-improving agents approved for this purpose include, for example, N-methyl-D-aspartate receptor antagonists such as memantine (Namenda®, Forrest Pharmaceuticals, Inc.), cholinesterase inhibitors such as donepezil (Aricept®, Pfizer), rivastigmine (Exelon®, Novartis), galantamine (Razadyne Reminyl®), and tacrine (Cognex®).

In AD, Aβ peptides, formed through β-secretase and *gamma*-secretase activity, can form tertiary structures that aggregate to form amyloid fibrils. Aβ peptides have also been shown to form Aβ oligomers (sometimes referred to as "Aβ aggregates" or "Abeta oligomers"). Aβ oligomers are small multimeric structures composed of 2 to 12 Aβ peptides that are structurally distinct from Aβ fibrils. Amyloid fibrils can deposit outside neurons in dense formations known as senile plaques, neuritic plaques, or diffuse plaques in regions of the brain important to memory and cognition. Aβ oligomers are cytotoxic when injected in the brains of rats or in cell culture. This Aβ plaque formation and deposition and/or Aβ oligomer formation, and the resultant neuronal death and cognitive impairment, are among the hallmarks of AD pathophysiology. Other hallmarks of AD pathophysiology include intracellular neurofibrillary tangles comprised of abnormally phosphorylated tau protein, and neuroinflammation.

Evidence suggests that Aβ, Aβ fibrils, aggregates, oligomers, and/or plaque play a causal role in AD pathophysiology. (Ohno et al., Neurobiology of Disease, No. 26 (2007), 134-145). Mutations in the genes for APP and presenilins 1/2 (PS1/2) are known to cause familial AD and an increase in the production of the 42-amino acid form of Aβ is regarded as causative. Aβ has been shown to be neurotoxic in culture and in vivo. For example, when injected into the brains

of aged primates, fibrillar Aβ causes neuronal cell death around the injection site. Other direct and circumstantial evidence of the role of Aβ in Alzheimer etiology has also been published.

BACE-1 has become an accepted therapeutic target for the treatment of Alzheimer's disease. For example, McConlogue et al., J. Bio. Chem., Vol. 282, No. 36 (Sept. 2007), have shown that partial reductions of BACE-1 enzyme activity and concomitant reductions of Aβ levels lead to a dramatic inhibition of Aβ-driven AD-like pathology, making β-secretase a target for therapeutic intervention in AD. Ohno et al. Neurobiology of Disease, No. 26 (2007), 134-145, report that genetic deletion of BACE-1 in 5XFAD mice abrogates Aβ generation, blocks amyloid deposition, prevents neuron loss found in the cerebral cortex and subiculum (brain regions manifesting the most severe amyloidosis in 5XFAD mice), and rescues memory deficits in 5XFAD mice. The group also reports that Aβ is ultimately responsible for neuron death in AD and concludes that BACE-1 inhibition has been validated as an approach for the treatment of AD. Roberds et al., Human Mol. Genetics, 2001, Vol. 10, No. 12, 1317-1324, established that inhibition or loss of β-secretase activity produces no profound phenotypic defects while inducing a concomitant reduction in Aβ. Luo et al., Nature Neuroscience, Vol. 4, No. 3, March 2001, report that mice deficient in BACE-1 have normal phenotype and abolished β-amyloid generation.

BACE-1 has also been identified or implicated as a therapeutic target for a number of other diverse pathologies in which Aβ or Aβ fragments have been identified to play a causative role. One such example is in the treatment of AD-type symptoms of patients with Down's syndrome. The gene encoding APP is found on chromosome 21, which is also the chromosome found as an extra copy in Down's syndrome. Down's syndrome patients tend to acquire AD at an early age, with almost all those over 40 years of age showing Alzheimer's-type pathology. This is thought to be due to the extra copy of the APP gene found in these patients, which leads to overexpression of APP and therefore to increased levels of Aβ causing the prevalence of AD seen in this population. Furthermore, Down's patients who have a duplication of a small region of chromosome 21 that does not include the APP gene do not develop AD pathology. Thus, it is thought that inhibitors of BACE-1 could be useful in reducing Alzheimer's type pathology in Down's syndrome patients.

Another example is in the treatment of glaucoma (Guo et al., PNAS, Vol. 104, No. 33, August 14, 2007). Glaucoma is a retinal disease of the eye and a major cause of irreversible blindness worldwide. Guo et al. report that Aβ colocalizes with apoptotic retinal ganglion cells

(RGCs) in experimental glaucoma and induces significant RGC cell loss in vivo in a dose- and time-dependent manner. The group report having demonstrated that targeting different components of the Aβ formation and aggregation pathway, including inhibition of β-secretase alone and together with other approaches, can effectively reduce glaucomatous RGC apoptosis in vivo. Thus, the reduction of Aβ production by the inhibition of BACE-1 could be useful, alone or in combination with other approaches, for the treatment of glaucoma.

Another example is in the treatment of olfactory impairment. Getchell et al., Neurobiology of Aging, 24 (2003), 663-673, have observed that the olfactory epithelium, a neuroepithelium that lines the posterior-dorsal region of the nasal cavity, exhibits many of the same pathological changes found in the brains of AD patients, including deposits of Aβ, the presence of hyperphosphorylated tau protein, and dystrophic neurites among others. Other evidence in this connection has been reported by Bacon AW, et al., Ann NY Acad Sci 2002; 855:723–31; Crino PB, Martin JA, Hill WD, et al., Ann Otol Rhinol Laryngol, 1995;104:655–61; Davies DC, et al., Neurobiol Aging, 1993;14:353-7; Devanand DP, et al., Am J Psychiatr, 2000;157:1399-405; and Doty RL, et al., Brain Res Bull, 1987;18:597–600. It is reasonable to suggest that addressing such changes by reduction of Aβ by inhibition of BACE-1 could help to restore olfactory sensitivity in patients with AD.

For compounds which are inhibitors of BACE-2, another example is in the treatment of type-II diabetes, including diabetes associated with amyloidogenesis. BACE-2 is expressed in the pancreas. BACE-2 immunoreactivity has been reported in secretory granules of beta cells, co-stored with insulin and IAPP, but lacking in the other endocrine and exocrine cell types. Stoffel et al., WO2010/063718, disclose the use of BACE-2 inhibitors in the treatment of metabolic diseases such as Type-II diabetes. The presence of BACE-2 in secretory granules of beta cells suggests that it may play a role in diabetes-associated amyloidogenesis. (Finzi, G. Franzi, et al., Ultrastruct Pathol. 2008 Nov-Dec;32(6):246-51.)

Other diverse pathologies characterized by the formation and deposition of Aβ or fragments thereof, and/or by the presence of amyloid fibrils, oligomers, and/or plaques, include neurodegenerative diseases such as scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI"), Creutzfeld-Jakob disease and the like, type II diabetes (which is characterized by the localized accumulation of cytotoxic amyloid fibrils in the insulin producing cells of the pancreas), and amyloid angiopathy. In this regard reference can be made to the patent literature. For example, Kong et al., US2008/0015180, disclose methods and compositions for treating

amyloidosis with agents that inhibit Aβ peptide formation. As another example, Loane, et al. report the targeting of amyloid precursor protein secretases as therapeutic targets for traumatic brain injury. (Loane et al., "Amyloid precursor protein secretases as therapeutic targets for traumatic brain injury", Nature Medicine, Advance Online Publication, published online March 15, 2009.) Still other diverse pathologies characterized by the inappropriate formation and deposition of Aβ or fragments thereof, and/or by the presence of amyloid fibrils, and/or for which inhibitor(s) of BACE-1 is expected to be of therapeutic value are discussed further hereinbelow.

The therapeutic potential of inhibiting the deposition of Aβ has motivated many groups to characterize BACE-1 and to identify inhibitors of BACE-1 and of other secretase enzyme inhibitors. Examples from the patent literature are growing and include WO2006009653, WO2007005404, WO2007005366, WO2007038271, WO2007016012, US2005/0282826, US2007072925, WO2007149033, WO2007145568, WO2007145569, WO2007145570,WO2007145571, WO2007114771, US20070299087, WO2005/016876, WO2005/014540, WO2005/058311, WO2006/065277, WO2006/014762, WO2006/014944, WO2006/138195, WO2006/138264, WO2006/138192, WO2006/138217, WO2007/050721, WO2007/053506, WO2007/146225, WO2006/138230, WO2006/138265, WO2006/138266, WO2007/053506, WO2007/146225, WO2008/073365, WO2008/073370, WO2008/103351, US2009/041201, US2009/041202, and WO2010/047372.

SUMMARY OF THE INVENTION

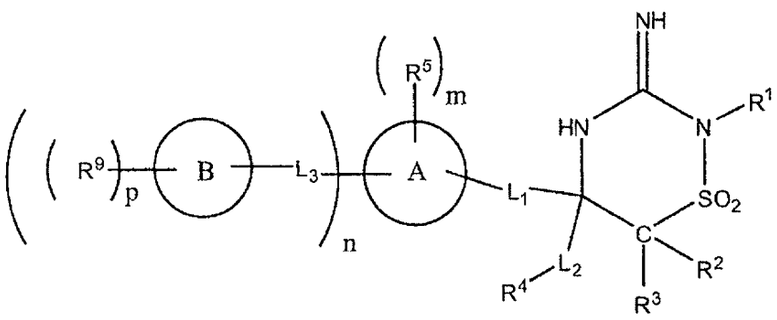
The present invention provides certain iminothiadiazine dioxide compounds which are collectively or individually referred to herein as "compound(s) of the invention", as described herein. The novel iminothiadiazine dioxide compounds of the invention have surprisingly been found to exhibit properties which are expected to render them advantageous as BACE inhibitors and/or for the treatment and prevention of the various pathologies described herein.

In each of the various embodiments of the compounds of the invention described herein, each variable including those of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), and the various embodiments thereof, each variable is selected independently of the others unless otherwise indicated.

In each of the various embodiments of the compounds of the invention described herein, including those of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), and the various embodiments thereof and the compounds of the examples, such formulas and examples

are intended to encompass all forms of the compounds such as, for example, any solvates, hydrates, stereoisomers, and tautomers of said compounds and of any pharmaceutically acceptable salts thereof.

In one embodiment, the compounds of the invention have the structural Formula (I):



(I)

and include tautomers, solvates, prodrugs, and esters thereof, and pharmaceutically acceptable salts of said compounds, tautomers, solvates, prodrugs, and esters,

wherein:

-L_1- represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, and -alkynyl-;

-L_2- represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, and -alkynyl-;

each -L_3- independently represents a bond or a divalent moiety independently selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, -alkynyl-, -$N(R^7)$-, –NHC(O)-, -C(O)NH-, -$NHS(O)_2$-, -$S(O)_2NH$-, -O-alkyl-, -alkyl-O-, -$N(R^7)$-alkyl-, -alkyl-$N(R^7)$-, -haloalkyl-NH-, and –NH-haloalkyl-;

m, n, and p are each independently selected integers, wherein:

m is 0 or more;

n is 0 or more; and

p is 0 or more,

wherein the maximum value of the sum of m and n is the maximum number of available substitutable hydrogen atoms on ring A, and wherein the maximum value of p is the maximum number of available substitutable hydrogen atoms on ring B;

R^1 is selected from the group consisting of: H, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein each of said alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl- of R^1 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^2 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^3 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^4 is selected from the group consisting of alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl,

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl of R^4 is unsubstituted or substituted with one or more independently selected R^{10} groups;

ring A is selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each ring B (when present) is independently selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each R^5 (when present) is independently selected from the group consisting of halo, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^5 (when present) is optionally independently unsubstituted or further substituted with one or more independently selected groups

selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, halo, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-N(R^8)_2$, $-OR^7$, $-C(O)N(R^8)_2$, and cycloalkyl;

each R^6 (when present) is independently selected from the group consisting of alkyl, aryl, arylalkyl-, haloalkyl, cycloalkyl, cycloalkylalkyl-, heteroaryl, and heteroarylalkyl-;

each R^7 (when present) is independently selected from the group consisting of H, alkyl, alkenyl, heteroalkyl, haloalkyl, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, and heterocycloalkylalkyl-;

each R^8 (when present) is independently selected from the group consisting of H, alkyl, alkenyl, heteroalkyl, haloalkyl, haloalkenyl, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, and heterocycloalkylalkyl-;

each R^9 (when present) is independently selected from the group consisting of: halogen, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl;

each R^{10} (when present) is independently selected from the group consisting of halo, -CN, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl,

wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl of R^{10} (when present) is optionally independently unsubstituted or further substituted with one or more independently selected groups selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, halo, -CN, $-NO_2$, $-N(R^8)_2$, $-OR^7$, and $-C(O)N(R^8)_2$.

In other embodiments, the invention provides compositions, including pharmaceutical compositions, comprising one or more compounds of the invention (e.g., one compound of the invention), or a tautomer thereof, or a pharmaceutically acceptable salt or solvate of said compound(s) and/or said tautomer(s), optionally together with one or more additional therapeutic agents, optionally in an acceptable (e.g., pharmaceutically acceptable) carrier or diluent.

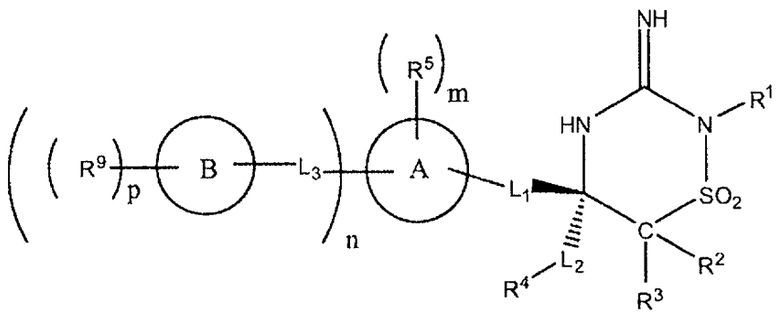
In other embodiments, the invention provides various methods of treating, preventing, ameliorating, and/or delaying the onset of an amyloid β pathology (Aβ pathology) and/or a symptom or symptoms thereof, comprising administering a composition comprising an effective amount of one or more compounds of the invention, or a tautomer thereof, or pharmaceutically acceptable salt or solvate of said compound(s) and/or said tautomer(s), to a patient in need thereof. Such methods optionally additionally comprise administering an effective amount of one or more additional therapeutic agents suitable for treating the patient being treated.

These and other embodiments of the invention, which are described in detail below or will become readily apparent to those of ordinary skill in the art, are included within the scope of the invention.

DETAILED DESCRIPTION:

In one embodiment, the compounds of the invention have the structural Formula (I) as described above.

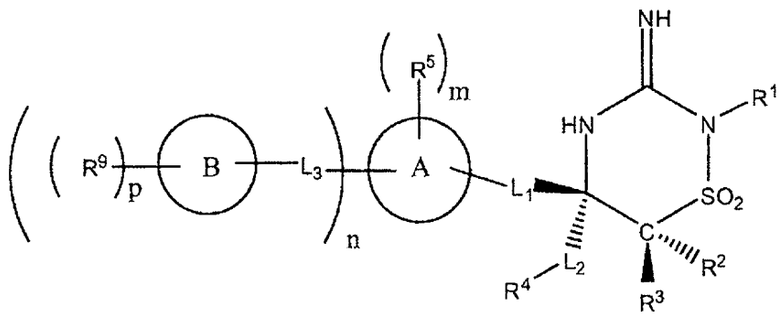
In one embodiment, the compounds of the invention have the structural Formula (IA):



(IA)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, ring A, ring B, m, n, and p are each as defined in Formula (I).

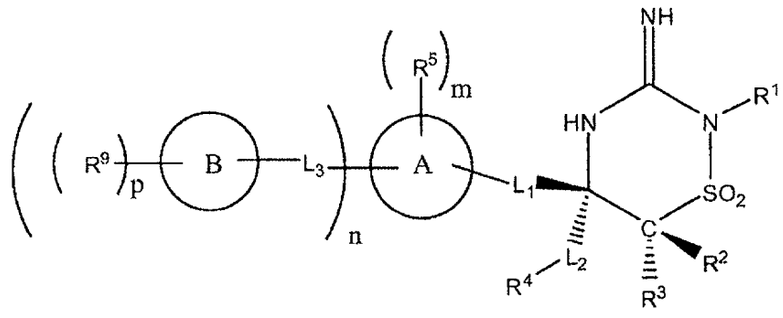
In one embodiment, the compounds of the invention have the structural Formula (IA-1):



(IA-1)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, ring A, ring B, m, n, and p are each as defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (IA-2):



(IA-2)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, ring A, ring B, m, n, and p are each as defined in Formula (I).

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is selected from the group consisting of H, lower alkyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is selected from the group consisting of H and methyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is methyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2):

R^1 is selected from the group consisting of H, lower alkyl, and cyclopropyl; and

R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is H and R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, lower alkyl, halo lower alkyl, and lower alkyl ether.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl; and R^2 is H.

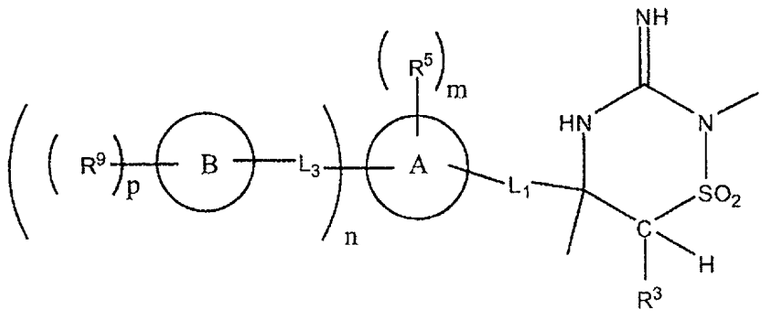
In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, lower alkyl, halo lower alkyl, and lower alkyl ether; and R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), $-L_2-$ is a bond and R^4 is lower alkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), $-L_2-$ is a bond and R^4 is methyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is lower alkyl, R^2 is H, $-L_2-$ is a bond, and R^4 is alkyl.

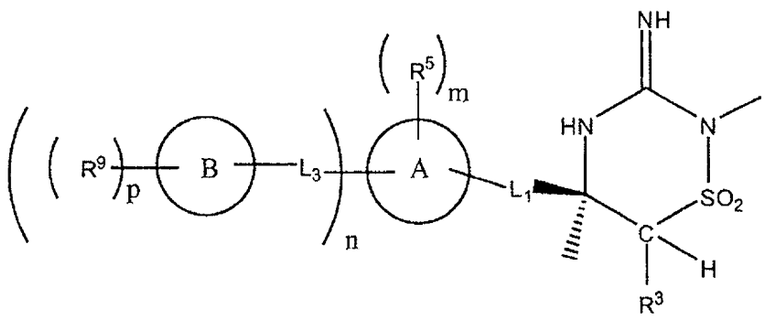
In one embodiment, the compounds of the invention have the structural Formula (II):



(II)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^3, L_1, L_2, ring A, ring B, R^5, R^9, m, n, and p are each as defined in Formula (I).

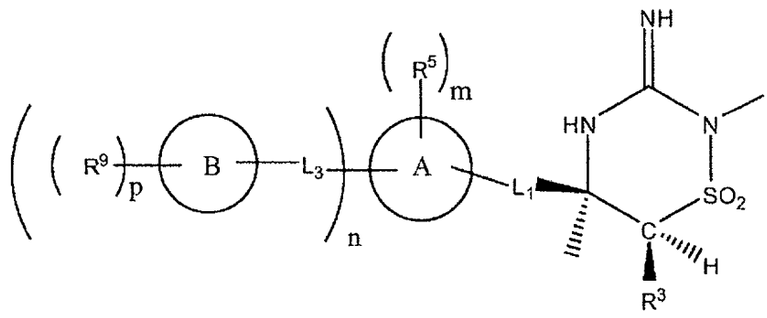
In one embodiment, the compounds of the invention have the structural Formula (IIA):



(IIA)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^3, L_1, L_3, ring A, ring B, R^5, R^9, m, n, and p are each as defined in Formula (I).

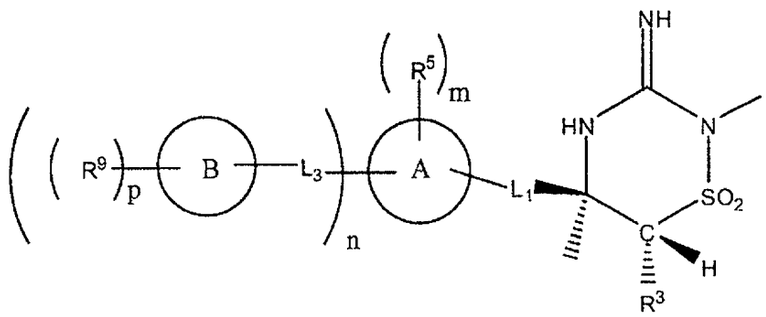
In one embodiment, the compounds of the invention have the structural Formula (IIA-1):



(IIA-1)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^3, L_1, L_3, ring A, ring B, R^5, R^9, m, n, and p are each as defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (IIA-2):



(IIA-2)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^3, L_1, L_3, ring A, ring B, R^5, R^9, m, n, and p are each as defined in Formula (I).

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2), R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (IIA-2), R^3 is selected from the group consisting H, lower alkyl, halo lower alkyl, and lower alkyl ether.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2), R^3 is H.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, and -alkenyl-.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, and -alkenyl-.

$-L_1-$ represents a divalent moiety selected from the group consisting of -alkyl-, and -haloalkyl-.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a bond or a divalent lower alkyl moiety.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a bond, $-CH_2-$, or $-CH_2CH_2-$.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a bond.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a divalent lower alkyl moiety.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents $-CH_2-$.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents $-CH_2CH_2-$.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 0 and m is 1 or more.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1 or more, p is 0 or more, and m is 0.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0 or more.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0, 1, 2, or 3.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0, 1, or 2.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0 or 1.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 1.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 2.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 3.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2): $-L_1-$ represents a bond or $-CH_2-$.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, quinazolinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, naphthyl, quinolyl, isoquinolyl, indazolyl, indolyl, and thienopyrazolyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

ring A is selected from the group consisting of phenyl, pyridyl, thienyl, thiazolyl, naphthyl, isoquinolinyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

each $-L_3-$ independently represents a bond or a divalent moiety selected from the group consisting of –NHC(O), –C(O)NH-, $-NHS(O)_2-$, $-S(O)_2NH-$, $-O-CH_2-$, $-CH_2-O-$, $-NHCH_2-$, $-CH_2NH-$, and $-CH(CF_3)NH-$.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

each $-L_3-$ independently represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and $-L_3-$ is represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and $-L_3-$ represents a bond.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and $-L_3-$ is a divalent moiety selected from the group consisting of -NHC(O)- and -C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and $-L_3-$ is –C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and $-L_3-$ is –NHC(O)-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 or more;

p is 0 or more; and

each ring B is independently selected from the group consisting of phenyl, pyridyl, pyrimidinyl, oxazolyl, isoxazolyl, pyrazinyl, thienyl, pyrazolyl, furanyl, thiazolyl, pyridazinyl, isothiazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridinyl, and pyrrolopyrimidinyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 or more;

p is 0 or more; and

each ring B is independently selected from the group consisting of phenyl, pyridyl, pyrimidinyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridyl, and pyrrolopyrimidinyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 1 or more and each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-OSF_5$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 1 or more and each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 1 or more and each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 0 or more, n is 1 or more, p is 1 or more, and each R^9 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-OSF_5$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl.

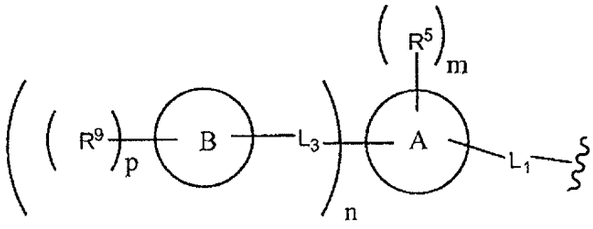
In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 0 or more, n is 1 or more, p is 1 or more, and each R^9 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cycloalkyl.

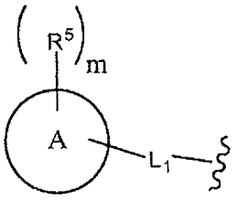
In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 0 or more, n is 1 or more, p is 1 or more, and each R^9 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 0 and the moiety:



, has the form



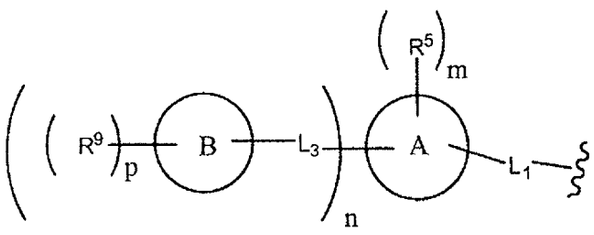
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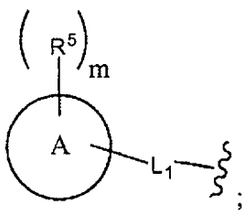
In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 0;

m is 1 or more;

the moiety:



, has the form 

;

$-L_1-$ represents a bond, $-CH_2-$, or $-CH_2CH_2-$;

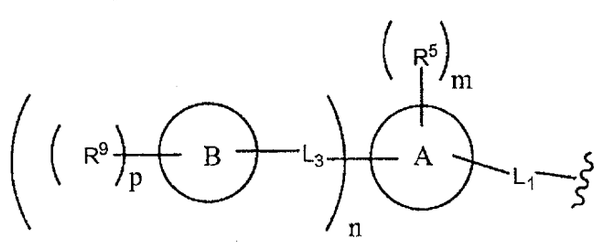
ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl; and

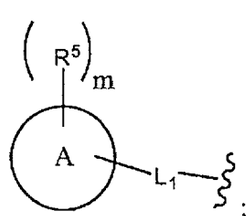
each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 0;

the moiety:



, has the form 

;

$-L_1-$ represents a bond, $-CH_2-$, or $-CH_2CH_2-$;

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl;

m is 0 or more; and

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl;

m is 0 or more;

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl;

n is 1;

$-L_3-$ represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-;

ring B is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridyl, and pyrrolopyrimidinyl;

p is 0 or more; and

each R^9 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

$-L_1-$ represents a bond;

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, quinazolinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, naphthyl, quinolyl, isoquinolyl, indazolyl, indolyl, and thienopyrazolyl.

m is 0 or more;

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cyclopropyl;

n is 1;

$-L_3-$ represents a bond or a divalent moiety selected from the group consisting of -NHC(O), -C(O)NH-, $-NHS(O)_2-$, $-S(O)_2NH-$, $-O-CH_2-$, $-CH_2-O-$, $-NHCH_2-$, $-CH_2NH-$, and $-CH(CF_3)NH-$;

ring B is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, oxazolyl, isoxazolyl, pyrazinyl, thienyl, pyrazolyl, furanyl, thiazolyl, pyridazinyl, isothiazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridinyl, and pyrrolopyrimidinyl;

p is 0 or more; and

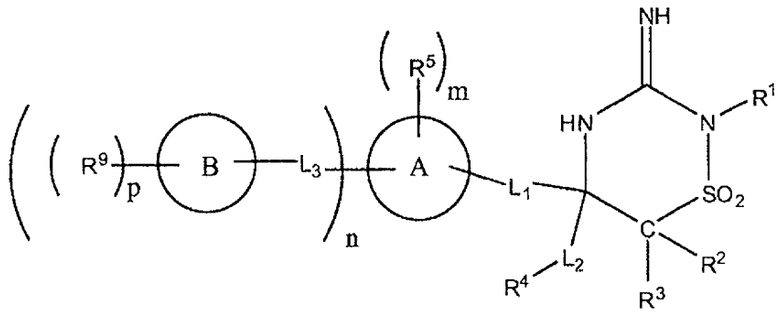
each R^9 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-OSF_5$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl. In one such embodiment, m and p are each independently 0, 1, 2, or 3 up to the maximum number of substitutable hydrogen atoms.

In one such embodiment, each R^5 (when present) is independently selected from the group consisting of halo.

In one such embodiment, each R^9 (when present) is independently selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, halo-substituted heteroalkyl, halo, -O-alkyl, -O-alkyl-OH, -O-deuteroalkyl, -O-heteroalkyl, -O-heteroalkyl-aryl, -O-haloalkyl, heteroaryl, alkyl-substituted heteroaryl, cycloalkyl, -O-alkyl-cycloalkyl, -O-cycloalkyl, OH, heterocycloalkyl, halo-substituted heteroaryl, CN, $-S(F)_5$, -S-alkyl, and $-S(O)_2$alkyl.

In another embodiment, the present invention encompasses deuterates of the compounds of the invention, or tautomers thereof, or a pharmaceutically acceptable salt of said deuterated compound or tautomer of the invention. Specific, non-limiting examples of deuterated compounds of the invention are as described and exemplified herein and include, deuterated compounds of Formulas (I^d), (II^d), and (III^d). Those of ordinary skill in the art will readily appreciate that, in addition to the non-limiting examples shown, other available hydrogen atoms may be deuterated in a similar manner as described hereinbelow. Such deuterated compounds are also to be considered as being among the compounds of the invention. The resulting compound is refered to herein as a "deuterated" compound of the invention or, alternatively, as "deuterate(s)" of compounds of the invention. The compounds of the invention may be deuterated in a manner known to those of ordinary skill in the art, e.g., as described herein.

Thus, in one non-limiting embodiment, deuterated compounds of the invention have the structural Formula (I^d):



(I^d)

wherein:

one or more hydrogen atoms present in R^1, R^2, R^3, R^4, R^5 (when present) and/or R^9 (when present), or one or more of any available hydrogen atom(s) present on ring A or ring B (when present) is replaced by deuterium; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of Formulas (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2) and the various embodiments thereof, are also within the scope of the compounds of Formula (I^d).

For example, in one non-limiting embodiment, in Formula (I^d), R^1 is $-CD_3$ and each of R^2, R^3, R^4, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^2 is D and each of R^1, R^3, R^4, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^3 is D and each of R^1, R^2, R^4, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

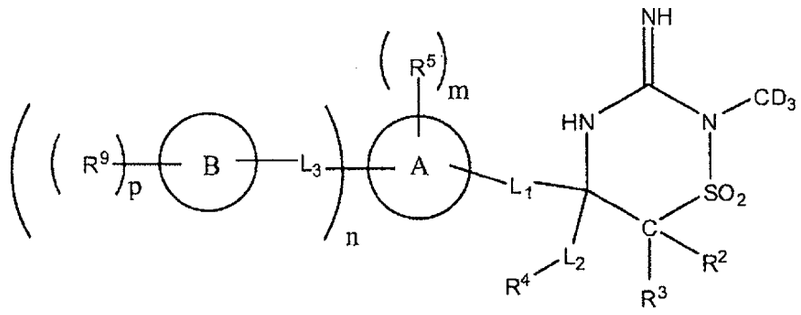
As another example, in another non-limiting embodiment, in Formula (I^d), R^4 is partially or fully deuterated lower alkyl and each of R^1, R^2, R^3, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m,

n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^5 is D and each of R^1, R^2, R^3, R^4, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^9 is D and each of R^1, R^2, R^3, R^4, R^5, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

By way of further illustration, in another non-limiting embodiment, deuterated compounds of the invention have the structural Formula (II^d):



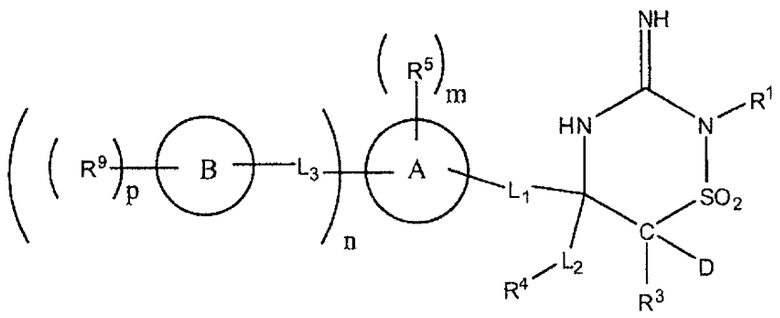
(II^d)

wherein:

the moiety $-CD_3$ represents a deuterated form of the moiety $-CH_3$; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of formulas (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), and (II-A2), and the various embodiments thereof, are also within the scope of the compounds of Formula (II^d).

By way of further illustration, in another non-limiting embodiment, deuterated compounds of the invention have the structural Formula (III^d):



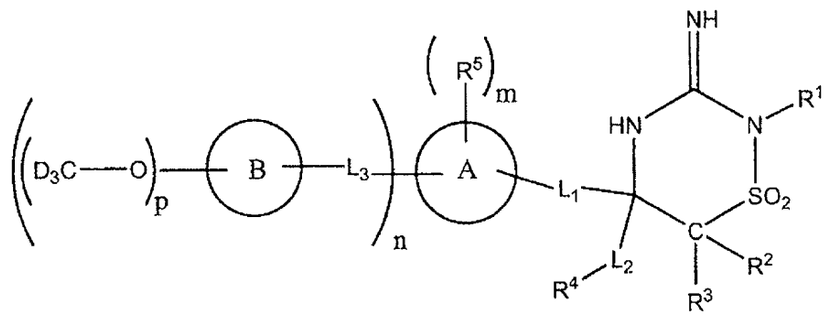
(III^d)

wherein:

the moiety –D represents a deuterated form of hydrogen; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of formulas (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), and (II-A2), and the various embodiments thereof, are also within the scope of the compounds of Formula (III^d). In one embodiment, in Formula (III^d), R^3 is D.

By way of further illustration, in another non-limiting embodiment, deuterated compounds of the invention have the structural Formula (IV^d):



(IV^d)

wherein:

the moiety –D represents a deuterated form of hydrogen; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of formulas (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), and (II-A2), and the various embodiments thereof, are also within the scope of the compounds of Formula (IV^d).

In another embodiment, the present invention encompasses a stereoisomer or racemic mixture of a compound of the invention, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer. It shall be appreciated that, while the present invention encompasses all stereoisomers and racemic mixtures of the compounds of the invention, the stereoconfiguration shown in the structural formulas and in the examples are also contemplated as being within the scope of the invention.

In another embodiment, 1 to 3 carbon atoms of the compounds of the invention may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

In another embodiment, the compounds of the invention are each of the compounds of the tables below and have a structure shown for the corresponding example in the preparative examples below.

The present invention includes tautomers and stereoisomers of each of the example compounds of the invention, and pharmaceutically acceptable salts and solvates of said compounds, said stereoisomers, and/or said tautomers. Such tautomers and stereosiomers of each of the example compounds, and pharmaceutically and solvates of said compounds, said stereoisomers, and/or said tautomers, each represent additional embodiments of the invention.

In another embodiment, the invention provides a composition comprising at least one compound of the invention, or a tautomer or stereoisomer thereof, or salt or solvate of said compound, said stereoisomer, or said tautomer, and a suitable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one solvate of a compound of the invention, or a tautomer or isomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one pharmaceutically acceptable salt of a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one tautomer of a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, together with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or diluent.

Non-limiting examples of additional therapeutic agents for use in combination with the compounds of the invention include drugs selected from the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease and/or drugs useful for treating one or more symptoms of Alzheimer's disease, (b) drugs useful for inhibiting the synthesis Aβ, and (c) drugs useful for treating neurodegenerative diseases.

Additional non-limiting examples of additional therapeutic agents for use in combination with the compounds of the invention include drugs useful for the treatment, prevention, delay of onset, amelioration of any pathology associated with Aβ and/or a symptom thereof. Non-limiting examples of pathologies associated with Aβ include: Alzheimer's disease, Down's syndrome, Parkinson's disease, memory loss, memory loss associated with Alzheimer's disease, memory loss associated with Parkinson's disease, attention deficit symptoms, attention deficit symptoms associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, dementia, stroke, microgliosis and brain inflammation, pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment, olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes, hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI"), and Creutzfeld-Jakob disease, comprising administering to said patient at least one compound of the invention, or a tautomer or isomer thereof, or pharmaceutically acceptable

salt or solvate of said compound or said tautomer, in an amount effective to inhibit said pathology or pathologies.

In embodiments of the invention comprising at least one additional therapeutic agent, additional non-limiting examples of additional therapeutic agents for use in combination with compounds of the invention include: muscarinic antagonists (e.g., m_1 agonists (such as acetylcholine, oxotremorine, carbachol, or McNa343), or m_2 antagonists (such as atropine, dicycloverine, tolterodine, oxybutynin, ipratropium, methoctramine, tripitamine, or gallamine)); cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors such as donepezil (Aricept®), galantamine (Razadyne®), and rivastigimine (Exelon®); N-methyl-D-aspartate receptor antagonists (e.g., Namenda® (memantine HCl, available from Forrest Pharmaceuticals, Inc.); combinations of cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists; gamma secretase modulators; gamma secretase inhibitors; non-steroidal anti-inflammatory agents; anti-inflammatory agents that can reduce neuroinflammation; anti-amyloid antibodies (such as bapineuzemab, Wyeth/Elan); vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; antibiotics; 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; Tau kinase inhibitors (e.g., GSK3beta inhibitors, cdk5 inhibitors, or ERK inhibitors); Tau aggregation inhibitors (e.g., Rember®); RAGE inhibitors (e.g., TTP 488 (PF-4494700)); anti-Abeta vaccine; APP ligands; agents that upregulate insulin, cholesterol lowering agents such as HMG-CoA reductase inhibitors (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin) and/or cholesterol absorption inhibitors (such as Ezetimibe), or combinations of HMG-CoA reductase inhibitors and cholesterol absorption inhibitors (such as, for example, Vytorin®); fibrates (such as, for example, clofibrate, Clofibride, Etofibrate, and Aluminium Clofibrate); combinations of fibrates and cholesterol lowering agents and/or cholesterol absorption inhibitors; nicotinic receptor agonists; niacin; combinations of niacin and cholesterol absorption inhibitors and/or cholesterol lowering agents (e.g., Simcor® (niacin/simvastatin, available from Abbott Laboratories, Inc.); LXR agonists; LRP mimics; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; 5-HT4 agonists (e.g., PRX-03140 (Epix Pharmaceuticals)); 5-HT6 receptor antagonists; mGluR1 receptor modulators or antagonists; mGluR5 receptor modulators or antagonists; mGluR2/3 antagonists; Prostaglandin EP2 receptor

antagonists; PAI-1 inhibitors; agents that can induce Abeta efflux such as gelsolin; Metal-protein attenuating compound (e.g, PBT2); and GPR3 modulators; and antihistamines such as Dimebolin (e.g., Dimebon®, Pfizer).

In another embodiment, the invention provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of the invention, and effective amount of one or more cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors), and a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of the invention, and effective amount of one or more muscarinic agonists or antagonists (e.g., m_1 agonists or m_2 antagonists), and a pharmaceutically acceptable carrier.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of 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), N-methyl-D-aspartate receptor inhibitors (such as, for example, Namenda® (memantine HCl)); anti-amyloid antibodies (such as bapineuzumab, Wyeth/Elan), gamma secretase inhibitors, gamma secretase modulators, and beta secretase inhibitors other than the compounds of the invention.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of 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), N-methyl-D-aspartate receptor inhibitors (such as, for example, Namenda® (memantine HCl)).

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more gamma secretase inhibitors.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more gamma secretase modulators.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in combination with an effective (i.e., therapeutically effective) amount of one or more gamma secretase inhibitors and in further combination with one or more gamma secretase modulators.

In another embodiment, the invention provides a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in pure form, in isolated form, and/or in isolated and pure form.

Prodrugs of the compounds of the invention, or tautomers or stereoisomers thereof, or pharmaceutically acceptable salts or solvates of said compounds, said stereoisomers, and/or said tautomers, are also contemplated as being included within the scope of the invention, and are described more fully below.

Deuterates of the compounds of the invention, or tautomers or stereoisomers of said deuterates, or pharmaceutically acceptable salts or solvates of said deuterates, said stereoisomers, and/or said tautomers, are also contemplated as being included within the scope of the invention, and are described more fully above.

In another embodiment, the invention provides a method of preparing a pharmaceutical composition comprising the step of admixing at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a method of inhibiting β-secretase comprising exposing a population of cells expressing β-secretase to at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit β-secretase.

In another embodiment, the invention provides a method of inhibiting β-secretase in a patient in need thereof comprising administering at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in a therapeutically effective amount to inhibit β-secretase in said patient.

In another embodiment, the invention provides a method of inhibiting BACE-1 comprising exposing a population of cells expressing BACE-1 to at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, in an amount effective to inhibit BACE-1 in said cells. In one such embodiment, said population of cells is *in vivo*. In another such embodiment, said population of cells is *ex vivo*. In another such embodiment, said population of cells is *in vitro*.

In another embodiment, the invention provides a method of inhibiting BACE-2 comprising exposing a population of cells expressing BACE-2 to at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, in an amount effective to inhibit BACE-2 in said cells. In one such embodiment, said population of cells is *in vivo*. In another such embodiment, said population of cells is *ex vivo*. In another such embodiment, said population of cells is *in vitro*.

In another embodiment, the invention provides a method of inhibiting BACE-1 in a patient in need thereof comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in a therapeutically effective amount to inhibit BACE-1 in said patient.

In another embodiment, the invention provides a method of inhibiting BACE-2 in a patient in need thereof comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in a therapeutically effective amount to inhibit BACE-2 in said patient.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ from APP in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ plaque in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ plaque formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ fibrils in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ oligomers in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ fibrils and Aβ oligomers in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of inhibiting the formation of senile plaques and/or neurofibrillary tangles in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of treating, preventing, and/or delaying the onset of an amyloid β pathology ("Aβ pathology") and/or one or more symptoms of said pathology comprising administering at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, to a patient in need thereof in an amount effective to treat said pathology.

In another embodiment, the invention provides a method of treating, preventing, and/or delaying the onset of one or more pathologies associated with Aβ and/or one or more symptoms of one or more pathologies associated with Aβ. Non-limiting examples of pathologies associated with Aβ include: Alzheimer's disease, Down's syndrome, Parkinson's disease, memory loss, memory loss associated with Alzheimer's disease, memory loss associated with Parkinson's disease, attention deficit symptoms, attention deficit symptoms associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, dementia, stroke, microgliosis and brain inflammation, pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment, olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes, diabetes-associated amyloidogenesis, hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI") and Creutzfeld-Jakob disease, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said pathology or pathologies.

In one embodiment, the invention 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 the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional therapeutic agents useful in treating one or more neurodegenerative diseases, to a patient in need of such treatment.

In one embodiment, the invention 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 the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional therapeutic agents useful in treating one or more neurodegenerative diseases, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional therapeutic agents useful in treating Alzheimer's disease, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating Down's syndrome, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with an effective (e.g., therapetucially effective) amount of one or more additional active agents useful in treating Down's syndrome, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating mild cognitive impairment, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating mild cognitive impairement, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating glaucoma, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating glaucoma, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating cerebral amyloid angiopathy, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treatingcerebral amyloid angiopathy, to a patient in need of such treatment. to a patient in need of treatment.

In one embodiment, the invention provides a method of treating stroke, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a

tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer) , alone or optionally in combination with one or more additional active agents useful in treating stroke, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating dementia, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating dementia, to a patient in need of such treatment. to a patient in need of treatment.

In one embodiment, the invention provides a method of treating microgliosis, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating microgliosis, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating brain inflammation, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating brain inflammation, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating traumatic brain injury, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating traumatic brain injury, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating olfactory function loss, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with

one or more additional active agents useful in treating olfactory function loss, to a patient in need of such treatment.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from 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).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors, gamma secretase modulators, and beta secretase inhibitors other than a compound of the invention.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is Exelon (rivastigmine).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from Cognex (tacrine).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from Tau kinase inhibitor (e.g., GSK3beta inhibitor, cdk5 inhibitor, ERK inhibitor).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from an anti-Aβ vaccine.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from an APP ligand.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more agents that upregulate insulin degrading enzyme and/or neprilysin.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more cholesterol lowering agents. Non-limiting examples of said cholesterol lowerin agents include: statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin, and cholesterol absorption inhibitors such as Ezetimibe and phytonutrients.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more fibrates. Non-limiting examples of said fibtrates include clofibrate, Clofibride, Etofibrate, and Aluminium Clofibrate.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more LXR agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more LRP mimics.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more 5-HT6 receptor antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more nicotinic receptor agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more H3 receptor antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more histone deacetylase inhibitors.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more hsp90 inhibitors.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more m1 muscarinic receptor agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more 5-HT6 receptor antagonists, mGluR1, and mGluR5 positive allosteric modulators or agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more mGluR2/3 antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more anti-inflammatory agents that can reduce neuroinflammation.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more prostaglandin EP2 receptor antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more PAI-1 inhibitors.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more agents that can induce Aß efflux. One non-limiting example of an agent that can induce Aß influx is gelsolin.

In one embodiment, the invention 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 the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer) in a pharmaceutically acceptable carrier, and, optionally, another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient (as described below), the combined quantities of the compound of the invention 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 BACE.

In its various embodiments, the invention provides any one of the methods disclosed above and below wherein the compound(s) of the invention is a compound or compounds selected from the group consisting of the exemplary compounds of the invention described below.

In its various embodiments, the invention provides any one of the pharmaceutical compositions disclosed above and below wherein the compound(s) of the invention is a compound or compounds selected from the group consisting of the exemplary compounds of the invention described below.

Other embodiments of this invention are directed to any one of the embodiments above or below that are directed to compounds of the invention, or the use of compounds of the invention (e.g. the embodiments directed to methods of treatment, pharmaceutical compositions and kits).

In another embodiment, the invention provides for the use of a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in the manufacture of a medicament for use in the treatment, the delay of onset, and/or the prevention of one or more Aβ pathologies and/or in the treatment, the delay of onset, and/or the prevention of one or more symptoms of one or more Aβ pathologies.

DEFINITIONS

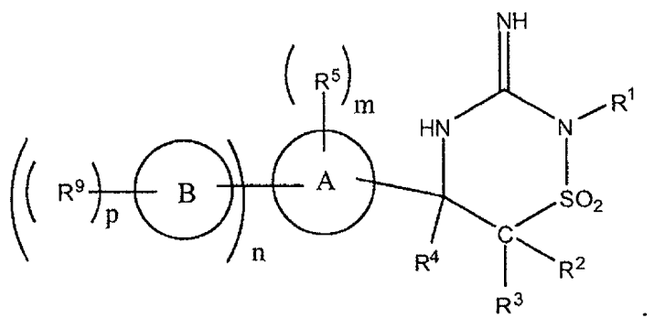
The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names and chemical structures may be used interchangeably to describe that same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portion of "hydroxyalkyl", "haloalkyl", arylalkyl-, alkylaryl-, "alkoxy" etc.

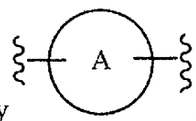
It shall be understood that, in the various embodiments of the invention described herein, any variable not specifically defined in the context of the embodiment is as defined in Formula (I). Any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

As described herein, the "example compounds of the invention" (or "example compounds" or "examples") include, collectively and individually, each of the compounds set forth with example numbers in the preparative examples.

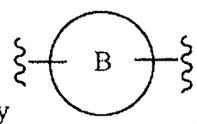
As described herein, variables such as R^1, R^2, R^3, and R^4 may be unsubstituted or substituted with one or more R^5 groups. It shall be understood that the upper limit of the number of substituents (referred to in the phrase "one or more substituents") is the number of available hydrogen atoms on the relevant moiety (R^1, R^2, R^3, or R^4) that are available for replacement by a substituent which will result in a chemically stable moiety.

As described herein, one or more of the variables $-L_1-$, $-L_2-$, and $-L_3-$ of the general formulae optionally independently represent a bond. It shall be understood that where such a variable represents a bond, the moieties which are shown connected by that variable are directly attached by covalent bond. Thus, by way of non-limiting illustration, a compound of Formula (I) wherein $-L_1-$, $-L_2-$ and $-L_3-$ each represent a bond can be shown as:



The moiety 

, which may be optionally substituted as described herein, represents a ring referred to herein as "ring A."

The moiety 

, which may be optionally substituted as described herein, represents a ring referred to herein as "ring B."

"At least one" means one or more than one, for example, 1, 2, or 3, or in another example, 1 or 2, or in another example 1.

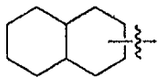
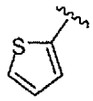
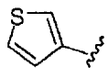
In the various Formulas of the compounds of the invention, e.g., in Formula (I), m, n, and p are each independently selected integers, wherein:

m is 0 or more;

n is 0 or more; and

p is 0 or more,

wherein the maximum value of the sum of m and n is the maximum number of available substitutable hydrogen atoms on ring A, and wherein the maximum value of p is the maximum number of available substitutable hydrogen atoms on ring B. Except for salt forms, the "maximum number of available substitutable hydrogen atoms" refers to the maximum number that will result in a neutral molecule.

By way of non-limiting illustration, when ring A is a  group, the maximum value of the sum of m and n 17. When ring A is a  or  group, the maximum value of the sum of m and n is 3.

In the compounds of the invention, e.g., in Formula (I), each of ring A and ring B (when present) is selected from the group consisting of a monocyclic aryl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycloalkyl, a monocyclic heterocycloalkenyl, and a multicyclic group, each of which groups may be unsubstituted or optionally further substituted as shown in Formula (I).

As used herein, the term "monocyclic aryl" refers to phenyl.

As used herein, the term "monocyclic heteroaryl" refers to a 4- to 7-membered monocyclic heteroaryl group comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, O, and S, and oxides thereof. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heteroaryl moities include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, pyridone, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl), pyrazinyl, pyridazinyl, imidazolyl, and triazinyl (e.g., 1,2,4-triazinyl), and oxides thereof.

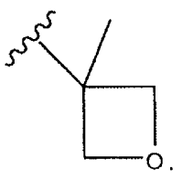
As used herein, the term "monocyclic cycloalkyl" refers to a 3- to 7-membered monocyclic cycloalkyl group. Non-limiting examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

As used herein, the term "monocyclic cycloalkenyl" refers to a non-aromatic 3- to 7-membered cycloalkyl group which contains one or more carbon-carbon double bonds. Non-limiting examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

As used herein, the term "monocyclic heterocycloalkyl" refers to a 4- to 7-membered monocyclic heterocycloalkyl group comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, N-oxide, O, S, S-oxide, S(O), and $S(O)_2$. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heterocycloalkyl groups

include piperidyl, oxetanyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, *beta* lactam, *gamma* lactam, *delta* lactam, *beta* lactone, *gamma* lactone, *delta lactone,* and pyrrolidinone, and oxides thereof.

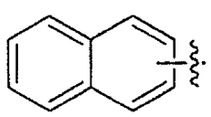
Non-limiting examples of lower alkyl-substituted oxetanyl include the moiety:



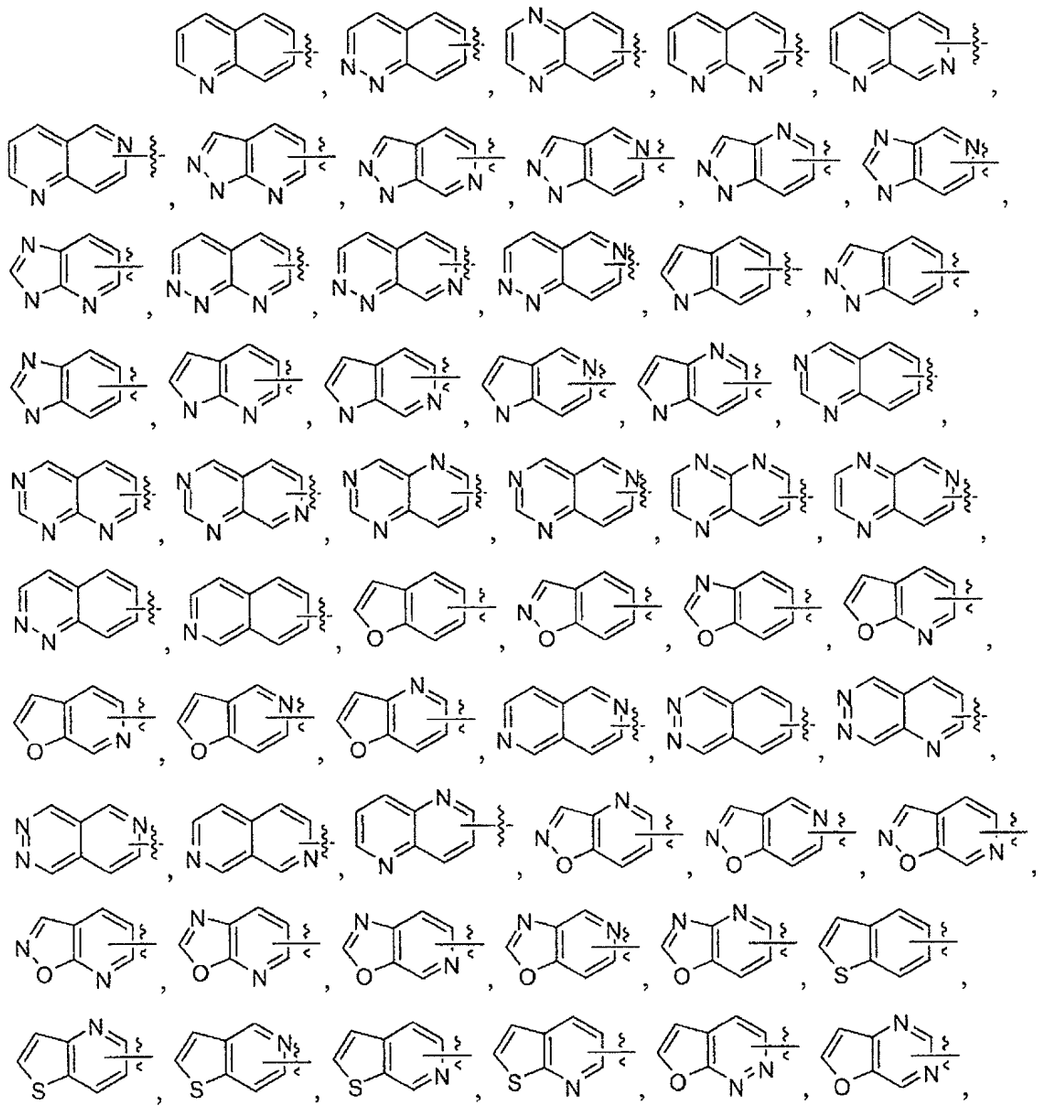
As used herein, the term "monocyclic heterocycloalkenyl" refers to a 4- to 7-membered monocyclic heterocycloalkenyl group comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, N-oxide, O, S, S-oxide, S(O), and $S(O)_2$. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heterocycloalkenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, dihydrothiophenyl, and dihydrothiopyranyl, and oxides thereof.

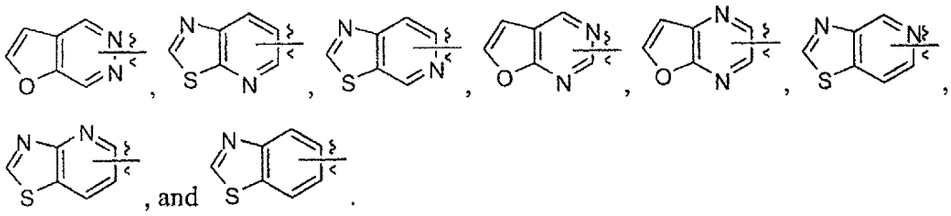
As used herein, the term "multicyclic group" refers to a fused ring system comprising two (bicyclic), three (tricyclic), or more fused rings, wherein each ring of the fused ring system is independently selected from the group consisting of phenyl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, and monocyclic heterocycloalkenyl. The point of attachment to the parent moiety is to any available ring carbon or (if present) ring heteroatom on any of the fused rings.

It shall be understood that each of the following multicyclic groups pictured may be unsubstituted or substituted, as described herein. Only the point of attachment to the parent moiety is shown by the wavy line.

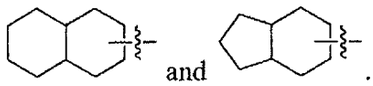
The term multicyclic groups includes bicyclic aromatic groups. Non-limiting examples of multicyclic groups which are bicyclic aromatic groups include: 

The term multicyclic groups includes bicyclic heteroaromatic groups comprising from 1 to 3 or more ring heteroatoms, each said ring heteroatom being independently selected from the group consisting of N, O, and S, S(O), $S(O)_2$, and oxides of N, O, and S, and oxides thereof. Non-limiting examples of multicyclic groups which are bicyclic heteroaromatic groups comprising from 1 to 3 ring heteroatoms, each said ring heteroatom being independently selected from N, O, and S include the following, and oxides thereof:

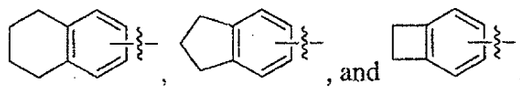




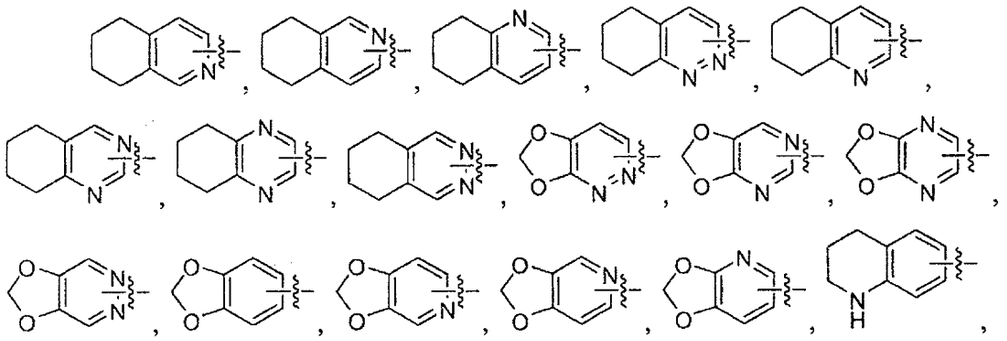
The term multicyclic groups includes saturated bicyclic cycloalkyl groups. Non-limiting examples of multicyclic groups which are saturated bicyclic cycloalkyl groups include the following:

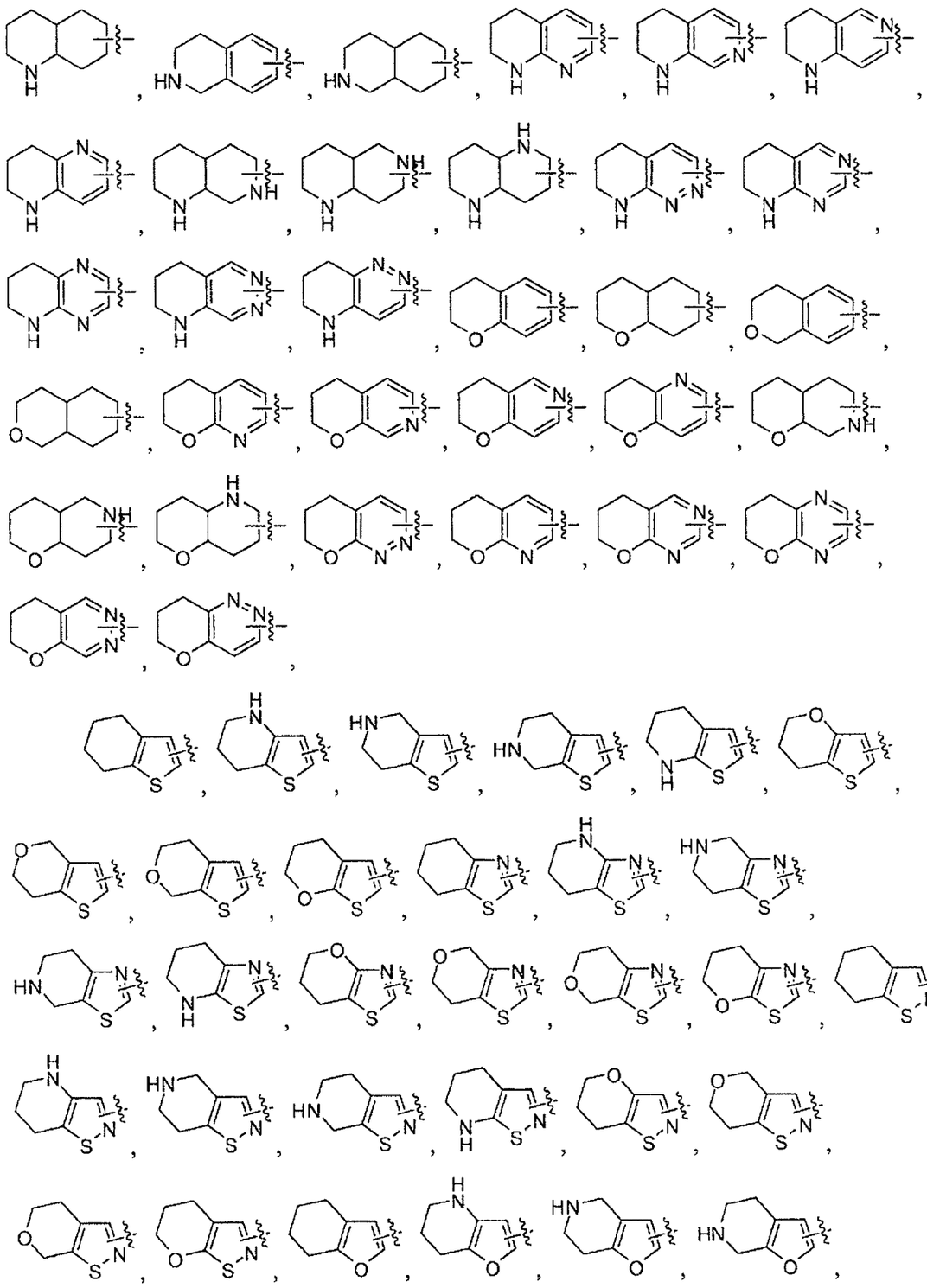


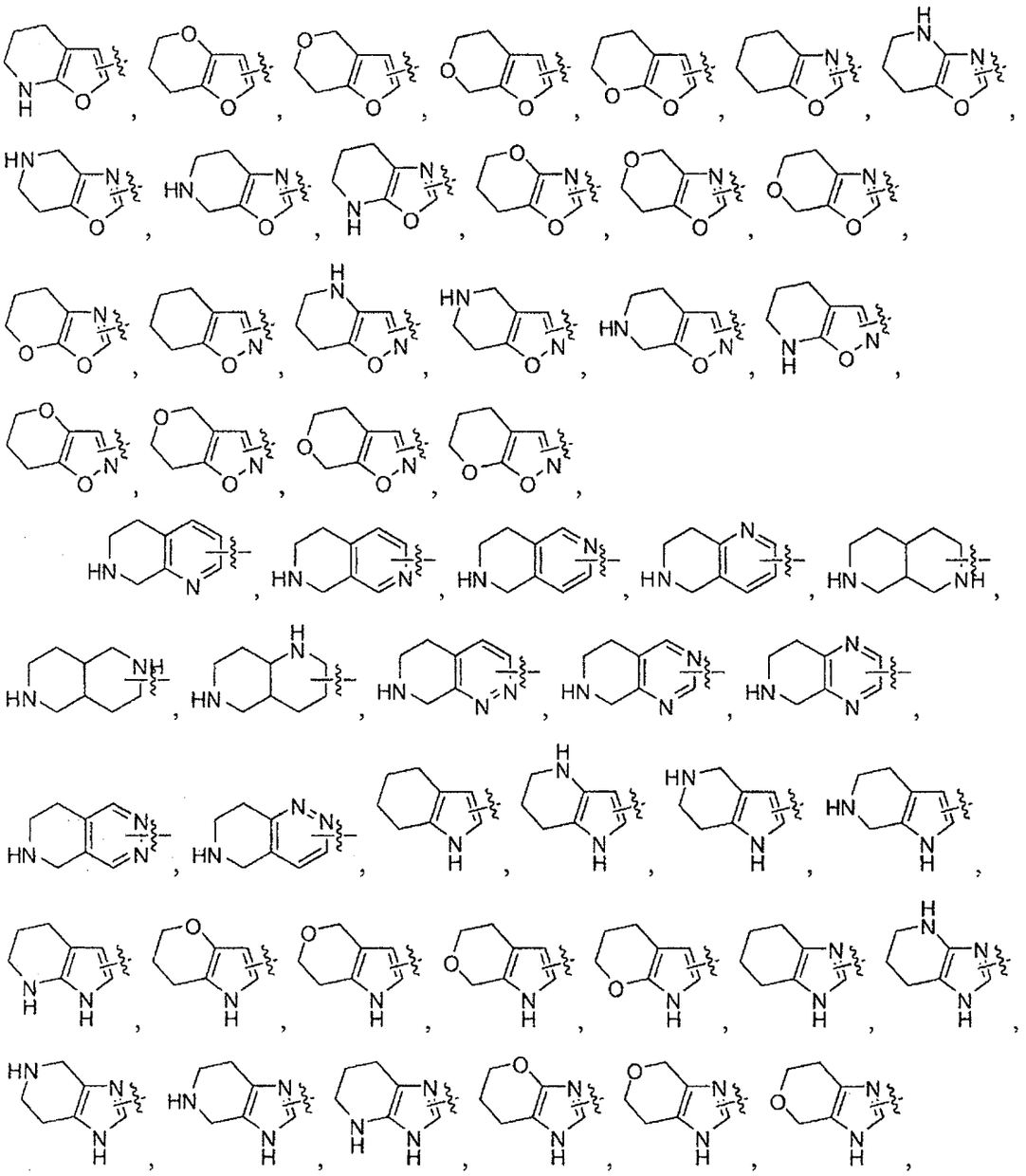
The term multicyclic group includes partially unsaturated bicyclic cycloalkyl groups. Non-limiting examples of multicyclic groups which comprise partially unsaturated bicyclic cycloalkyl groups include the following:

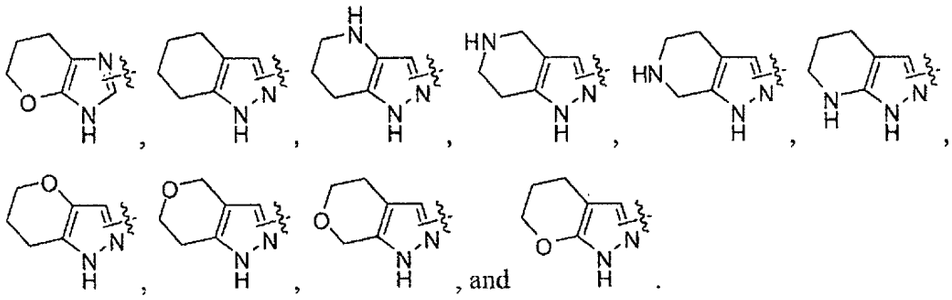


The term multicyclic groups includes partially or fully saturated bicyclic groups comprising from 1 to 3 ring heteroatoms, each said ring heteroatom is independently selected from the group consisting of N, O, and S, S(O), $S(O)_2$, and oxides of N and S. Such rings may also optionally contain one or more oxo groups, as defined herein. Non-limiting examples of multicyclic groups which are partially or fully saturated bicyclic groups comprising from 1 to 3 ring heteroatoms, each said ring heteroatom being independently selected from N, O, and S include the following, and oxides thereof:

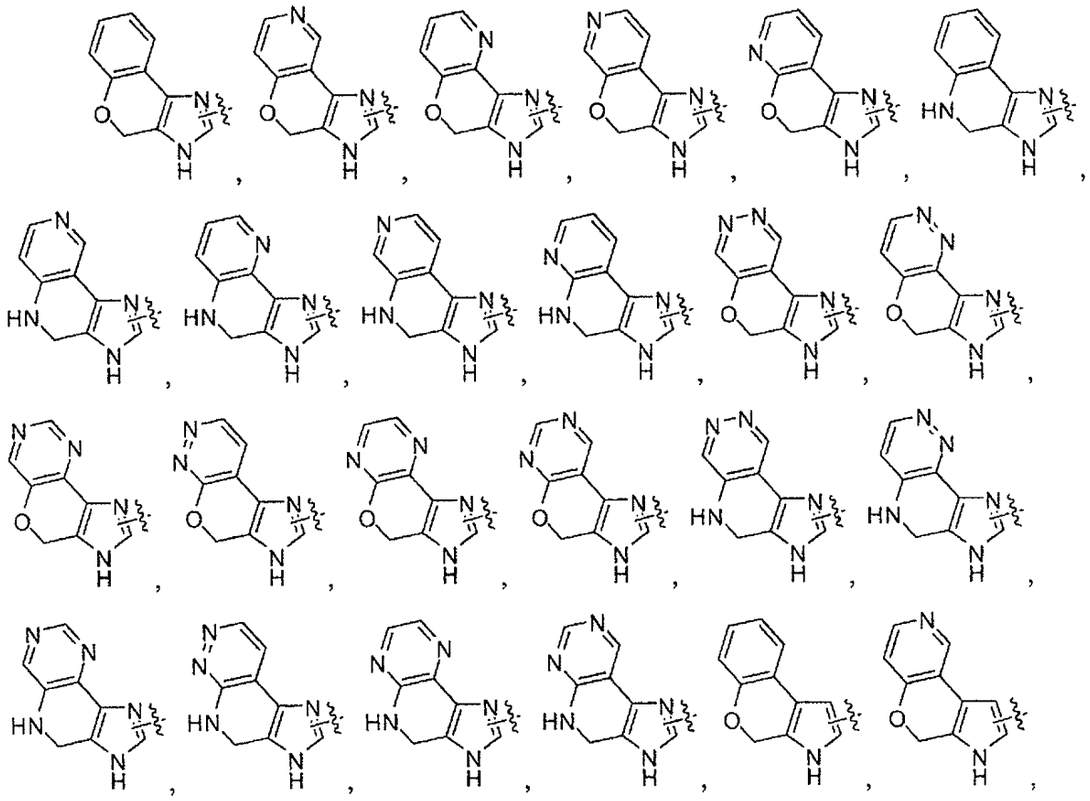


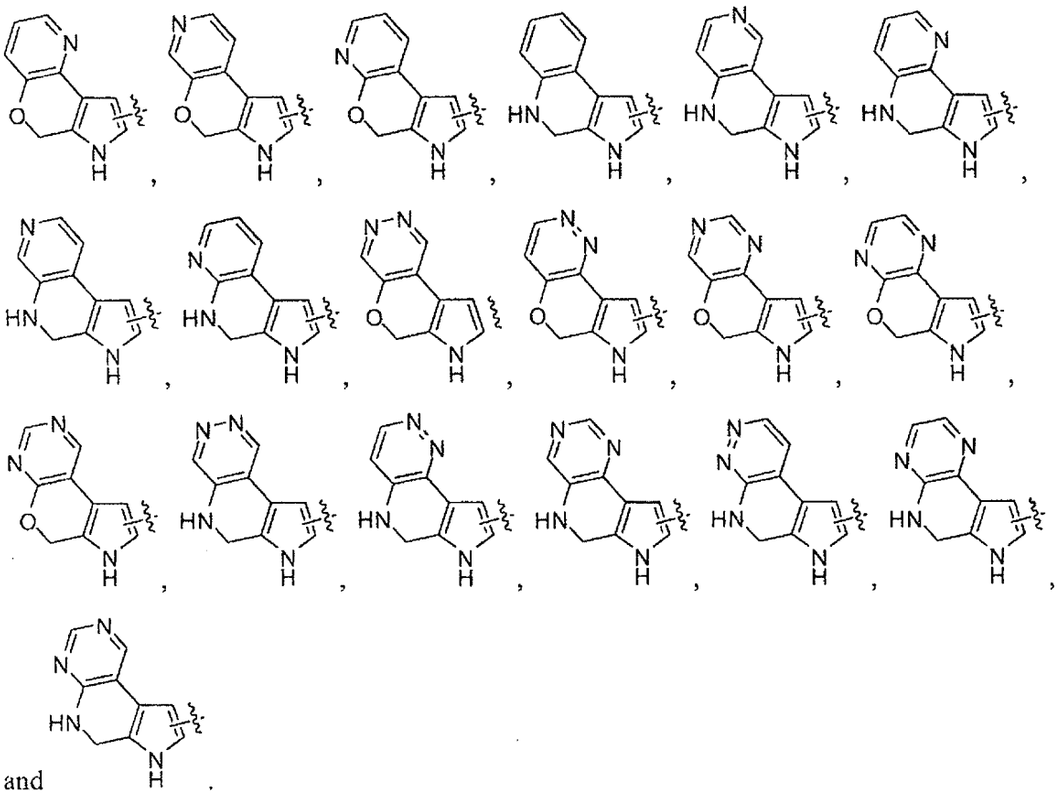






The term multicyclic groups includes aromatic tricyclic groups, cycloalkyl tricyclic groups, as well as heteroaromatic and partially and fully saturated tricyclic groups. For tricyclic groups comprising ring heteroatoms, said tricyclic groups comprise one or more (e.g., from 1 to 5) ring heteroatoms, wherein each said ring heteroatom is independently selected from N, O, and S, S(O), $S(O)_2$, and oxides of N, O, and S: Non-limiting examples of tricyclic multicyclic groups include the following, and, where possible, oxides thereof:





and .

"Patient" includes both human and non-human animals. Non-human animals include those research animals and companion animals such as mice, primates, monkeys, great apes, canine (*e.g.*, dogs), and feline (*e.g.*, house cats).

"Pharmaceutical composition" (or "pharmaceutically acceptable composition") means a composition suitable for administration to a patient. Such compositions may contain the neat compound (or compounds) of the invention or mixtures thereof, or salts, solvates, prodrugs, isomers, or tautomers thereof, or they may contain one or more pharmaceutically acceptable carriers or diluents. 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.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

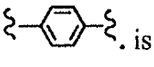
"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. 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. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being as described herein or independently selected from the group consisting of halo, alkyl, haloalkyl, spirocycloalkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Heteroalkyl" means an alkyl moiety as defined above, having one or more carbon atoms, for example one, two or three carbon atoms, replaced with one or more heteroatoms, which may be the same or different, where the point of attachment to the remainder of the molecule is through a carbon atom of the heteroalkyl radical. Suitable such heteroatoms include O, S, S(O), S(O)$_2$, and -NH-, -N(alkyl)-. Non-limiting examples include ethers, thioethers, amines, hydroxymethyl, 3-hydroxypropyl, 1,2-dihydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-dimethylaminoethyl, and the like.

"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 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 alkenyl chain.

"Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally 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, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. More generally, the suffix "ene" on alkyl, aryl, hetercycloalkyl, etc. indicates a divalent moiety, e.g., $-CH_2CH_2-$ is ethylene, and  . is para-phenylene.

"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. "Alkynyl" may be unsubstituted or optionally 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.

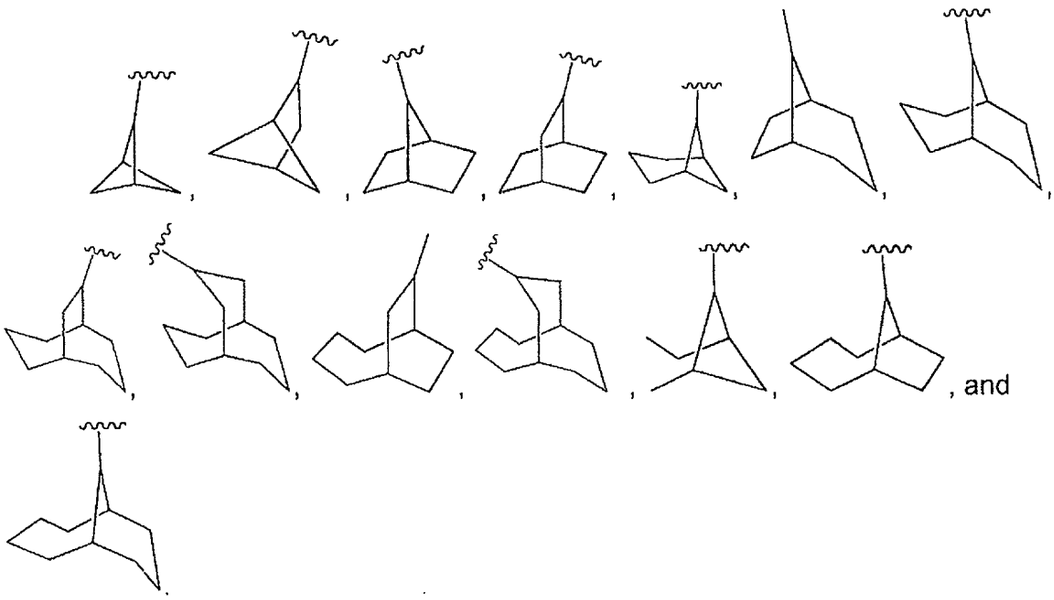
"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include –CH=CH-, $-C(CH_3)=CH-$, and $-CH=CHCH_2-$.

"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. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl (alternatively referred to as thiophenyl), 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 monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following:

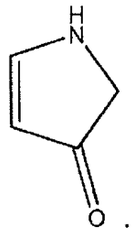


"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Heterocycloalkyl" (or "heterocyclyl") means a non-aromatic saturated 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 heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl 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 heterocyclyl can be

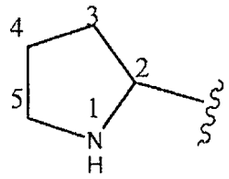
optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Thus, the term "oxide," when it appears in a definition of a variable in a general structure described herein, refers to the corresponding N-oxide, S-oxide, or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Such =O groups may be referred to herein as "oxo," as described below.

"Heterocycloalkenyl" (or "heterocyclenyl") 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 atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclenyl includes rings having a carbonyl group in the ring). Example of such moiety is pyrrolidenone (or pyrrolone):



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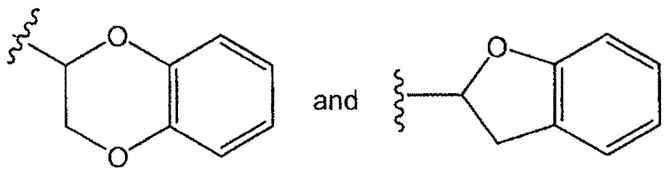
It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

"Arylcycloalkyl" (or "arylfused cycloalkyl") means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted as described herein. Non-limiting examples of suitable arylcycloalkyls include indanyl (a benzofused cycloalkyl) and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" (or "arylfused heterocycloalkyl") means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylheterocycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted, and/or contain the oxide or oxo, as described herein. Non-limiting examples of suitable arylfused heterocycloalkyls include:



The bond to the parent moiety is through a non-aromatic carbon atom.

It is also understood that the terms "arylfused aryl", "arylfused cycloalkyl", "arylfused cycloalkenyl", "arylfused heterocycloalkyl", arylfused heterocycloalkenyl", "arylfused heteroaryl", "cycloalkylfused aryl", "cycloalkylfused cycloalkyl", "cycloalkylfused cycloalkenyl", "cycloalkylfused heterocycloalkyl", "cycloalkylfused heterocycloalkenyl", "cycloalkylfused heteroaryl, "cycloalkenylfused aryl", "cycloalkenylfused cycloalkyl", "cycloalkenylfused cycloalkenyl", "cycloalkenylfused heterocycloalkyl", "cycloalkenylfused

heterocycloalkenyl", "cycloalkenylfused heteroaryl", "heterocycloalkylfused aryl", "heterocycloalkylfused cycloalkyl", "heterocycloalkylfused cycloalkenyl", "heterocycloalkylfused heterocycloalkyl", "heterocycloalkylfused heterocycloalkenyl", "heterocycloalkylfused heteroaryl", "heterocycloalkenylfused aryl", "heterocycloalkenylfused cycloalkyl", "heterocycloalkenylfused cycloalkenyl", "heterocycloalkenylfused heterocycloalkyl", "heterocycloalkenylfused heterocycloalkenyl", "heterocycloalkenylfused heteroaryl", "heteroarylfused aryl", "heteroarylfused cycloalkyl", "heteroarylfused cycloalkenyl", "heteroarylfused heterocycloalkyl", "heteroarylfused heterocycloalkenyl", and "heteroarylfused heteroaryl" are similarly represented by the combination of the groups aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, as previously described. Any such groups may be unsubstituted or substituted with one or more ring system substituents at any available position as described herein.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl. The term (and similar terms) may be written as "arylalkyl-" to indicate the point of attachment to the parent moiety.

Similarly, "heteroarylalkyl", "cycloalkylalkyl", "cycloalkenylalkyl", "heterocycloalkylalkyl", "heterocycloalkenylalkyl", etc., mean a heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, etc. as described herein bound to a parent moiety through an alkyl group. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

Similarly, "arylfused arylalkyl-", arylfused cycloalkylalkyl-, etc., means an arylfused aryl group, arylfused cycloalkyl group, etc. linked to a parent moiety through an alkyl group. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents

adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl, adamantylpropyl, and the like.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Heterocyclylalkyl" (or "heterocycloalkylalkyl") means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, 2-pyridinylmethyl, quinolinylmethyl, and quinolin-3-ylmethyl, and the like. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- 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.

"Cyanoalkyl" means a NC-alkyl- group in which alkyl is as previously defined. Preferred cyanoalkyls contain lower alkyl. Non-limiting examples of suitable cyanoalkyl groups include cyanomethyl and 2-cyanoethyl.

"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.

"Heteroaroyl" means an heteroaryl-C(O)- group in which the heteroaryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include pyridoyl.

"Alkoxy" means an alkyl-O- 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.

"Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Aryloxy" means an aryl-O- 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.

"Aralkyloxy" (or "arylalkyloxy") means an aralkyl-O- group (an arylaklyl-O- group) in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkenyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Alkylthio" means an alkyl-S- 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 aryl-S- 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.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio 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.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl 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 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.

"Spirocycloalkyl" means a cycloalkyl group attached to a parent moiety by replacement of two available hydrogen atoms at a single carbon atom. Non-limiting examples of spirocycloalkyl wherein the parent moiety is a cycloalkyl include spiro [2.5] octane, spiro [2.4] heptane, etc. The moiety may optionally be substituted as described herein. Non-limiting spirocycloalkyl groups include spirocyclopropyl, spriorcyclobutyl, spirocycloheptyl, and spirocyclohexyl.

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.

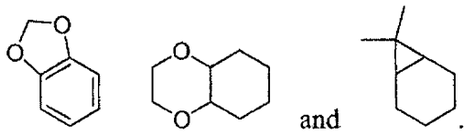
The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylfused cycloalkylalkyl- moiety or the like includes substitution on any ring portion and/or on the alkyl portion of the group.

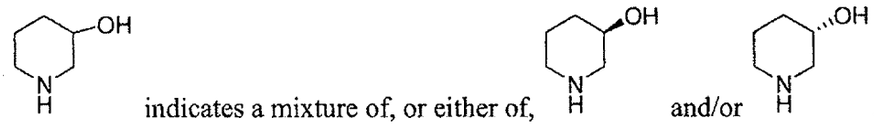
When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in a structure presented herein, the variables can be the same or different.

With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of the invention, e.g., of Formula (II)," one to three compounds of the invention, e.g., of Formula (II) can be administered at the same time, preferably one.

Compounds of the invention may contain one or more rings having one or more ring system substituents. "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 as described herein or independently selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, -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 aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moieties are rings such as heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl rings. Additional non-limiting examples include methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



The line —— as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example:



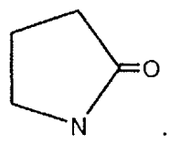
The wavy line ∿∿∿, as used herein, indicates a point of attachment to the rest of the compound.

Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

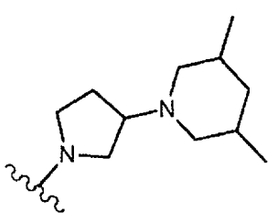
"Oxo" is defined as a oxygen atom that is double bonded to a ring carbon in a cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or other ring described herein, e.g.,



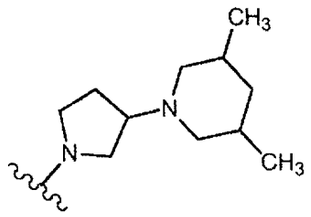
In this specification, where there are multiple oxygen and/or sulfur atoms in a ring system, there cannot be any adjacent oxygen and/or sulfur present in said ring system.

It is noted that the carbon atoms for compounds of the invention may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



represents



In the compounds of Formula (I)

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer) after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be suitable for in vivo or medicinal use and/or characterizable by standard analytical techniques described herein or well known to the skilled artisan.

When a functional group in a compound is termed "protected", this means that the group is 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.

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.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. 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. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use

of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of the invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of the invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "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. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of the invention can form salts which are also within the scope of this invention. Reference to a compound of the invention 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 the invention 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 invention may be formed, for example, by reacting a compound of the invention 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.

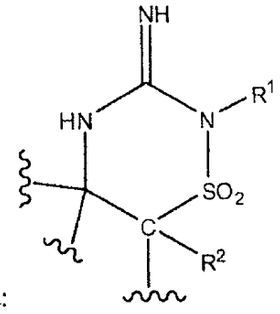
All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight

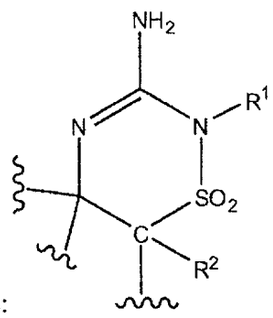
or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of the invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of the invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention. Thus, for example, the compounds of the invention conforming to the formula:



,

and their tautomers:  are both contemplated as being within the scope of the compounds of the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters 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). (For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. 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", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of the invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent. Non-limiting examples of deuterated compounds of the invention are described hereinbelow.

Polymorphic forms of the compounds of the invention, and of the salts, solvates, esters and prodrugs of the compounds of the invention, are intended to be included in the present invention.

Suitable doses for administering compounds of the invention to patients may readily be determined by those skilled in the art, e.g., by an attending physician, pharmacist, or other skilled worker, and may vary according to patient health, age, weight, frequency of administration, use with other active ingredients, and/or indication for which the compounds are administered. Doses may range from about 0.001 to 500 mg/kg of body weight/day of the compound of the invention. In one embodiment, the dosage is from about 0.01 to about 25 mg/kg of body weight/day of a compound of the invention, or a pharmaceutically acceptable salt or solvate of said compound. In another embodiment, the quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application. In another embodiment, a typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

As discussed above, 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.

When used in combination with one or more additional therapeutic agents, the compounds of this invention may be administered together or sequentially. When administered sequentially, compounds of the invention may be administered before or after the one or more additional therapeutic agents, as determined by those skilled in the art or patient preference.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an effective amount of one or more additional agents described above.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. Certain assays are exemplified elsewhere in this document.

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 ingredient. 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.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. 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.

The compounds of this invention may also be delivered subcutaneously.

In one embodiment, the compound is administered orally.

In some embodiments, it may be advantageous for the pharmaceutical preparation compring one or more compounds of the invention be prepared in a unit dosage form. In such forms, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

PREPARATIVE EXAMPLES

Compounds of the invention can be made using procedures known in the art. The following reaction schemes show typical procedures, but those skilled in the art will recognize that other procedures can also be suitable.

Techniques, solvents and reagents may be referred to by their following abbreviations:

Thin layer chromatography: TLC

High performance liquid chromatography: HPLC

ethyl acetate: AcOEt or EtOAc

methanol: MeOH

ether or diethyl ether: Et_2O

tetrahydrofuran: THF

Acetonitrile: MeCN or ACN

1,2-dimethoxyethane: DME

Trifluoroacetic acid: TFA

Dimethylacetamide: DMA

Dimethylformamide: DMF

Dimethylsulfoxide: DMSO

triethylamine: Et_3N or TEA

tert-Butoxycarbonyl: t-Boc or Boc

2-(Trimethylsilyl)ethoxycarbonyl: Teoc

liquid chromatography mass spectrometry: LCMS

milliliters: mL

millimoles: mmol

micromoles : μmol

microliters: μl

grams: g

milligrams: mg

N-iodosuccinimide: NIS

room temperature (ambient, about 25°C): rt (or RT)

Retention time: t_R

N-bromosuccinimide: NBS

Methyl magnesium bromide: MeMgBr

iron(III) acetylacetonate: $Fe(acac)_3$

Diphenylphosphoryl azide: DPPA

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDCI

Diisopropylethylamine: DIEA or iPr_2NEt

Diisopropylamine: iPr_2NH

2-(Trimethylsilyl)ethanol: TMSethanol

3-Chloroperoxybenzoic acid: mCPBA

n-Butyllithium: nBuLi

lithium diisopropylamide: LDA

[1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II): $PdCl_2dppf$

Palladium(II) acetate: $Pd(OAc)_2$

Methanesulfonyl chloride: $MeSO_2Cl$

Benzyl: Bn

4-methoxy benzyl: PMB

Phenyl: Ph

Ethanol: EtOH

Liter: L

Minutes: min

Reverse phase: RP

Hexanes: Hex

Methylene Chloride: DCM

Acetic acid: HOAc or AcOH

Saturated: Sat (or sat)

Bis(2-oxo-3-oxazolidinyl) phosphinic chloride: BOPCl

4-(dimethylamino)pyridine: DMAP

Molar: M

2-((trimethylsilyl)ethoxy)methyl: SEM

Diisopropyl azodicarboxylate: DIAD

Triethylborane: Et_3B

Tris(dibenzylideneacetone)dipalladium(0): Pd_2dba_3

Pyridine: Pyr

(2-Biphenyl)di-*tert*-butylphosphine: John-Phos

2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl: X-Phos

2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate: HATU

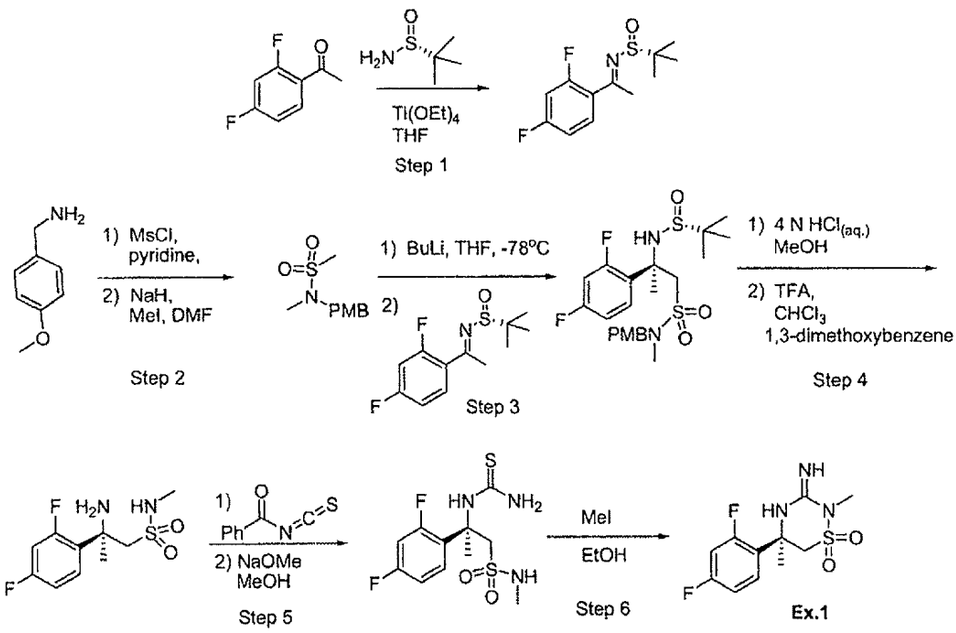
Concentrated: conc.

Tetrabutyl ammonium fluoride: TBAF

2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl: RuPhos

Tetrakis(triphenylphosphine)palladium: $Pd(PPh_3)_4$

Scheme 1a



Step 1: To a solution of 2,4-difloroacetophenone (15.0 g, 96 mmol) in THF (100 mL) was added (R)-2-methyl-2-propanesulfinamide (12.8 g, 106 mmol) and $Ti(OEt)_4$, (32.0 g, 120 mmol). The resultant solution was heated to reflux overnight. After that time, the solution was cooled to RT and poured onto ice. To this mixture was added CH_2Cl_2 and the resultant mixture was stirred at RT for 10 min. The mixture was then filtered through Celite. The filter cake was washed with CH_2Cl_2. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 45:55 hexanes:EtOAc) to afford the ketimine (12.3 g).

Step 2: To a stirred solution of 4-methoxybenzyl amine (198.9 g, 1.45 mol) in anhydrous pyridine (400 mL) at 0°C was added dropwise via an addition funnel methanesulfonyl chloride (116 mL, 1.45 mol) over 45 min. After the addition was complete, the cooling bath was removed and the resultant solution was stirred at RT overnight. The reaction was concentrated *in vacuo* (water bath 60-65°C) to remove most of the pyridine. The residue was taken up in CH_2Cl_2 (1 L). The organic solution was washed with 1 N $HCl_{(aq.)}$ (2 x 1 L), sat. $NaHCO_3$ (aq) (2 x 1 L) and brine (1 x 500 mL). The organic layer was dried over Na_2SO_4, filtered and

concentrated to afford a crude solid. This solid was dissolved in 95% EtOH (430 mL) using a steam bath to warm the solution. The solution was allowed to cool, causing the product to precipitate from solution. The product was removed by filtration and the solid was washed with cold EtOH (3 x 150 mL). A second crop was obtained after allowing the mother liquor to stir at RT overnight. The overall yield of the product was 246.5 g (79% yield).

This product was dissolved in anhydrous DMF (3.0 L), cooled to 0°C and placed under an atmosphere of N_2. To this solution was added in small portions sodium hydride (60% in mineral oil, 60.2 g, 1.51 mol, 1.3 eq.). After the addition was complete, the mixture was stirred for an additional 10 min. To this mixture was added dropwise via an addition funnel methyl iodide (250 g, 1.76 mol, 1.5 eq.). After the addition was complete, the cooling bath was removed and the mixture was allowed to stir at RT overnight. The mixture was then concentrated *in vacuo* (p = 10 torr, bath temp = 55-60°C) to remove ca. 2.5 L of DMF. Some solids precipitated from the solution. The remaining mixture was partitioned between 5 L ice water, 5 L Et_2O and 500 mL of EtOAc. The organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 1 L). The combined organic layers were washed with brine (2 x 1 L), dried over Na_2SO_4, filtered and concentrated. The solid was stirred with hexanes using a wire stir blade to powderize the solid. The solid was removed by filtration and washed with hexanes (2 x 250 mL). The solid was dissolved in hexanes/EtOAc (1:1, 450 mL) using a steam bath to warm the mixture. An off white precipitate formed on cooling and was filtered off (182 g). The remaining mother liquor was purified via flash chromatography (SiO_2: 1:1 hexanes:EtOAc) to afford additional product (51.8 g) for an overall yield of 233.8g (89% yield).

Step 3: To a solution of the sulfonamide from step 2 (4.18 g, 18.2 mmol) in anhydrous THF (50 mL) at -78°C under an atmosphere of N_2 was added dropwise a solution of *n*-BuLi (1.6 M in hexanes, 11.4 mL, 18.2 mmol). The resultant solution was stirred at -78°C for 30 min. After that time, a solution of the ketimine from step 1 (3.15 g, 12.1 mmol) in THF (50 mL) precooled to -78°C in a separate round bottom flask was transferred via cannula to the solution above. The resultant solution was stirred at -78°C for 3.5 hours. Water was added and the mixture was allowed to warm to RT. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and

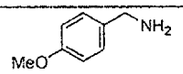
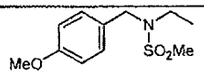
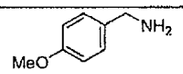
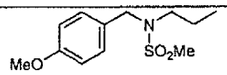
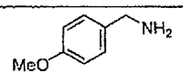
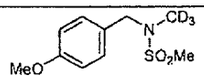
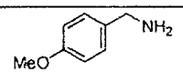
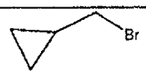
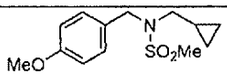
concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 40:60 hexanes:EtOAc) to afford the sulfinamide (3.95 g, 67% yield).

Step 4: To a solution of the sulfinamide from step 3 (3.80 g, 7.6 mmol) in CH_2Cl_2/MeOH (3:1 80 mL) was added a solution of 4 M HCl $_{(dioxane)}$ (11.4 mL, 45.4 mmol). The resultant solution was stirred at RT for 1.5 hours. The solution was concentrated. The residue was re-concentrated from toluene (1x). The residue was then taken up in $CHCl_3$ and TFA (26 mL, 1:1). To this solution was added 1,3-dimethoxybenzene (6.5 mL, 50 mmol). The resultant solution was stirred at RT overnight. The resultant solution was concentrated. The resultant oil was partitioned between Et_2O and 1 M HCl $_{(aq.)}$. The aqueous layer was extracted with Et_2O (2x). The aqueous layer was then adjusted to pH 10 with the addition of sat. Na_2CO_3 $_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were extracted from the basic aqueous layer, combined, dried over Na_2SO_4, filtered and concentrated to afford the amine (1.88 g, 85%).

Step 5: To a solution of the amine from step 4 (1.80 g, 6.8 mmol) in CH_2Cl_2 (30 mL) was added benzoyl isothiocyanate (1.01 mL, 7.49 mmol). The resultant solution was stirred at RT overnight. The solution was then concentrated. The residue was redissolved in MeOH (20 mL). To this solution was added a solution of NaOMe in MeOH (25%, 3.9 mL). The resultant solution was stirred at RT for 45 min. The solution was concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 and water. The pH of the aqueous layer was adjusted to ca 11 with the addition of $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the thiourea (1.90 g, 86%).

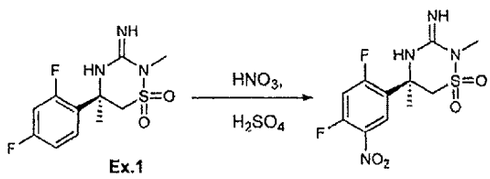
Step 6: To the thiourea from step 5 (1.90 g, 5.88 mmol) in EtOH (40 mL) was added methyl iodide (0.42 mL, 6.7 mmol). The resultant solution was heated to reflux for 3 hours. The solution was cooled to RT and concentrated *in vacuo*. The residue was partitioned between EtOAc and Na_2CO_3 $_{(aq.)}$. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 92:8 CH_2Cl_2:MeOH) to afford **Ex. 1** (1.12 g, 66% yield). LCMS (conditions D): t_R = 1.73 min, *m/e* = 290.2 (M+H).

Table I: The following sulfonamides were prepared using a procedure similar to that described in Scheme 1a step 2.

Entry	Amine	Alkyl halide	sulfonamide
1			
2			
3*		CD_3I	
4*			

* Cesium carbonate was used as the base instead of NaH for entries 3 and 4.

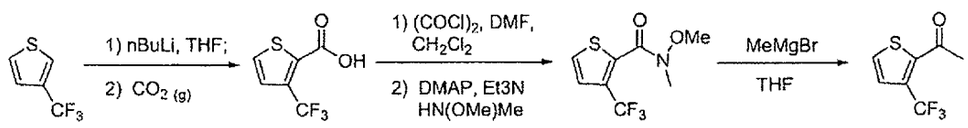
Scheme 1b:



Ex.1

Step 1: To a mixture of **Ex. 1** (8.00 g, 28.0 mmol) and concentrated sulfuric acid (16 mL) was added fuming nitric acid (2.24 mL) at 0 °C. The reaction mixture was stirred from 0 °C to room temperature over 2 h. After this time, the reaction mixture was basified with sodium carbonate to pH 10 and extracted with ethyl acetate (2 × 200 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the nitro compound (8.81 g, 94%).

Scheme 2:



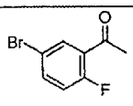
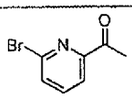
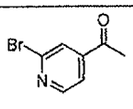
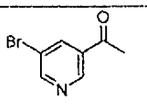
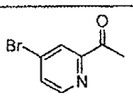
Step 1: To a solution of 3-trifluoromethyl thiophene (3.75g, 24.6 mmol) in anhydrous THF (60 mL) at -78°C was added a solution of n-BuLi (2.5 M in hexanes, 13 mL, 32.5 mmol). The

resultant solution was stirred at -78°C for 10 min. To the solution was bubbled $CO_{2\,(g)}$ for 20 min at -78°C. The solution was allowed to warm to RT and stirred for an additional 40 min at RT while bubbling of $CO_{2\,(g)}$ through the solution was continued. After that time,1 M $HCl_{(aq.)}$ was added to the solution. The aqueous layer was then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: 85:15:1 CH_2Cl_2:MeOH:AcOH) to afford the carboxylic acid (4.33 g, 90%).

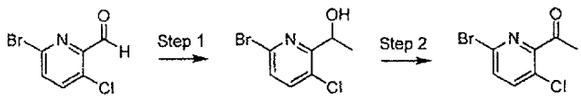
Step 2: To a solution of a portion of the acid from step 1 (465 mg, 2.37 mmol) in CH_2Cl_2 (12 mL) and DMF (0.20 mL) at 0°C was added dropwise a solution of oxalyl chloride (2 M in CH_2Cl_2, 3.5 mL, 3 eq.). The resultant solution was stirred at 0°C for 15 min followed by an additional 1 hour at RT. The solution was concentrated. To the residue was added N,O-dimethylhydroxylamine hydrochloride (470 mg, 2 eq.) followed by CH_2Cl_2 (18 mL). The resultant mixture was cooled to 0°C. To this mixture was added Et_3N (1.4 mL) and DMAP (10 mg). The solution was stirred at 0°C for 1 hour. To the solution was added 1 M $HCl_{(aq.)}$ (60 mL) and CH_2Cl_2 (60 mL). The layers were separated. The organic layer was washed with brine, dried and concentrated. The crude residue was purified via flash chromatography (SiO_2: gradient elution 100:0 to 60:40 heptane:EtOAc) to afford the amide (426 mg, 75%).

Step 3: To a solution of the amide from step 2 (4.10 g, 17.1 mmol) in THF (70 mL) at 0°C was slowly added a solution of methyl magnesium bromide (3 M in Et_2O, 7 mL). The resultant solution was stirred at 0°C for 3 hours. After that time, 1 M $HCl_{(aq.)}$ was added. The mixture was then extracted with Et_2O. The organic layer was dried, filtered and concentrated. The residue was purified via flash chromatography (SiO_2: gradient elution 100:0 to 60:40 pentane:EtOAc) to afford the ketone (3.22 g, 97%) as a colorless oil.

Table Ib: The following ketones were prepared using similar procedures to that described in Scheme 2, Steps 2 and 3 using the appropriate carboxylic acids.

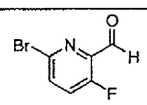
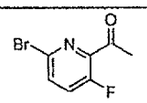
Scheme 2b:



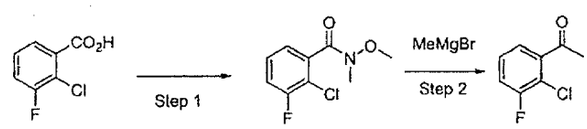
Step 1: To a solution of 6-bromo-3-chloropicolinaldehyde (10.0 g, 45.45 mmol) in 200 mL THF stirring at -78°C under N_2 was slowly added methylmagnesium bromide (3.0 M in diethyl ether, 16.63 mL, 50 mmol). The reaction was stirred at this temperature for 3 hours, and then saturated ammonium chloride was added. The mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hexanes over 20 minutes) to provide 1-(6-bromo-3-chloropyridin-2-yl)ethanol (8.4 g, 78%).

Step 2: The material prepared above (8.4 g, 35.5 mmol) was stirred overnight at room temperature in 100 mL DCM along with pyridinium chlorochromate (15 g, 71 mmol) and approximately 5 g celite. The reaction was filtered through celite and washed with DCM. The filtrate was concentrated to dryness *in vacuo* and the residue was purified by silica gel chromatography (0-10% EtOAc/hexanes over 22 minutes) to provide 1-(6-bromo-3-chloropyridin-2-yl)ethanone (6.85 g, 82%).

Table Ic: The following ketone was made using methods similar to those described in Scheme 2b:

Entry	Aldehyde	Ketone
1		

Scheme 2c:

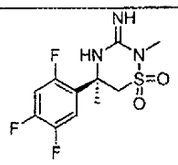
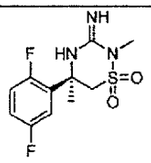
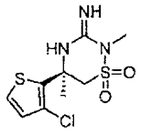
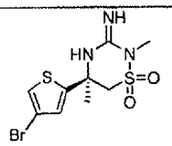
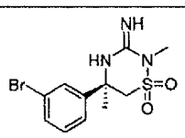
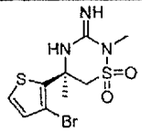
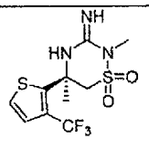
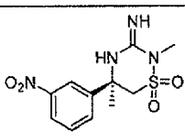
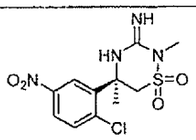
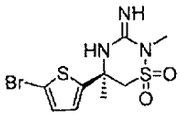
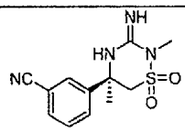
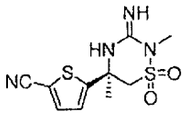
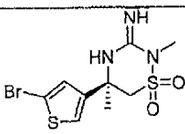
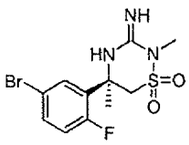
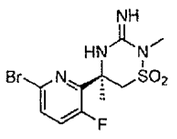


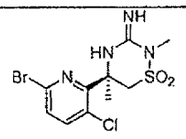
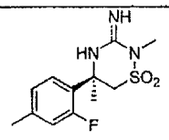
Step 1: To a solution of 2-chloro-3-fluorobenzoic acid (30 g, 172 mmol) in 300 mL of DCM was added carbonyldiimidazole (CDI) (32.0 g, 198 mmol) in portions. After addition and then stirring at RT for 1 h, N,O-dimethylhydroxylamine HCl salt (18.5 g, 189 mmol) was added into the mixture followed by Et_3N (20 mL). The mixture was stirred at RT overnight. After the reaction was quenched with water, the aqueous layer was extracted with DCM (2x). The

organic layers were washed with 2N HCl (aq), water, sat. $NaHCO_3$ (aq) and brine. The solution was dried ($MgSO_4$) and concentrated. The product 2-chloro-3-fluoro-N-methoxy-N-methylbenzamide (32.0 g) was obtained by silica gel chromatography (elution with 0-30% EtOAc/Hex).

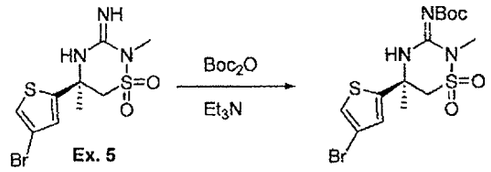
Step 2: The above material was treated according to Scheme 2, Step 3 to provide the ketone product (89% yield).

Table II: The following examples were prepared using similar procedures to that described in Scheme 1a using the appropriate starting materials.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
2	 MH^+: 308.2, 1.64 min, D	**3**	 MH^+: 290.0, 1.99 min, B	**4**	 MH^+: 294.2, 1.43 min, A
5	 MH^+: 340.2, 2.64 min, A	**6**	 MH^+: 331.9, 1.95 min, B	**7**	 MH^+: 340.2, 2.19 min, A
8		**9**		**10**	
11	 MH^+: 339.8, 1.87 min, A	**12**	 MH^+: 278.9, 1.73 min, B	**13**	 MH^+: 285.0, 1.54 min, B
14	 MH^+: 340.2, 2.44 min, A	**14a**		**14b**	

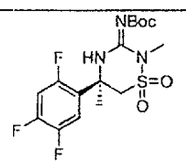
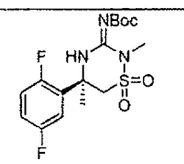
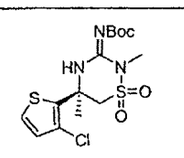
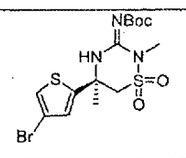
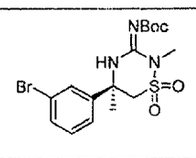
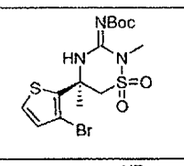
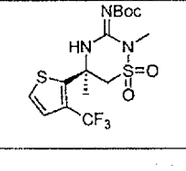
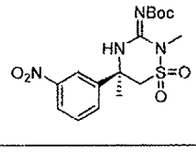
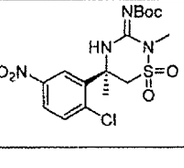
			MH+: 350.0, 1.72 min, D		
14c		14d			

Scheme 3:



To a solution of **Ex. 5** (1.60 g, 5.53 mmol) in CH_2Cl_2 was added Boc_2O (1.24 g, 5.68 mmol) and Et_3N (0.82 mL, 5.91 mmol). The resultant solution was stirred at RT overnight. The solution was washed with 1/2 saturated $NaHCO_{3\ (aq.)}$. The aqueous layer was back extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 70:30 hexanes:EtOAc) to afford the *tert*-butyl carbamate (1.74 g, 84% yield).

Table IIb: The following carbamates were prepared using similar procedures to that described in Scheme 3 using the appropriate starting materials.

Entries					
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4		5		6	
7		8		9	

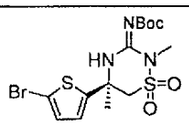
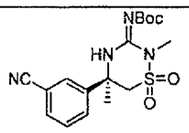
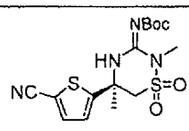
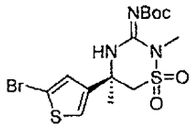
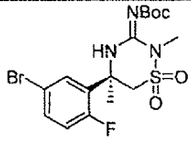
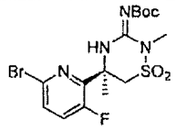
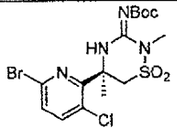
10		11		12	
13		14		15	
16					

Table IIc: The following example was prepared using a procedure similar to that described in Scheme 1b, using the following modified temperature profile: nitric acid addition at -40 degrees C, then warming to 0 degrees C.

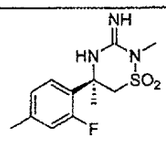
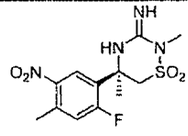
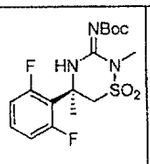
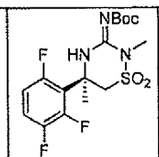
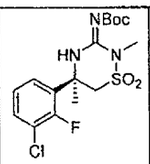
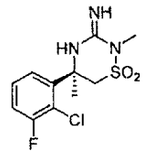
Example	Starting material	Product
14e	 Example 14d	

Table IId: The following thiadiazine dioxides were made according to methods similar to those in Schemes 1a and 3, with the noted exceptions:

Entries							
1[a,b]		2[a,b]		3[c]		Ex. 14f[d,e]	

a: (S)-2-Methyl-2-propanesulfinamide was used in Step 1 Scheme 1a instead of (R)-2-methyl-2-propanesulfinamide.

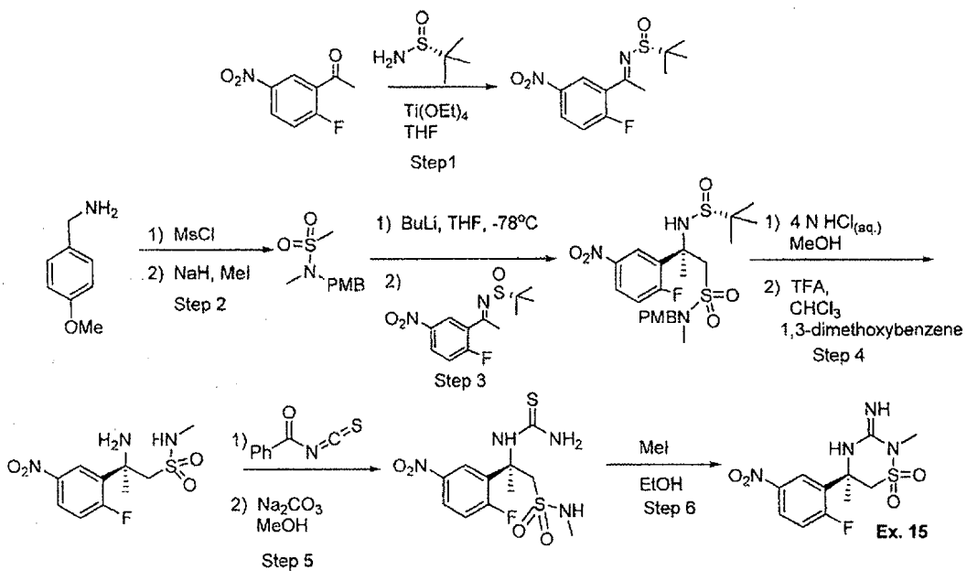
b: Re-crystallization from 95% MeOH / 5% water was used to remove a diastereomeric product after silica gel purification in Step 3 Scheme 1a.

c: SFC chromatography (TharSFC80, Chiralpak OD-H, 50 x 250 mm, 5 μm, 150 bar with 30% iPrOH, 250 g/min, 40 °C) used to remove a diastereomeric product after silica gel purification in Step 3 Scheme 1a.

d: SFC chromatography (TharSFC80, Chiralpak OJ-H, 50 x 250 mm, 5 μm, 150 bar with 25% iPrOH, 250 g/min, 40 °C) used to remove a diastereomeric product after silica gel purification in Step 3 Scheme 1a.

e: The product of Scheme 1a Step 4 was treated according to Scheme 3b to afford Example 14f directly, instead of employing Scheme 1a, Steps 5 and 6.

Scheme 3a:



Steps 1-4: These steps were performed using similar procedures to those described in steps 1-4 of Scheme 1a.

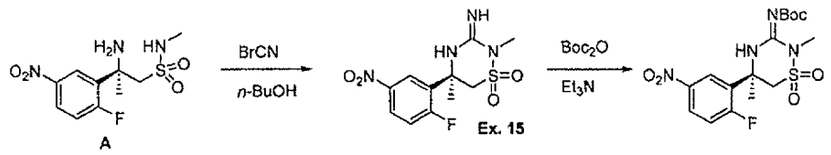
Step 5: To a solution of the amine from step 4 (10.5 g, 36 mmol) in CH_2Cl_2 (200 mL) was added benzoylisothiocyanate (4.3 mL, 1.1 eq.). The resulting solution was stirred at RT for 2.5 days. Additional benzoylisothiocyanate (0.86 mL, 0.2 eq.) was added and the solution was stirred at RT for an additional 2 hours. The solution was then concentrated *in vacuo*.

A portion of this material (6.5 g, ~14 mmol) was dissolved in MeOH (200 mL). To this solution was added $Na_2CO_{3\,(s)}$ (1.52 g, 14 mmol). The resultant mixture was stirred at RT for 45 min. After that time, a slight excess of HOAc was added to the solution. The mixture was then concentrated. The residue was partitioned between CH_2Cl_2 and ½ sat. $NaHCO_{3\,(aq.)}$. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried

over Na_2SO_4, filtered and concentrated. The thiourea (~ 4.9 g) was carried onto the next reaction without further purification.

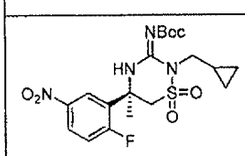
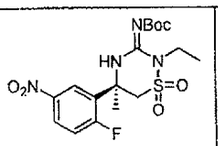
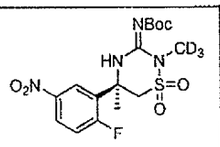
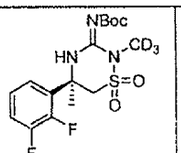
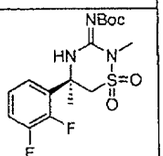
Step 6: Example 15 was prepared using a method similar to that described in Scheme 1a step 6.

Scheme 3b:

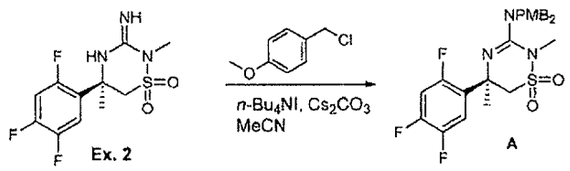


To a slurry of amine **A** (Scheme 3a step 4) (13.7 grams) in n-butanol (150 mL) was added a solution of cyanogen bromide (5M in MeCN). The resultant mixture was heated to reflux for 4 hours. The mixture was concentrated to 1/3 of the original volume. To the mixture was added Et_2O (200 mL). The resultant solid was removed via filtration and the solid was washed with Et_2O (2x). The solid was partitioned between EtOAc and sat. Na_2CO_3 (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 10.6 grams of **Ex. 15**. This material was converted to the t-butyl carbamate using a procedure similar to that described in Scheme 3.

Table IIe: The following thiadiazine dioxides were prepared using procedures similar to those described in Schemes 3a (entry 1), 3b (entries 2-5) and 3 using the sulfonamides shown in Table I and Scheme 1a.

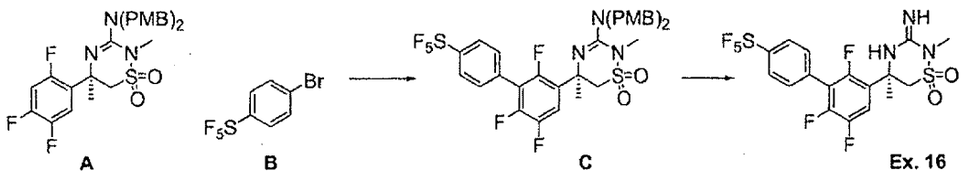
Entries				
				
1	2	3	4	5

Scheme 4:



To a solution of **Ex. 2** (3.8 g, 12.2 mmol) in MeCN (40 mL) was added 4-methoxybenzyl chloride (4.6 g, 29 mmol), Cs_2CO_3 (9.9 g, 31 mmol) and n-Bu_4NI (450 mg, 1.2 mmol). The resultant mixture was heated to reflux for 16 hours. After that time, additional 4-methoxybenzyl chloride (1.9 g, 12 mmol) and Cs_2CO_3 (4.4 g, 12 mmol) were added and the mixture was heated to reflux for an additional 4 hours. The mixture was then concentrated *in vacuo* at RT. The residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via flash chromatography (SiO_2: gradient elution 100:0 to 80:20 hexanes:EtOAc) to afford the bis-PMB compound **A** (4.9 g, 73%).

Scheme 5:

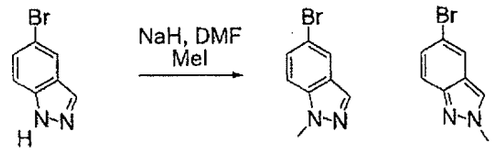


A 20 mL microwave vessel was flame-dried and cooled under vaccum, then backfilled with N_2, followed by two cycles of vacuum/N_2 backfill. NaHMDS (1 M in THF, 2.2 mL, 2.2 mmol) was added to a solution of thiadiazine dioxide **A** ((Scheme 4) 547 mg, 1.0 mmol) in dioxane (5 mL) at RT, and stirred for 30 min. A freshly prepared solution of $ZnCl_2$ (1.2 M in THF, 2.0 mL, 2.4 mmol) was added, and stirring continued for 30 min at RT. $Pd(OAc)_2$ (45 mg, 0.2 mmol), X-Phos (190 mg, 0.4 mmol) and arylbromide **B** (509 mg 1.80 mmol) were added and the reaction mixture was degassed (4 x vacuum/N_2), capped and placed into a preheated 100°C oil bath for 3h. The crude reaction was cooled to RT, diluted with EtOAc/water, filtered through a pad of celite, and the aqueous layer extracted with EtOAc (2x). The combined organic layers were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude residue that was subjected to silica gel chromatography

(0→30 % EtOAc/hexanes) followed by RP-HPLC conditions (monitoring at 220 nm) to give intermediate **C** (73 mg, 97 umol).

A solution of intermediate **C** (73 mg, 97 umol) in CH_3CN (4 mL) was heated to 75° C, and a solution of K_2HPO_4 (26 mg, 147 umol), KH_2PO_4 (20 mg, 147 umol) and $K_2S_2O_8$ (158 mg, 588 umol) in water (2 mL) was added via pipette. After 60 min at 75° C, the reaction mixture was cooled to RT and concentrated under vacuum. The residue was subjected to RP-HPLC conditions to give **Ex. 16** (TFA salt, 26 mg). LCMS data: (method D): t_R = 2.17 min, *m/e* = 510.0 (M+H).

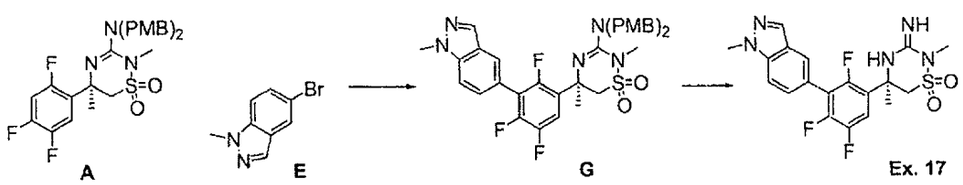
Scheme 6a:



D **E** R = Me **F**

Sodium hydride (60% in oil, 1.5 g, 37.5 mmol) was added to a solution of 5-bromoindazole **D** (6 g, 30.6 mmol) in DMF (60 mL) at RT. After stirring for 30 min, methyl iodide (2.83 mL, 45.9 mmol) was added and the reaction stirred for another 2 h at RT. The reaction was quenched with sat. $NaHCO_3$ (aq), extracted with EtOAc (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of *N*-1 and *N*-2 methylated 5-bromoindazoles **E** and **F**, which were separated by silica-gel chromatography using 0→30 % EtOAc/hexanes.

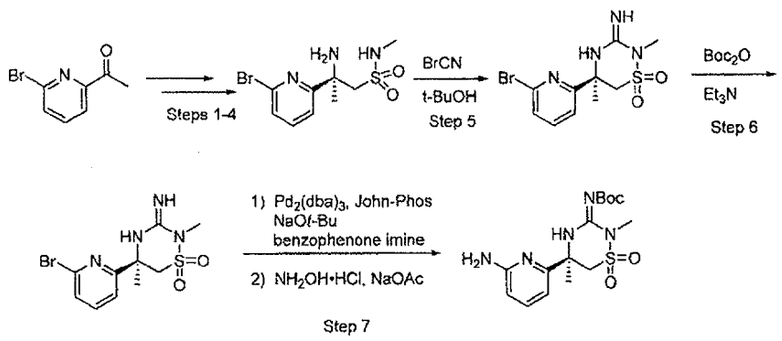
Scheme 6b:



A **E** **G** **Ex. 17**

Example 17 was prepared as described for **Example 16** in Scheme 5, substituting arylbromide **E** for **B**. LCMS data: (method C): t_R = 3.12 min, *m/e* = 438.2 (M+H).

Scheme 7a:



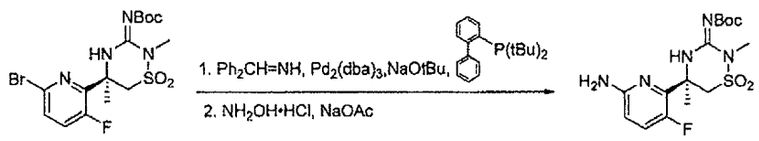
Steps 1-4: These steps were performed using similar procedures to those described in steps 1-4 of Scheme 1a.

Step 5: This step was performed using a procedure similar to that described in Scheme 3b except *t*-BuOH was used as the solvent instead of n-BuOH.

Step 6: The *t*-butyl carbamate was installed using a procedure similar to that described in Scheme 3.

Step 7: A mixture of the bromide (3.00 g, 6.92 mmol), benzophenone imine (1.39 mL, 8.30 mmol), $Pd_2(dba)_3$ (0.634 g, 0.692 mmol), John-Phos (0.413 g, 1.38 mmol), sodium *tert*-butoxide (2.13 g, 22.1 mmol), and toluene (51 mL) was degassed (vacuum/N_2). The mixture was then stirred at 65 °C under nitrogen for 3 h. After this time, the reaction mixture was cooled to room temperature and filtered through a pad of Celite and rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure. The residue was then dissolved in methanol (76 mL) and the resulting solution was charged with hydroxyl amine hydrochloride (2.16 g, 31.1 mmol) and sodium acetate (2.55 g, 31.1 mmol). The reaction mixture was stirred at room temperature for 40 min. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL), and brine (100 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0–100% ethyl acetate/heptane) to afford the amino pyridine (0.880 g, 34%).

Scheme 7b:



To a flame-dried flask was added a pyridyl bromide (Table IIb, Entry 15, 1.5 g, 3.3 mmol), $Pd_2(dba)_3$ (305 mg, 0.3 mmol), (2-biphenyl)di-*tert*-butylphosphine (200 mg, 0.7 mmol), sodium *tert*-butoxide (1.02 g, 0.011 mmol), benzophenone imine (670ul, 4 mmol), and toluene (21 mL). The mixture was evacuated under vacuum and back-filled with N_2 (3X). The mixture was stirred at 60 °C for 1 h. After filtration through celite, the filtrate was concentrated. The crude residue was dissolved in 36 mL of methanol, and hydroxyl amine hydrochloride (458 mg, 6.6 mmol) and sodium acetate (541 mg, 6.6 mmol) were added. The reaction was stirred for 35 min and then quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the combined organic portions were dried over magnesium sulfate and concentrated. The crude residue was purified by a flash silica column (50% ethyl acetate/hexane) to get an aminopyridine product (730 mg, 68%).

Table IIIa: The following amino-pyridines were prepared using similar procedures to those described in Scheme 7a using the appropriate ketones from Table Ib.

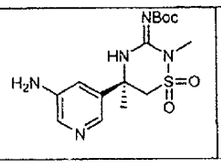
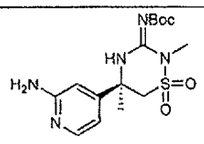
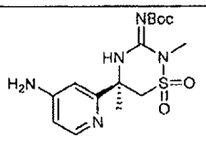
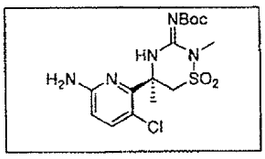
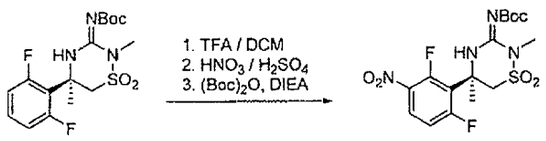
Entries					
1		2		3	

Table IIIb: The following compound was prepared from the bromide (Table IIb entry 16) using methods similar to those described in Scheme 7b:



Scheme 7c:



To a solution of a halophenyl thiadiazine (Table IId, entry 1: 2.31 g, 5.9 mmol) in 5 mL of DCM was added 1 mL of TFA. The mixture was stirred for 4 h and then concentrated. At 0 °C, to a solution of this crude residue in 4 mL of sulfuric acid was carefully added a mixture of 0.5 mL of fuming nitric acid and 1.2 mL of sulfuric acid. The mixture was stirred at 0 °C for 2 h and then poured into 150 mL of ice. The mixture was neutralized by carefully adding saturated sodium bicarbonate solution and solid sodium hydroxide. The resulting mixture was extracted with ethyl acetate, and the combined organic layers were dried over magnesium sulfate and concentrated. This crude residue was dissolved in 20 mL of DCM, and $(Boc)_2O$ (1.29g, 5.9 mmol), and DIEA (2.56 mL, 14.75 mmol) were added. The reaction was stirred overnight, and then quenched with 1N HCl. The mixture was extracted with DCM, the organic portions were combined, dried over magnesium sulfate, and concentrated. The crude residue was purified by a flash silica column (25% ethyl acetate/hexane) to give a nitrophenyl thiadiazine product (1.93 g, 76% yield).

Table IIIc: The following compounds were made using methods similar to those described in Scheme 7c starting from the appropriate starting materials shown in Table IIb:

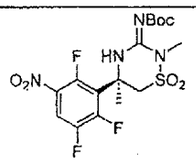
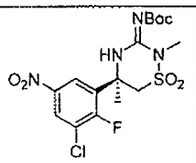
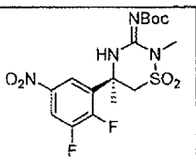
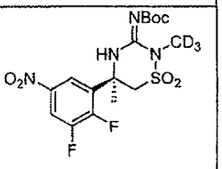
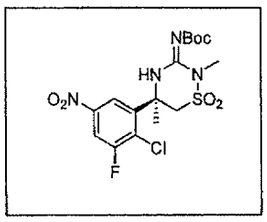
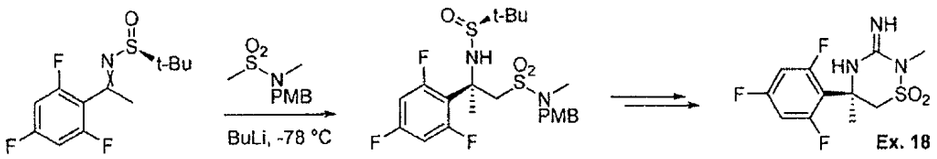
Entries			
			
1	2	3	4

Table IIId: The following compound was made from Ex. 14f using methods similar to those described in Scheme 7c, omitting the initial treatment with TFA:



Scheme 8:



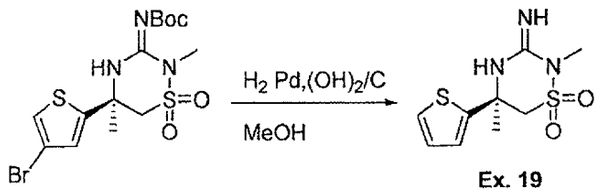
To a solution of N-(4-methoxybenzyl)-N-methylmethanesulfonamide (26.8 g, 117 mmol) in THF (200 mL) at -78 °C was added n-butyllithium (2.5 M in hexanes, 47 mL, 118 mmol) over 10 minutes. After the addition was complete, the mixture was allowed to stir at -78 °C for 1h.

To this mixture was then added a solution of (S)-2-methyl-N-(1-(2,4,6-trifluorophenyl)ethylidene)propane-2-sulfinamide (21.6 g, 77.9 mmol, prepared from 2,4,6-trifloroacetophenone and (S)-2-methyl-2-propanesulfinamide according to Scheme 1a, Step 1) in THF (150 mL) at -78 °C. The resulting mixture was allowed to stir at -78 °C for 4h. At that time, the reaction was quenched by rapid dilution with water (~ 400 mL). The mixture was then warmed to RT, further diluted with EtOAc and brine. The phases were separated, and the aqueous layer was extracted with EtOAc (4X). The organic portions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. This crude residue was subjected to column chromatography (600g silica, 100 mL/min, 0% to 60% EtOAc/hexanes) to give (R)-2-((S)-1,1-dimethylethylsulfinamido)-N-(4-methoxybenzyl)-N-methyl-2-(2,4,6-trifluorophenyl)propane-1-sulfonamide as a 4:1 mixture with its diastereomer (14.5 g total mass, 37%).

This material was further subjected to SFC chromatography (TharSFC80, Chiralpak OJ-H, 21 x 250 mm, 5 μm, 200 bar with 5% MeOH, 55 g/min, 35 °C) to give (R)-2-((S)-1,1-dimethylethylsulfinamido)-N-(4-methoxybenzyl)-N-methyl-2-(2,4,6-trifluorophenyl)propane-1-sulfonamide).

The above material was treated according to Scheme 1a, Steps 4–6 to afford Example 18, dihydro-2,5(R)-dimethyl-5-(2,4,6-trifluorophenyl)-2H-1,2,4-thiadiazin-3(4H)-imine-1,1-dioxide. LCMS (conditions A): t_R = 1.45 min, *m/e* = 308.2 (M+H).

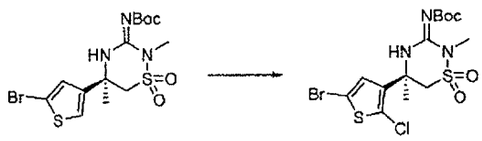
Scheme 9:



Ex. 19

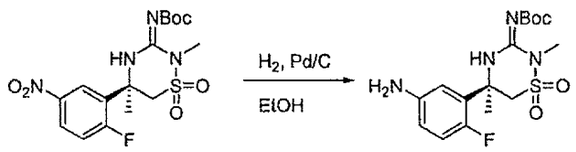
To a degassed solution the *tert*-butyl carbamate (Scheme 3) (348 mg, 0.794 mmol) in MeOH (10 mL) was added 20% $Pd(OH)_2/C$ (50% water) (52 mg, 0.074 mmol). The flask was purged with H_2 and allowed to stir at RT under a balloon of H_2 for 2.75 hours. The mixture was purged with N_2, filtered through Celite and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 95:5 CH_2Cl_2:MeOH) to afford **Ex. 19** (69 mg). LCMS (conditions A): t_R = 2.00 min, *m/e* = 260.1 (M+H).

Scheme 9a:



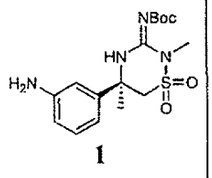
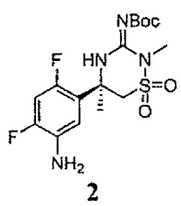
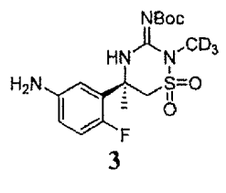
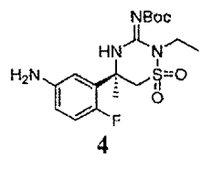
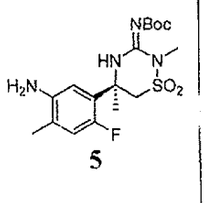
To the bromide (Table IIb, entry 13) (0.8 g, 1.8 mmol) in DMF (6 mL) was added *N*-chlorosuccinimide (0.7 g, 5.5 mmol). The reaction was warmed to 60°C and stirred for 5 h. Ethyl acetate was added and the mixture was washed with saturated $NaHCO_3$ (aq), water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide a white foam that was further purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid) to afford the chlorothiophene (0.63 g, 1.3 mmol).

Scheme 10:

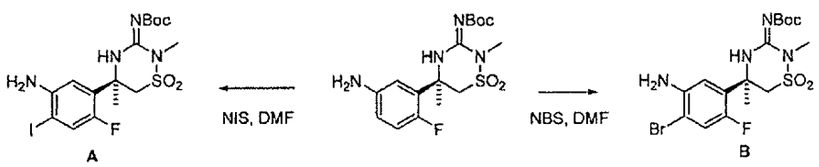


A solution of the nitro compound (Scheme 3b) (2.50 g, 6.0 mmol) in EtOH (150 mL) was degassed by bubbling N_2 through the solution for 3 min. To this solution was added Pd/C (10% w/w, 50% H_2O, 698 mg.). The mixture was placed under an atmosphere of N_2. The atmosphere was evacuated and back-filled with H_2 (3x). The resulting mixture was stirred at RT under a H_2 balloon for 2 h. The mixture was purged by bubbling N_2 through it, filtered through Celite and concentrated. The product was purified by filtering through a small plug of silica gel column eluting with EtOAc to afford the aniline (2.2g, 97%) .

Table IV: The following anilines were prepared from the corresponding nitro compounds using a procedure similar to that described in Scheme 10.

Entries				
 1	 2	 3	 4	 5

Scheme 10a:

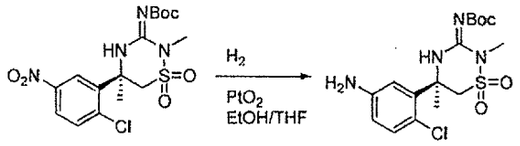


Iodoaniline A preparation: NIS (2.52 g, 11.2 mmol) was added at 0°C to a solution of the aniline (3.6 g, 9.31 mmol, Scheme 10) in DMF (40 mL). After 60 minutes at 0°C and 60 min at RT, the reaction was quenched with saturated aq. $NaHCO_3$ (aq), extracted with EtOAc (3 x), and the combined organic layers dried over Na_2SO_4. After removal of the volatiles under

reduced pressure, the residue was subjected to silica gel chromatography (gradient elution 100:0 to 70:30 hexanes:EtOAc) to give the iodoaniline (3.2 g, 67%).

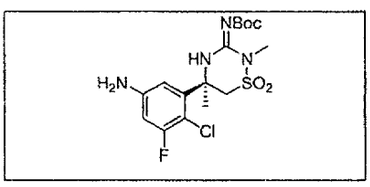
Bromoaniline **B** preparation: NBS (1.05 g, 6.21 mmol) was added at RT to a solution of the aniline (2.0 g, 5.17 mmol, Scheme 10) in DMF (21 mL). After 30 minutes, the reaction was quenched with 10% aq. Na_2SO_3 (aq), diluted with EtOAc, and the organic layer was washed with saturated aq. $NaHCO_3$ (2 x), brine (1x) and dried over Na_2SO_4. After removal of the volatiles under reduced pressure, the residue (2.57 g) was subjected to silica gel chromatography (gradient elution 100:0 to 50:50 hexanes:EtOAc) to give the bromoaniline (2.065 g, 86%).

Scheme 11a:

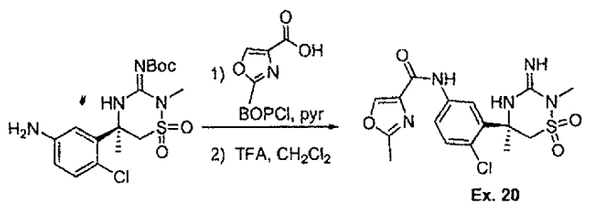


A solution of the nitro compound (Entry 9, Table IIb) (515 mg, 1.19 mmol) in 1:1 EtOH:THF (24 mL) in a pressure vessel was degassed by bubbling N_2 through it for 5 min. To this solution was added PtO_2 (27 mg, 0.12 mmol). The vessel was sealed. The vessel was then evacuated and backfilled with N_2 (3x). The vessel was then evacuated and purged with H_2 (3x). The vessel was pressurized to 60 psi with H_2 and shaken at RT overnight. After that time, the vessel was purged with N_2. The mixture was then filtered through Celite. The solvent was removed *in vacuo* to afford the aniline (500 mg, 100%).

Table IVa: The following compound was prepared from the corresponding nitro compound (Table IIId) according the methods described in Scheme 11a:



Scheme 11b:

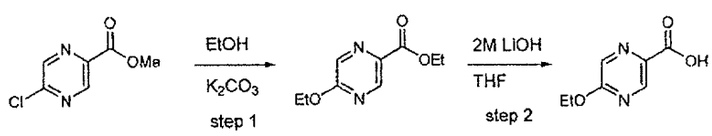


Ex. 20

Step 1: To a flask containing the aniline (Scheme 11a) (100 mg, 0.25 mmol) and 2-methyl-1,3-oxazole-4-carboxylic acid (47 mg, 0.37 mmol) was added BOPCl (145 mg, 0.57 mmol). The flask was sealed and purged with N_2. To the flask was added pyridine (1.0 mL). The resultant solution was stirred at RT for 1 hour. After that time, the solution was partitioned between EtOAc and water. The mixture was filtered through Celite to remove the solids. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 65:35 hexanes:EtOAc) to afford the amide (81 mg, 64%).

Step 2: To a solution of the amide from step 1 (81 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL). The resultant solution was stirred at RT for 2 hours. The solution was concentrated *in vacuo* to afford **Ex. 20** (83 mg) as the trifluoroacetate salt. LCMS data: (method D): t_R = 1.75 min, *m/e* = 412.0 (M+H).

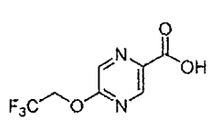
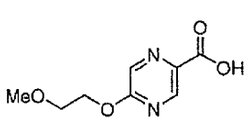
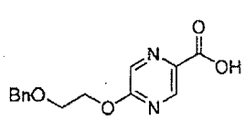
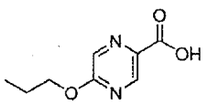
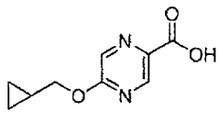
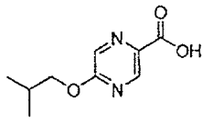
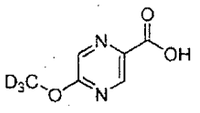
Scheme 11c:



Step 1: To a slurry of methyl 5-chloropyrazine-2-carboxylate (250 mg, 1.45 mmol) in EtOH (5 mL) was added potassium carbonate (300 mg, 2.18 mmol). The resultant solution was stirred at RT for 2 hours. The mixture was concentrated. The residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford ethyl 5-ethoxypyrazine-2-carboxylate (110 mg, 39%) as a yellow solid.

Step 2: To a solution of the material from step 1 (110 mg, 0.60 mmol) in THF (3 mL) was added a solution of LiOH (2M in water, 0.90 mL, 1.8 mmol). The solution was stirred at RT for 1 h. The solution was adjusted to pH 1 using 1M HCl (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the acid (75 mg, 74%).

Table IVb: The following pyrazine carboxylic acids were prepared using a procedure similar to that described in Scheme 11c using the appropriate alcohol in step 1. Modifications for specific examples are listed below the table.

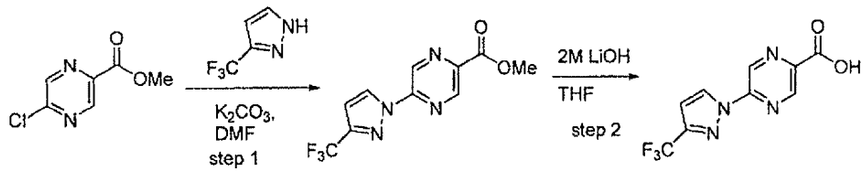
Entries					
1		2[a]		3[b]	
4[a]		5[b]		6[c]	
7					

[a] Step 1 modification: the ether was purified via flash chromatography (SiO_2 gradient elution 100:0 to 70:30 hexanes:EtOAc).

[b] Step 1 modification: the ether was purified via flash chromatography (C_{18} gradient elution 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid).

[c] Step 2 modification: the pyrazine acid was purified via flash chromatography (C_{18} gradient elution 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid).

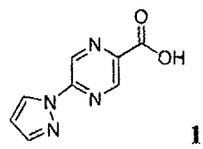
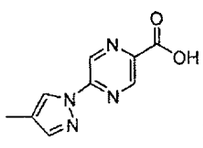
Scheme 11d:



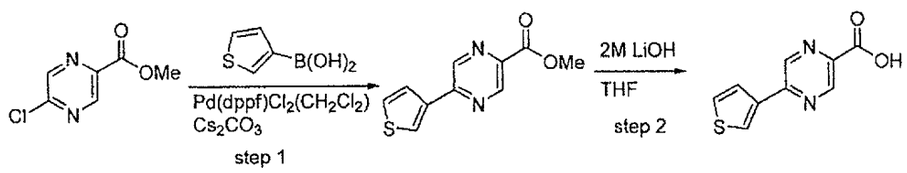
Step 1: To a solution of methyl 5-chloropyrazine-2-carboxylate (500 mg, 2.90 mmol) and 3-(trifluoromethyl)-1H-pyrazole (591 mg, 4.35 mmol) in DMF (7 mL) was added potassium carbonate (591 mg, 4.35 mmol). The resultant solution was stirred at RT overnight. The mixture was partitioned between water and EtOAc and separated. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the biaryl ester (560 mg, 71%).

Step 2: The acid was formed using a procedure similar to that described in Scheme 11c step 2.

Table IVc: The following pyrazine carboxylic acids were prepared using a procedure similar to that described in Scheme 11d using the appropriate pyrazole.

Entries	
 1	 2

Scheme 11e:

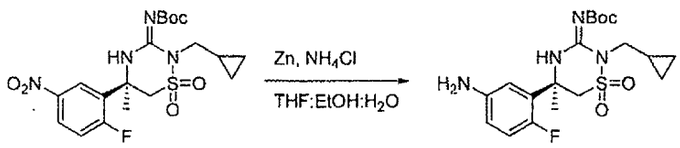


Step 1: A degassed mixture of 5-chloropyrazine-2-carboxylate (500 mg, 2.90 mmol), Cs_2CO_3 (1.1 g, 3.5 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (237 mg, 0.29 mmol) and thiophen-3-ylboronic acid (445 mg, 3.5 mmol) in dioxane (10 mL) was heated to reflux for 2 hours. The mixture was concentrated. The residue was partitioned between water and CH_2Cl_2 and filtered through

Celite. The aqueous layer of the filtrate was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified via flash chromatography (SiO_2 gradient elution 100:0 to 10:90 hexanes:EtOAc) to afford the biaryl ester (560 mg, 88%).

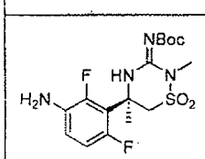
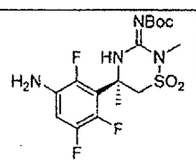
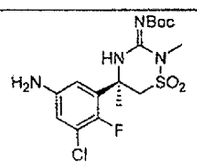
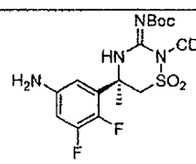
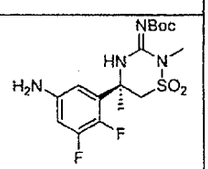
Step 2: The acid was formed using a procedure similar to that described in Scheme 11c step 2.

Scheme 11f:

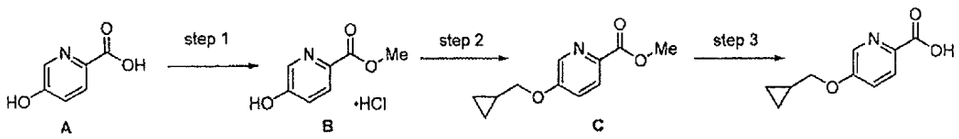


A solution of the nitro compound (Table IIe, entry 1, 1.70 grams, 3.7 mmol) in THF:EtOH:H_2O (30 mL, 3:1:0.3) was degassed by bubbling N_2 through the solution for 3 min. To the solution was added Zn (2.4 g, 37 mmol) and NH_4Cl (996 mg, 18 mmol). The resultant mixture was heated to reflux under an atmosphere of N_2 for 3 hours. The mixture was filtered through celite and concentrated. The residue was purified via reverse phase flash chromatography (C_{18}, gradient elution 90:10:0.1 to 0:100:0.1 H_2O:MeCN:formic acid). The resultant formate salt was partitioned between EtOAc and sat $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the aniline (847 mg, 54%).

Table IVd: The following compounds were prepared according the methods described in Scheme 11f except they were purified via SiO_2 flash chromatography:

Entries				
				
1	2	3	4	5

Scheme 11g:

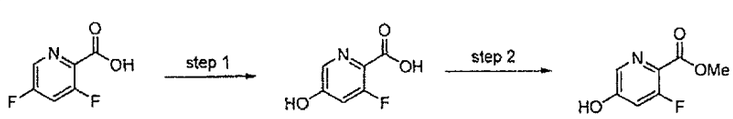


Step 1: To 5-hydroxypyridine-2-carboxylic acid (4.40 g, 32 mmol) suspended in methanol (77 mL) was added thionyl chloride (6.9 mL, 95 mmol) dropwise. The reaction was warmed to reflux and stirred for 22 h. After cooling to room temperature, the mixture was concentrated *in vacuo* to provide the methyl ester (5.71 g, 95%).

Step 2: To the methyl ester (0.40 g, 2.1 mmol) formed in step 1 in DMF (3 mL) was added potassium carbonate (0.88 g, 6.3 mmol) and cyclopropylmethyl bromide (0.41 mL, 4.2 mmol). The reaction was warmed to 65 °C and stirred for 18 h. The reaction was cooled to room temperature and then concentrated *in vacuo*. The residue was triturated with EtOAc and filtered washing with EtOAc. The filtrate was concentrated *in vacuo* to provide a crude product that was purified by silica gel chromatography (0-50% EtOAc/hex over 30 minutes) to provide the cyclopropylmethyl ether (0.27 g, 61%).

Step 3: To the product of step 2 (0.27 g, 1.3 mmol) in THF (2 mL) was added 2N $LiOH_{(aq.)}$ (1.9 mL, 3.9 mmol). The reaction was stirred at room temperature for 2 h. The pH was adjusted to pH 4 using saturated aqueous citric acid. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the carboxylic acid (0.23 g, 94%).

Scheme 11h:

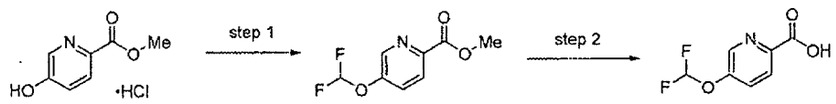


Step 1: To 3,5-difluoropyridine-2-carboxylic acid (3.0 g, 19 mmol) in THF (30 mL) in a glass tube reaction vessel was added 2N $LiOH_{(aq)}$. The reaction mixture was capped and warmed to 100 °C. The reaction was stirred for 18 h and then cooled to room temperature. TFA (5 mL) was added and the reaction was concentrated *in vacuo*. The residue was purified by reverse phase chromatography [C18 (360g) 0.1% formic acid/water for 20 minutes followed by 0-

100% 0.1% formic acid/acetonitrile//0.1% formic acid/water] to provide the hydroxy pyridine (2.1 g) as a ~1:1 mixture of starting material and product. The mixture was carried on directly.

Step 2: To the hydroxy pyridine prepared in the previous step (2.1 g) in methanol (20 mL) was added thionyl chloride (2.2 mL, 31 mmol). The reaction was warmed to 70 °C and stirred for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purified by reverse phase chromatography [C18 (205 g), 0-100% over 20 minutes 0.1% formic acid/acetonitrile//0.1% formic acid/water] to provide the methyl ester (1.0 g, 31% over 2 steps).

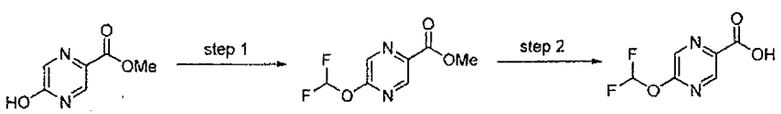
Scheme 11i:



Step 1: To the methyl 5-hydroxypicolinate hydrochloride prepared in step 1 of Scheme 11g (0.21 g, 1.1 mmol) in a glass tube reactor in acetonitrile (4 mL) was added water (4 mL), potassium carbonate (5.5 g, 40 mmol) and 2-chloro-2,2-difluoroacetophenone (1.0 g, 5.5 mmol). The reaction vessel was capped and warmed to 80 °C. The reaction was stirred at 80 °C for 3h and cooled to room temperature. The mixture was filtered washing with ether. The filtrate was washed with ether. The ether washes were combined and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a tan oil. The oil was purified by silica gel chromatography (0-40% EtOAc/hex over 30 minutes) to provide the ether (0.13 g, 60%).

Step 2: Using the procedure described in step 3 of Scheme 11g, the product of step 1 was converted to the carboxylic acid.

Scheme 11j:

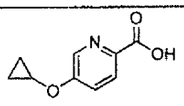
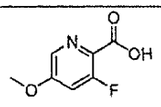
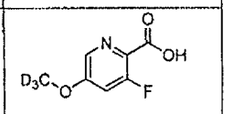
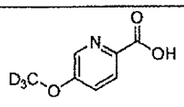
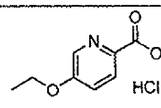
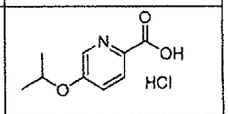
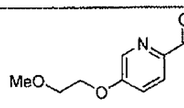
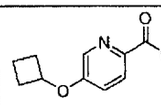
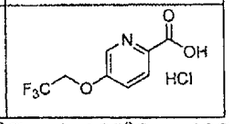


Step 1: To 5-hydroxypyrazine-2-carboxylic acid methyl ester (2.0 g, 13 mmol) in a glass tube reaction vessel in DMF (26 mL) was added potassium carbonate (5.3 g, 39 mmol) and sodium 2-chloro-2,2-difluroacetate (4.0 g, 26 mmol). The reaction vessel was capped and warmed to 100 °C. The reaction was stirred for 30 minutes and cooled to room temperature. The

reaction was filtered washing with EtOAc. The filtrate was concentrated *in vacuo*. The residue was taken up into EtOAc and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-40% EtOAc/hex) to give methy-5-(difluoromethoxy)pyrazine-2-carboxylate (0.09 g, 0.46 mmol) (0.40 g, 20%).

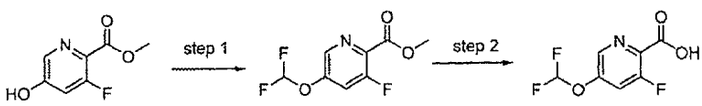
Step 2: To the product of step 1 (0.09 g, 0.46 mmol) was added 3N $HCl_{(aq)}$. The reaction was heated in a sealed microwave reactor vial to 100 °C for 2 h. The reaction was concentrated in vacuo to provide the carboxylic acid (0.88 g, 100%).

Table IVf: The following pyridine carboxylic acids were prepared from either intermediate **B**, Scheme 11g or the hydroxypyridine from Scheme 11h using conditions similar to those described in Scheme 11g steps 2 and 3. Modifications of the experimental conditions are noted below the table.

Entry		Entry		Entry	
1[a]		**2**[b]		**3**[b]	
4[b]		**5**[c, g]		**6**[c, g]	
7[f]		**8**[d]		**9**[e]	

Alkylation conditions: a: Cs_2CO_3, NaI, 150°C, 7 h; b: rt; c: 45°C; d: 100°C; e:130°C, microwave, 1 h; f: 70°C.
Hydrolysis conditions: g: See Scheme 11j, step 2.

Scheme 11k:

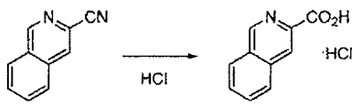


Step 1: To the hydroxypyridine prepared in Scheme 11h (0.19 g, 1.1 mmol) in acetonitrile (4 mL) and water (4 mL) was added potassium carbonate (5.5 g, 40 mmol) and 2-chloro-2,2-difluoroacetophenone. The glass reaction tube was sealed and warmed to 80 °C. After 3.5 h,

the reaction was cooled to room temperature and filtered washing with EtOAc. The filtrate was extracted with ether. The combined ether layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide product (0.15 g, 60%).

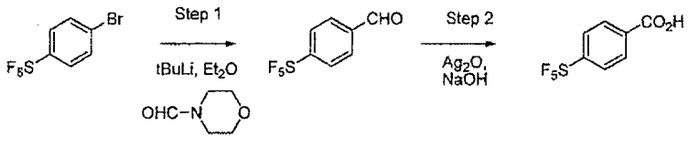
Step 2: The product of step 1 was converted to the carboxylic acid using the conditions found in step 3 of Scheme 11g.

Scheme 11l:



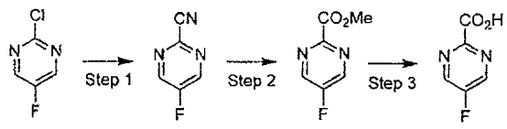
3-Cyanoisoquinoline (1.047 g, 6.79 mmol) was suspended in 6 M HCl (aq) (50 mL) and refluxed at 95°C for 18 h. The reaction was cooled to RT, and the volatiles removed under vacuum to provide the carboxylic acid (2.07 g) that was used as is.

Scheme 11m:



4-Pentafluorosulfur benzoic acid was obtained in two steps from 4-bromophenyl sulfurpentafluoride according to the literature procedure by Zarantonello et al., *J. Fluor. Chem.* **2007**, *128*, 1449-1453.

Scheme 11n:



Step 1: To 2-chloro-5-fluoropyrimidine (2 g, 15 mmol) in a 250-mL round bottom flask was added DMA (8 mL), tris(dibenzylideneacetone)dipalladium (0.544 g, 0.6 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.67 g, 1.2 mmol), zinc cyanide (1.15 g, 9.8 mmol), and zinc dust (0.237 g, 3.62 mmol). The flask was capped, flushed with nitrogen, and stirred for 2.5 h at 100°C. The reaction was cooled to room temperature, filtered through celite, and

washed with DCM. The filtrate was poured into water and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hexanes over 20 minutes) to provide the nitrile compound (0.58 g, 31%).

Step 2: To the nitrile compound prepared in Step 1 (0.51 g, 4.14 mmol) stirring in 5 mL MeOH was added 5 mL conc. HCl. The reaction was fitted with a reflux condenser and heated at 80°C for 2 hours, then cooled to room temperature. Saturated aqueous sodium bicarbonate was added and stirred for 1 hour at room temperature. The mixture was acidified to pH 4 using 1 N HCl (aq) and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the methyl ester (0.256 g, 40%).

Step 3: To the methyl ester compound prepared in Step 2 (0.256 g, 1.64 mmol) in 6 mL 1:1:1 THF: H_2O: MeOH was added LiOH hydrate (0.272 g, 4.04 mmol), and the mixture stirred at room temperature for 1 hour. The reaction was acidified to pH 4 using 1 N HCl (aq) and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the carboxylic acid (0.136 g, 58%).

Table IVg: The following acids were made using methods similar to those described in Scheme 11n using the appropriate aryl chloride (entries 1-3) or bromide (entries 4 and 5):

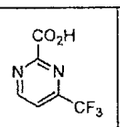
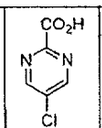
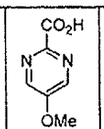
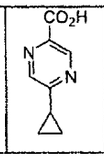
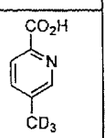
Entries									
1		2		3		4		5	

Table IVh: The following acid was made using methods similar to those described in Scheme 11n, Step 3:

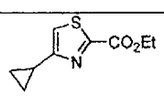
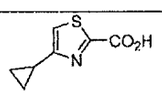
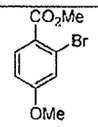
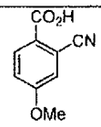
Entry	Starting material	Acid
1		

Table IVi: The following acid was made according to methods similar to those described in Scheme 11n, using Step 1 and then Step 3, omitting Step 2:

Entry	Starting material	Acid
1		

Scheme 11o:

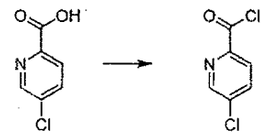


To 2-bromo-5-(methyl-D_3)-pyrazine (400 mg, 2.27 mmol) stirring in 8 mL anhydrous THF at -78 °C under N_2 atmosphere was slowly added *n*-BuLi (2.5 M in hexanes, 1.14 mL, 2.85 mmol). The reaction was stirred for 30 minutes at this temperature, upon which carbon dioxide was bubbled through the solution for 15 minutes via cannulating needle. The cold bath was removed and the reaction allowed to come to room temperature slowly over 1 hour. Water was then added and the reaction was extracted with ethyl acetate. The organics were combined, dried ($MgSO_4$), and concentrated *in vacuo* to provide an oil (120 mg, 38%) that was used without further purification.

3-Fluoro-5-(trifluoromethyl)picolinic acid was prepared from 2-bromo-3-fluoro-5-(trifluoromethyl)pyridine using a procedure similar to that described above in Scheme 11o.



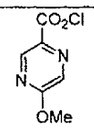
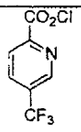
Scheme 11p:



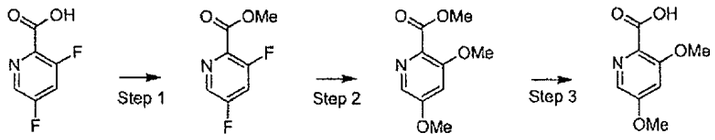
To 5-chloropicolinic acid (0.3 g, 1.9 mmol) stirring at room temperature in 6 mL THF and 1 drop of DMF was slowly added dropwise oxalyl chloride (0.48 mL, 5.7 mmol). Vigourous

outgassing was observed. The reaction was stirred at room temperature for 1.5 hours, then concentrated to dryness *in vacuo* and the product used without further purification.

Table IVj: The following acid chlorides were made using methods similar to those described in Scheme 11p from the appropriate carboxylic acid.

Entries	
	
1	**2**

Scheme 11q:

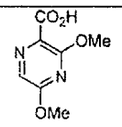
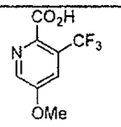


Step 1: To 3,5-difluoropyridine-2-carboxylic acid (2 g, 12.6 mmol) stirring in 20 mL 4:1 toluene:MeOH at room temperature was slowly added dropwise trimethylsilyldiazomethane (2.0 M in hexanes, 15.1 mmol, 7.5 mL). The reaction was allowed to stir for 30 minutes, and then was concentrated to dryness *in vacuo* and used without further purification.

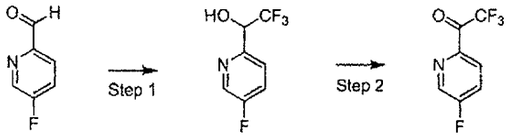
Step 2: To the methyl ester prepared in step 1 (1.09 g, 6.3 mmol) stirring at room temperature in 20 mL MeOH in a 350-mL sealed vessel was added 25 weight % sodium methoxide in methanol (3.4 g sodium methoxide, 13.6 g solution, 63 mmol). The reaction was flushed with nitrogen, sealed, and stirred 16 hours in a 100°C oil bath. The next day the reaction was cooled to room temperature and acidified to pH 4 using 1 N HCl. The solution was extracted with 1:1 EtOAc:THF (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes over 20 minutes) to provide the desired *bis*-methoxy compound (0.53 g, 43%).

Step 3: The methyl ester was converted to the carboxylic acid using methods similar to those described in Scheme 11n, Step 3.

Table IVk: The following acids were made using methods similar to those described in Scheme 11q using the appropriate aryl chloride:

Entries	
	
1	**2**

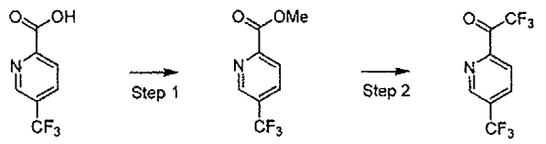
Scheme 11r:



Step 1: To 2-fluoro-5-formylpyridine (1.57 g, 12.55 mmol) stirring in anhydrous THF (20 mL) at 0°C under a nitrogen atmosphere was slowly added (trifluoromethyl)-trimethylsilane (2.67 g, 18.78 mmol). The mixture was stirred at 0°C for 15 minutes, and then tetrabutylammonium fluoride (1.0 M in THF, 31.38 mL, 31.38 mmol) was slowly added dropwise, upon which the ice bath was removed, and the reaction was allowed to stir at room temperature overnight (total reaction time 16 hours). The reaction was then poured into water and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes over 20 minutes) to provide the trifluoromethyl alcohol product (2.01 g, 82%).

Step 2: To the trifluoromethyl alcohol prepared in step 1 (1 g, 5.12 mmol) stirring in anhydrous DCM (20 mL) was added Dess-Martin periodinane (2.63 g, 6.14 mmol). The reaction was stirred at room temperature overnight (total reaction time 16 hours). Hexanes were added upon which a precipitate formed. The solid was filtered off and washed with DCM. The filtrate was taken and poured into saturated aqueous sodium bicarbonate and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes over 20 minutes) to provide the trifluoromethyl ketone product (0.453 g, 46%).

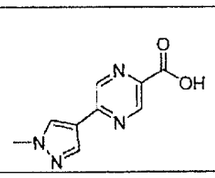
Scheme 11s:



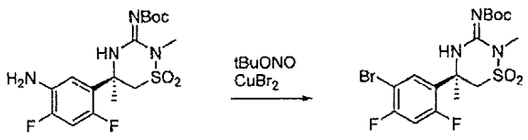
Step 1: The carboxylic acid (1.5 g, 7.84 mmol) was converted to the methyl ester using methods similar to those described in Scheme 11q, Step 1. The crude reaction was evaporated to dryness *in vacuo*, and purified by silica gel chromatography (0-30% EtOAc/hexanes over 20 minutes, 30-40% EtOAc/hexane from 20-30 minutes) to provide the methyl ester product as a solid (1.02 g, 63%).

Step 2: To a mixture of methyl 5-(trifluoromethyl)pyridine-2-carboyxlate prepared above (0.2 g, 0.97 mmol) and (trifluoromethyl)trimethylsilane (0.173 g, 1.22 mmol) stirring at -78°C in pentante (3 mL) under a nitrogen atmosphere was slowly added tetrabutylammonium fluoride (1.0 M in THF, 25 μL, 0.024 mmol). The reaction was allowed to come to room temperature and stirred overnight (total reaction time 16 hours). At that time, 2 N HCl was added, and the mixture was stirred vigorously at room temperature for 2 hours. The solution was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes over 20 minutes) to provide the trifluoromethyl ketone product (0.084 g, 35%).

Table IVl: The following pyrazine carboxylic acid was prepared using a procedure similar to that described in Scheme 11e.

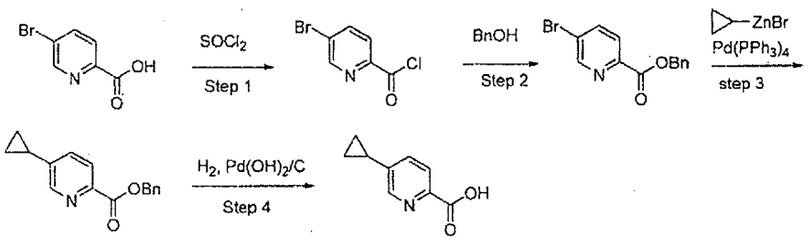
Entry	
1	

Scheme 11t:



A large microwave tube was charged sequentially with MeCN (9 mL), *tert*-butyl nitrite (0.15 mL, 1.2 mmol), and copper(II) bromide (0.331 g, 1.48 mmol). The tube was crimp sealed and immersed in an oil bath at 60 °C. To the resulting black-green mixture was added a solution of 1,1-dimethylethyl [5(R)-(5-amino-2,4-difluorophenyl)dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-3(4H)-ylidene]carbamate (Table IV, Entry 2, 500 mg, 1.24 mmol) in MeCN (3 mL) via syringe over ~ 2 min. After the addition was complete, the reaction was stirred at 60 °C for 20 min. At that time, the reaction was cooled, diluted with EtOAc, and filtered through Celite. The filtrate was diluted with water and EtOAc. The phases were separated and the aqueous layer was extracted 2X with EtOAc. The organic portions were combined, washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. This crude sample was subjected to column chromatography (80 g silica, 60 mL/min, 0% to 50% EtOAc/hexanes) to give product 1,1-dimethylethyl [5(R)-(5-bromo-2,4-difluorophenyl)dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-3(4H)-ylidene]carbamate (0.30 g, 52%).

Scheme 11u:



Step 1: To a suspension of 5-bromopicolinic acid (20.2 g, 100 mmol) in 200 mL of toluene was added thionyl chloride (11 mL, 150 mmol). The mixture was stirred at room temperature for 20 min and then heated to reflux for 30 min. The resulting solution was cooled to room temperature and concentrated to dryness. The crude product 5-bromopicolinoyl chloride was used directly in the next step.

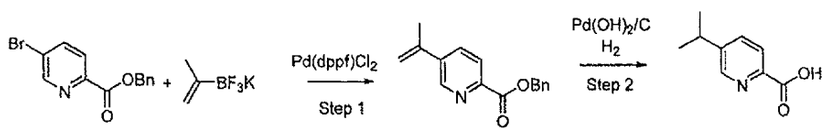
Step 2: After addition of THF (200 mL) and Et_3N (42 mL) to the above residue, the mixture was cooled in an ice-water bath. Benzyl alcohol (31.1 mL, 300 mmol) was added slowly. The mixture was warmed up to room temperature and stirred overnight.

The reaction mixture was diluted with ether, washed with sat. $NaHCO_{3(aq.)}$, H_2O, brine and then dried ($MgSO_4$). After concentration and crystallization, the desired product benzyl 5-bromopicolinate (20.6 g) was obtained.

Step 3: To a solution of benzyl 5-bromopicolinate (876 mg, 3.0 mmol) in THF (10 mL) was added $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) under N_2. After addition of a solution of cyclopropylzinc bromide in THF (0.5 M, 10 mL), the mixture was heated at 80 °C for 3 hours and then cooled to room temperature. The reaction mixture was quenched with sat. NH_4Cl (aq) and extracted with EtOAc (3x). The organic layer was washed with sat. $NaHCO_{3(aq.)}$, brine, and dried ($MgSO_4$). The product benzyl 5-cyclopropylpicolinate (510 mg) was obtained by silica gel chromatography (elution with 0-15% EtOAc/Hex, then 15% EtOAc/Hex).

Step 4: To a solution of benzyl 5-cyclopropylpicolinate in MeOH (15 mL) was added 20% $Pd(OH)_2/C$ (100 mg). The hydrogenolysis with H_2 was carried out at room temperature under a H_2 balloon. The desired product 5-cyclopropylpicolinic acid (305 mg) was obtained after filtration and concentration.

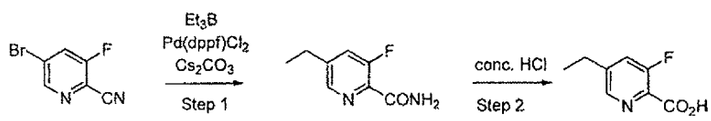
Scheme 11v:



Step 1: A mixture of benzyl 5-bromopicolinate (2.92 g, 10 mmol), potassium isopropenyl trifluoroborate (3.05 g, 21 mmol), $Pd(dppf)Cl_2$ (445 mg, 0.54 mmol), and Et_3N (1.4 mL) in isopropyl alcohol (20 mL) was degassed with N_2 and heated at 80 °C for 7 h. The mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with H_2O, 5% citric acid, sat.$NaHCO_{3\,(aq.)}$ and brine, then dried ($MgSO_4$) and concentrated. The product benzyl 5-isopropenylpicolinate (1.27 g) was obtained by silica gel chromatography (elution with 0-16% EtOAc/Hex).

Step 2: A solution of benzyl 5-isopropenylpicolinate (1.27 g, 5 mmol) in MeOH (25 mL) was subjected to hydrogenation with 20% $Pd(OH)_2/C$ (200 mg) with a H_2 balloon for 2h. The product 5-isopropenylpicolinic acid (780 mg) was obtained by filtration and concentration.

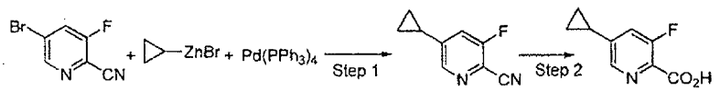
Scheme 11w:



Step 1: A mixture of 5-bromo-3-fluoropicolinonitrile (1.0 g, 5 mmol), $Pd(dppf)Cl_2$ (82 mg, 0.1 mmol) and cesium carbonate (3.26, 10 mmol) in THF (20 mL) was degassed with N_2. After addition of a solution of triethylborane (1.0 M THF, 10 mL), the mixture was heated at 65 °C for 5 h. The mixture was cooled down to room temperature, and then further cooled down in an ice bath. Into the mixture was added a solution of NaOH (1.2 g) in 20 mL of H_2O, followed by H_2O_2 (30 % aqueous 7 mL). The mixture was stirred at 0°C for 30 min and extracted with ether (4x). The organic layer was washed with brine and dried ($MgSO_4$), and concentrated. The product 5-ethyl-3-fluoropicolinamide (370 mg) was obtained from silica gel chromatography (elution with 0-40% EtOAc/Hex).

Step 2: A mixture of amide (475 mg, 2.8 mmol) in 10 mL of conc. HCl was heated at reflux for 5 h. The mixture was concentrated and dried *in vacuo* to give the product 5-ethyl-3-fluoropicolinic acid.

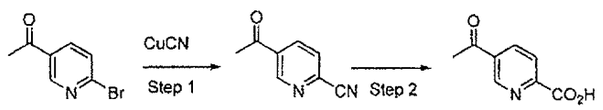
Scheme 11x:



Step 1: To solution of 5-bromo-3-fluoropicolinonitrile (603 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) in 10 mL of THF was added cyclopropyl zinc bromide (0.5 M, 10 mL) under N_2. After being heated 80 °C for 4 h, the mixture was cooled to room temperature and quenched with sat. NH_4Cl (aq). The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with sat. $NaHCO_{3\,(aq.)}$ and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel chromatography (elution with 0-8% EtOAc/Hex) to afford 5-cyclopropyl-3-fluoropicolinonitrile (406 mg).

Step 2: The product of step 1 was heated at reflux in 10 mL of conc. HCl overnight. After concentration, the solid product 5-cyclopropyl-3-fluoropicolinic acid (400 mg) was washed with cold water and dried *in vacuo*.

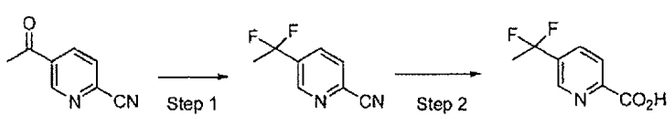
Scheme 11y:



Step 1: A mixture of 1-(6-bromopyridin-3-yl)ethanone (200 mg, 1.0 mmol) and CuCN (179 mg, 2.0 mmol) in anhydrous DMF (5 mL) was heated at 110°C for 18 h under N_2. The mixture was cooled to room temperature and diluted with water. After addition of EtOAc and filtration, the aqueous layer was extracted with EtOAc. The organic layer was washed with sat. $NaHCO_3$ (aq), brine, and then dried ($MgSO_4$) and concentrated. The product 5-acetylpicolinonitrile (120 mg) was obtained by silica gel chromatography (elution with 0-20% EtOAc/Hex).

Step 2: 5-Acetylpicolinonitrile (146 mg, 1.0 mmol) in 5 mL of conc. HCl was heated at reflux for 2.5 h. The mixture was concentrated and dried *in vacuo*. The crude product 5-acetylpicolinic acid was used without further purification.

Scheme 11z:



Step 1: A mixture of 5-acetylpicolinonitrile (146 mg, 1.0 mmol) and Deoxo-Fluor™ (1.0 mL, 50% in toluene) was heated at 80 °C for 3h under N_2. The mixture was cooled to room temperature and diluted with DCM. The organic layer was washed with sat. $NaHCO_{3\,(aq.)}$, and brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (elution with 0-15% EtOAc/Hex) to afford 5-(1,1-difluoroethyl)picolinonitrile (120 mg).

Step 2: 5-(1,1-Difluoroethyl)picolinonitrile (120 mg, 0.71 mmol) in 9 mL of conc. HCl was heated at 110 °C for 5h. The mixture was concentrated. To the residue was added diisopropylethylamine (2 mL) and the mixture was concentrated. The residue was dried *in vacuo* and used without further purification.

20 min at -78°C. Then the cooling bath was changed to an ice bath. After stirring for another 30 min, the reaction was quenched with sat. $NH_4Cl_{(aq.)}$. The mixture was extracted with EtOAc (3x). The organic layer was washed with sat. $NaHCO_{3\,(aq.)}$, brine, then dried ($MgSO_4$) and concentrated. The product 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinonitrile (600 mg) was obtained by silica gel chromatography (elution with 0-40% EtOAc/Hex).

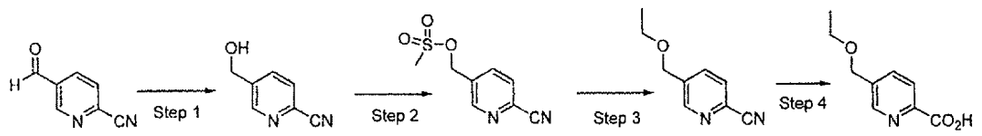
Step 2: A mixture of 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinonitrile (202 mg, 1.0 mmol) , conc. HCl (0.5 mL) and conc. H_2SO_4 (0.25 mL) in 10 mL of anhydrous MeOH was heated at reflux for 19 h. The solution was concentrated and neutralized with sat. $NaHCO_{3\,(aq.)}$. Extraction with EtOAc followed by concentration of the organic layer and purification of the residue by silica gel chromatography (elution with 0-45% EtOAc/Hex) afforded methyl 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinate (76 mg).

Step 3: To a solution of methyl 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinate (76 mg, 0.32 mmol) in 3mL of DCM was added triethylamine (0.22 mL), followed by a solution of methanesulfonyl chloride (45 mg, 0.39 mmol) in 1 mL of DCM. The mixture was stirred at room temperature for 7h and then diluted with DCM. The solution was washed with 5% citric acid and sat. $NaHCO_{3\,(aq.)}$, dried ($MgSO_4$), and concentrated. The product methyl 5-(2,2,2-trifluoro-1-(methylsulfonyloxy)ethyl)picolinate (95 mg) was purified by chromatography.

Step 4: To a solution of methyl 5-(2,2,2-trifluoro-1-(methylsulfonyloxy)ethyl)picolinate (95 mg, 0.3 mmol) in 5 mL of MeOH was added 10% Pd/C (45 mg). Hydrogenation with 1 atm H_2 was carried out at room temperature for 2h. After the catalyst was removed by filtration, the filtrated was concentrated. The residue was dissolved in DCM and washed with sat. $NaHCO_{3\,(aq.)}$, and brine. The solution was dried ($MgSO_4$) and concentrated to give methyl 5-(2,2,2-trifluoroethyl)picolinate that was used without purification.

Step 5: A mixture of methyl 5-(2,2,2-trifluoroethyl)picolinate (57 mg, 0.26 mmol) and LiOH (12.5 mg, 0.52 mmol) in 6 mL MeOH/water (5:1) was stirred at room temperature for 3.5 h. The reaction mixture was acidified with 5% citric acid, and then concentrated. The residue was extracted with DCM (4x). The organic layer was washed with brine and dried (Na_2SO_4). After concentration, the product 5-(2,2,2-trifluoroethyl)picolinic acid was dried *in vacuo* and used without further purification.

Scheme 11ac:



Step 1: To a 0°C solution of 5-formylpicolinonitrile (490 mg, 3.71 mmol) in 15 mL of MeOH was added $NaBH_4$ (140 mg, 3.71 mmol). The reaction mixture was stirred at 0°C for 1 h and quenched with 5% citric acid. After most MeOH was removed by concentration, the residue was partitioned between DCM and sat. $NaHCO_{3\,(aq.)}$. The aqueous layer was extracted with DCM (10x). The organic layer was washed with brine and dried (Na_2SO_4). The product 5-(hydroxymethyl)picolinonitrile (431 mg) was obtained by concentration under vaccum.

Step 2: To a solution of 5-(hydroxymethyl)picolinonitrile (1.59 g, 11.9 mmol) in 80 mL of DCM was added diisopropylethylamine (3.2 mL), followed by a solution of methanesulfonyl chloride (1.49g, 13.0 mmol) in 20 mL of DCM at 0°C. The solution was stirred at 0°C for 40 min and washed with 5% citric acid, sat. $NaHCO_{3\,(aq.)}$ and brine. After concentration, the residue was purified by silica gel chromatography (elution with 0-30% EtOAc/Hex) to afford (6-cyanopyridin-3-yl)methyl methanesulfonate (2.33 g).

Step 3: (6-Cyanopyridin-3-yl)methyl methanesulfonate (199 mg, 0.94 mmol) in 2 mL anhydrous EtOH was heated at 85 °C in a sealed tube for 3.5 h. The mixture was concentrated and purified by silica gel chromatography (elution with 0-25% EtOAc/Hex) to afford 5-(ethoxymethyl)picolinonitrile (104 mg).

Step 4: A solution of 5-(ethoxymethyl)picolinonitrile (104 mg) in 10 mL of conc. HCl was heated at reflux for 3.5 h. After concentration, diisopropylethylamine (3mL) was added into the residue. The mixture was concentrated and dried *in vacuo*. The product 5-(ethoxymethyl)picolinic acid was used without further purification.

Table IVm: The following acids were prepared using similar procedures described in Scheme 11ac, substituting the appropriate alcohol in Step 3.

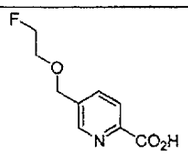
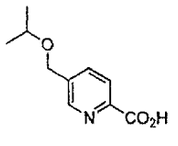
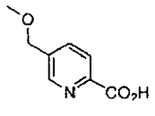
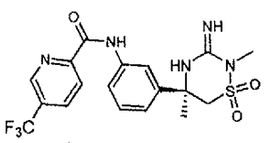
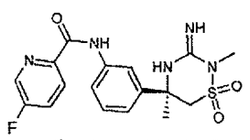
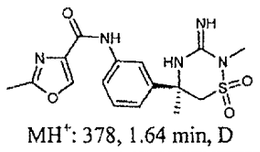
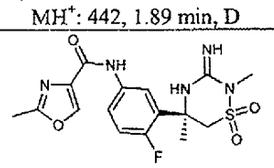
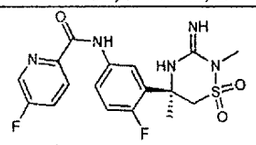
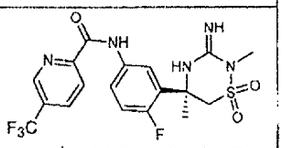
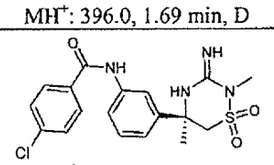
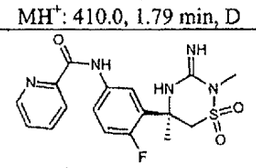
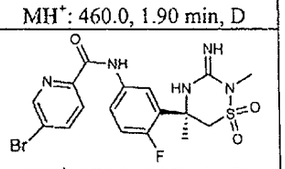
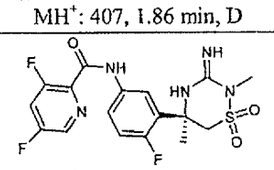
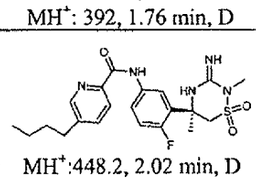
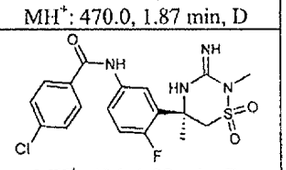
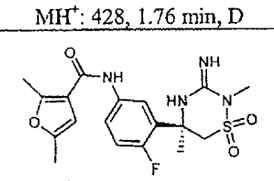
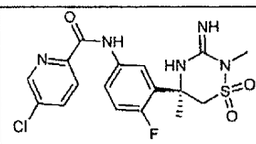
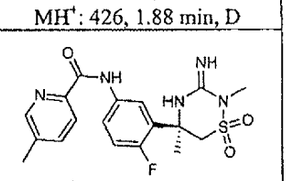
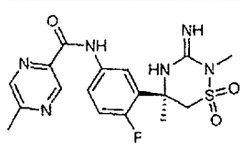
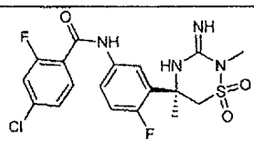
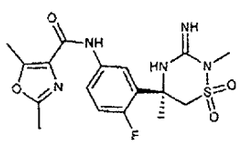
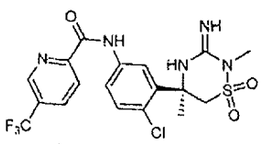
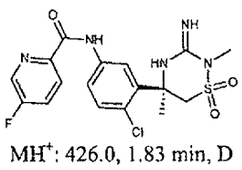
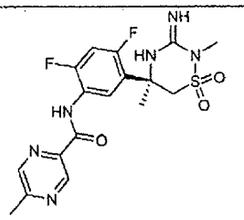
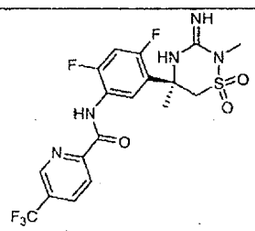
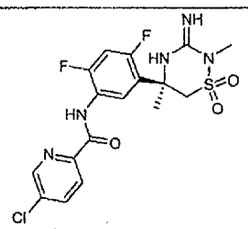
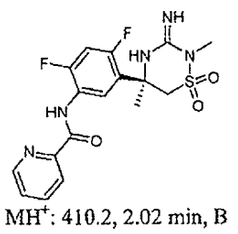
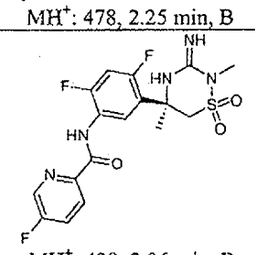
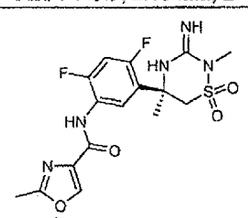
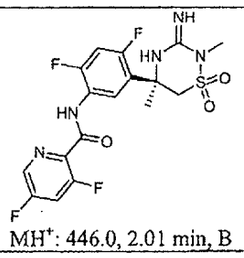
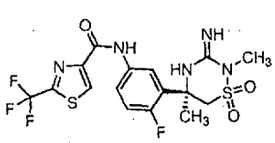
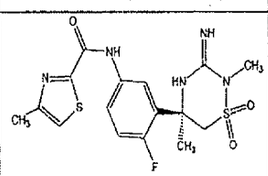
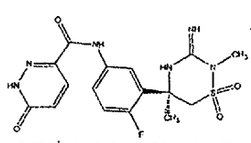
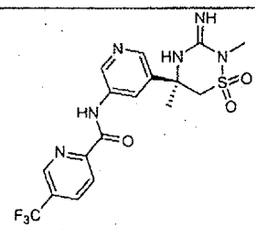
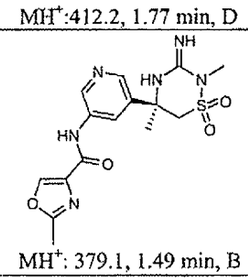
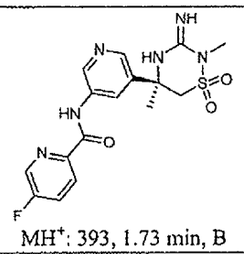
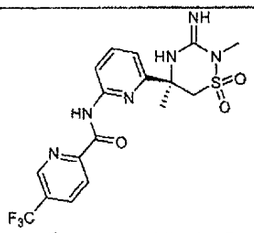
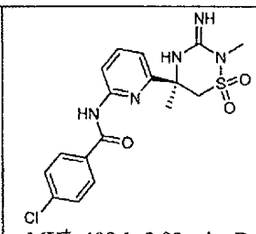
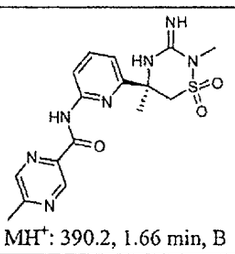
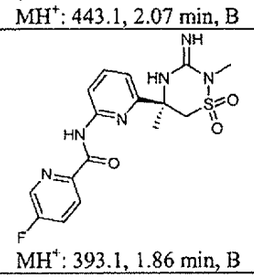
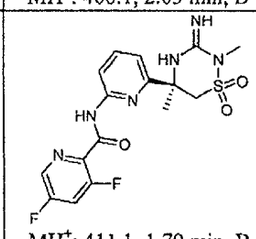
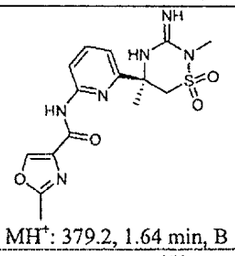
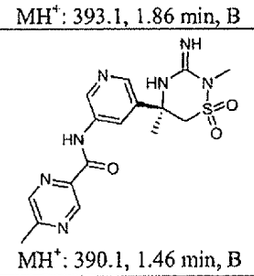
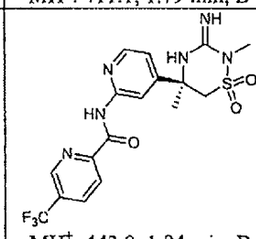
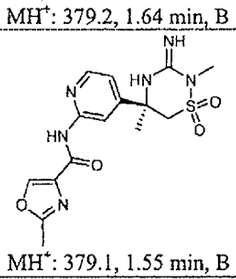
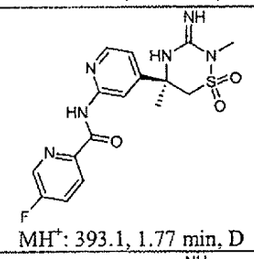
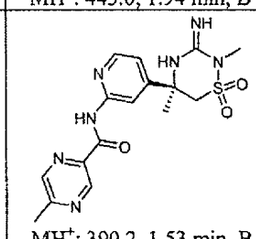
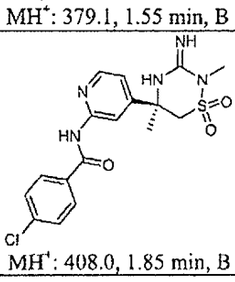
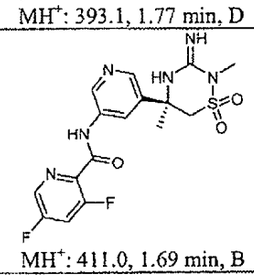
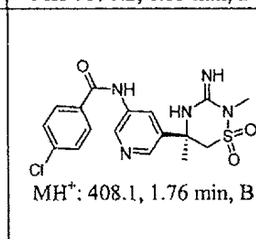
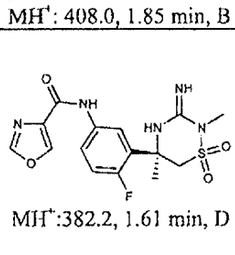
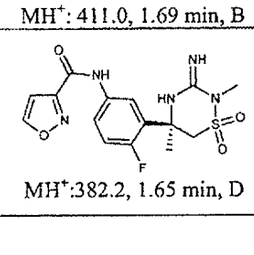
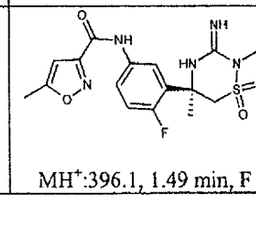
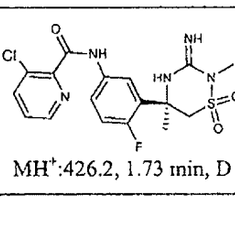
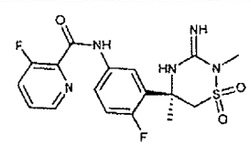
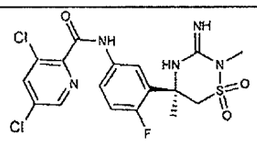
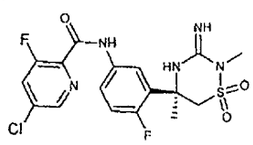
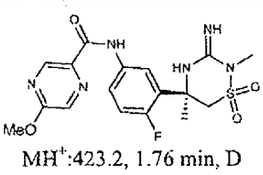
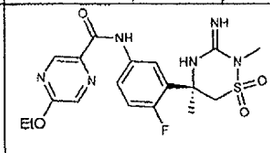
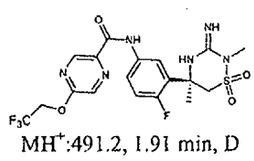
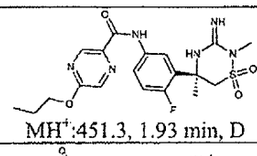
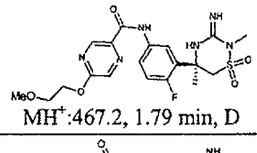
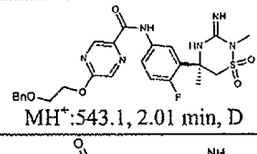
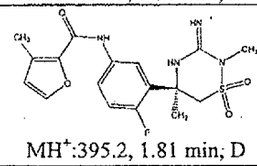
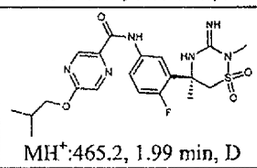
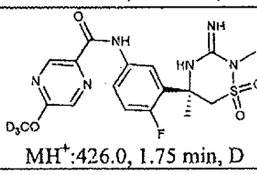
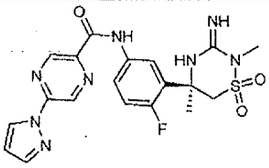
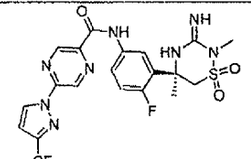
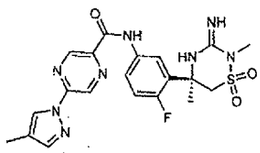
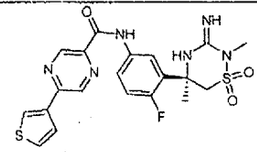
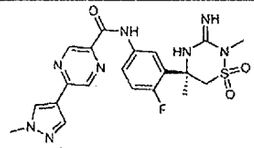
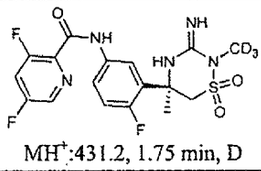
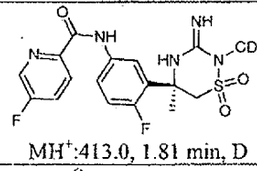
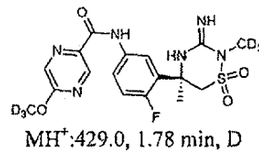
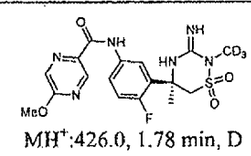
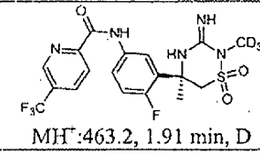
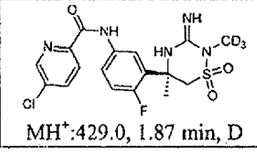
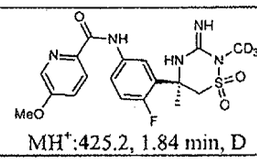
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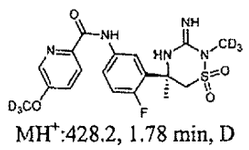
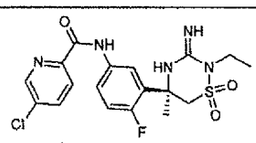
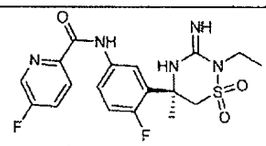
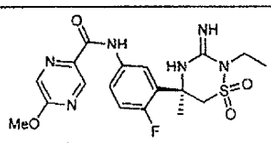
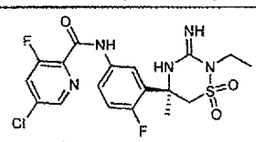
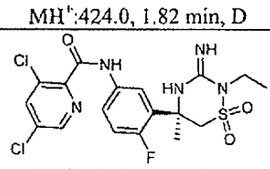
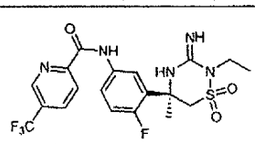
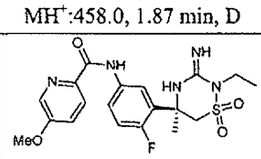
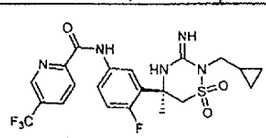
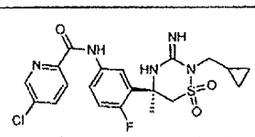
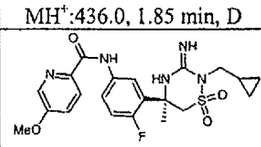
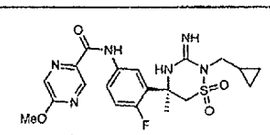
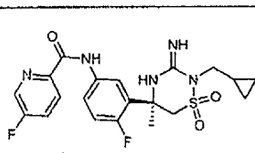
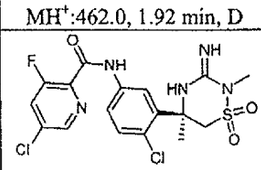
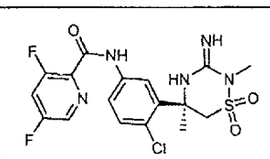
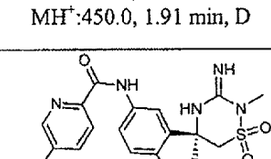
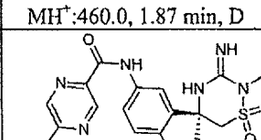
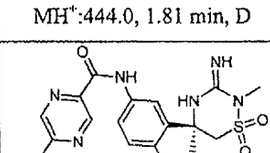
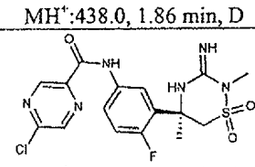
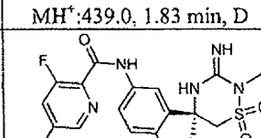
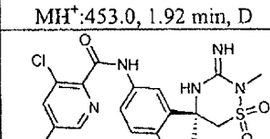
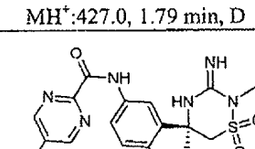
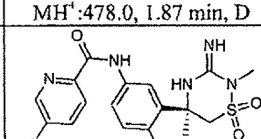
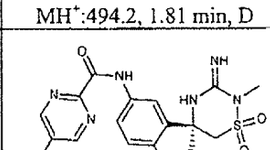
Table V: The following examples were prepared using a procedure similar to that described in Scheme 11b using the appropriate aryl amines and carboxylic acids.

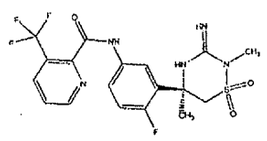
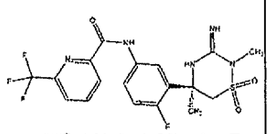
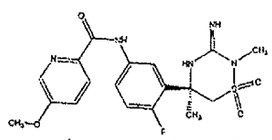
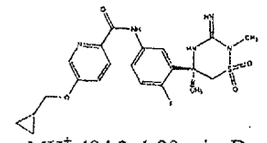
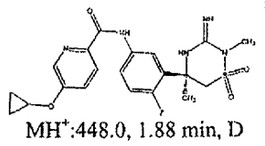
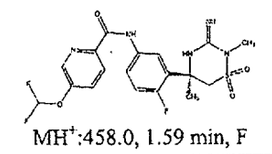
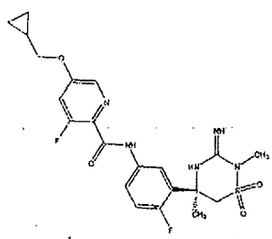
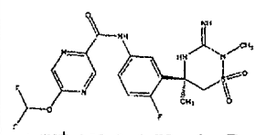
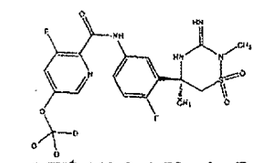
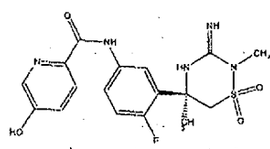
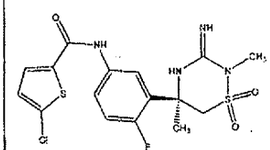
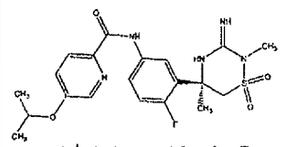
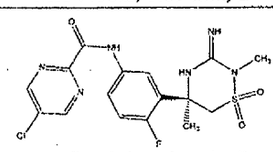
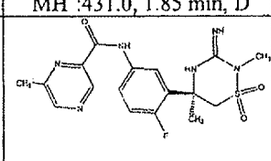
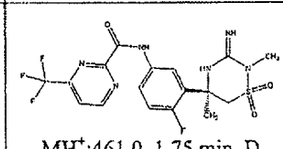
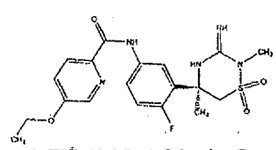
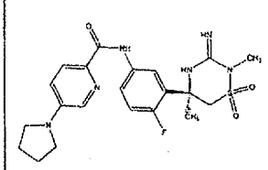
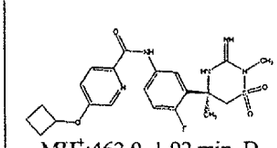
Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
21	 MH^+: 442, 1.89 min, D	22	 MH^+: 392, 1.76 min, D	23	 MH^+: 378, 1.64 min, D
24	 MH^+: 396.0, 1.69 min, D	25	 MH^+: 410.0, 1.79 min, D	26	 MH^+: 460.0, 1.90 min, D
27	 MH^+: 407, 1.86 min, D	28	 MH^+: 392, 1.76 min, D	29	 MH^+: 470.0, 1.87 min, D
30	 MH^+: 428, 1.76 min, D	31	 MH^+:448.2, 2.02 min, D	32	 MH^+: 426, 1.88 min, D
33	 MH^+: 409.2, 1.68 min, D	34	 MH^+: 426.2, 3.25 min, A	35	 MH^+: 406.2, 1.8 min, D

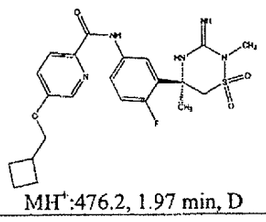
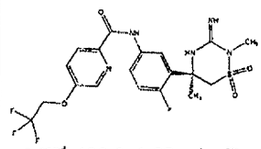
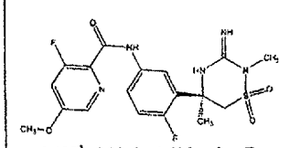
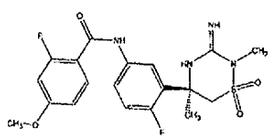
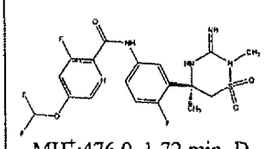
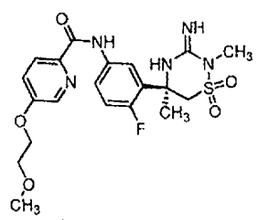
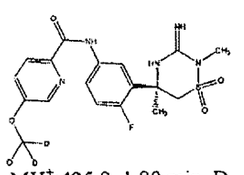
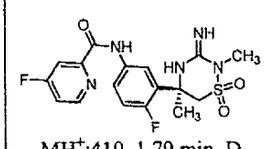
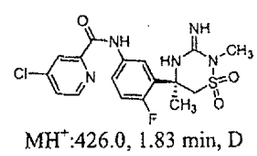
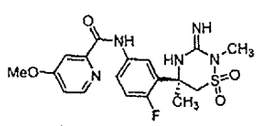
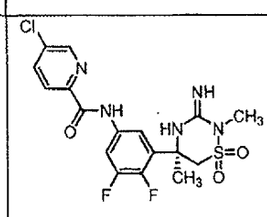
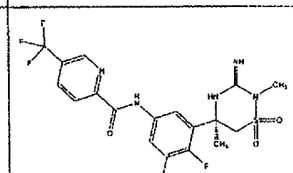
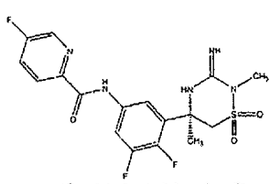
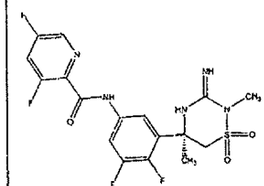
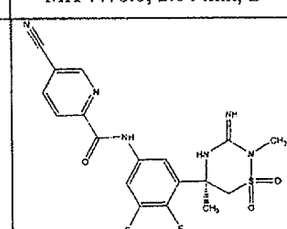
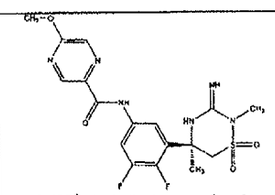
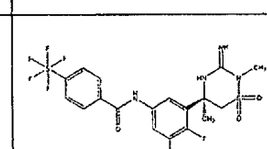
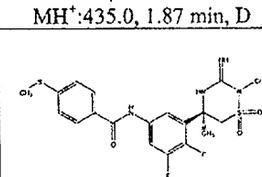
36	 MH+: 407.2, 1.71 min, D	**37**	 MH+: 444, 1.86 min, D	**38**	 MH+: 410.2, 1.78 min, D
39	 MH+: 476.0, 1.91 min, D	**40**	 MH+: 426.0, 1.83 min, D	**40a**	 MH+: 425.1, 1.91 min, B
40b	 MH+: 478, 2.25 min, B	**40c**	 MH+: 443.9, 2.18 min, B	**40d**	 MH+: 410.2, 2.02 min, B
40e	 MH+: 428, 2.06 min, B	**40f**	 MH+: 414.1, 1.86 min, B	**40g**	 MH+: 446.0, 2.01 min, B
40h	 MH+:466.2, 1.84 min, D	**40i**	 MH+:412.2, 1.77 min, D	**40j**	 MH+:409.3, 1.55 min, D
40k	 MH+: 443.1, 1.94 min, B	**40l**	 MH+: 379.1, 1.49 min, B	**40m**	 MH+: 393, 1.73 min, B

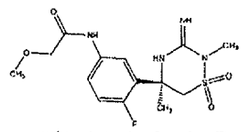
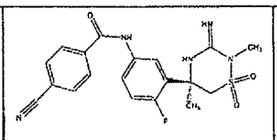
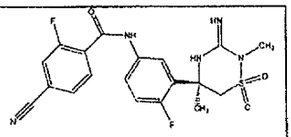
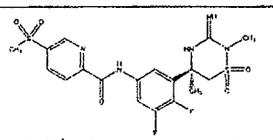
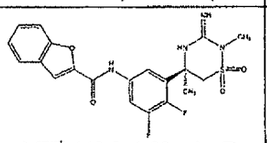
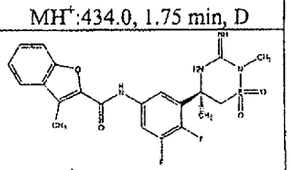
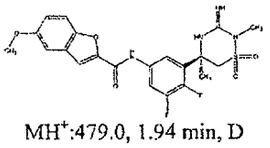
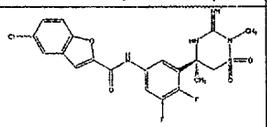
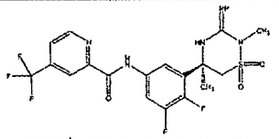
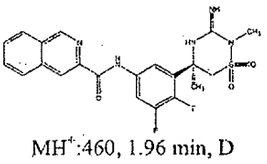
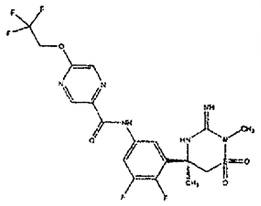
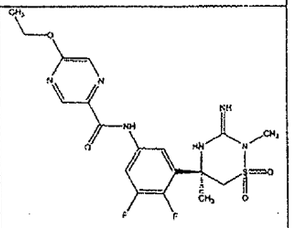
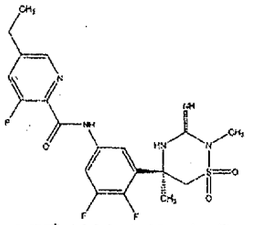
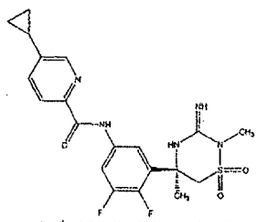
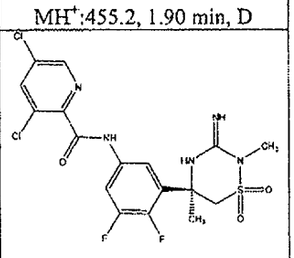
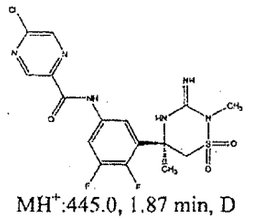
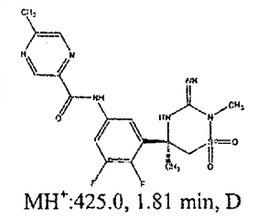
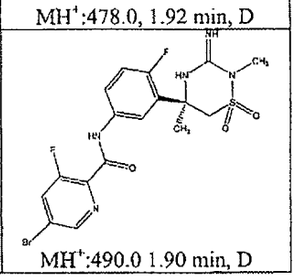
40n	 MH+: 443.1, 2.07 min, B	**40o**	 MH+: 408.1, 2.03 min, B	**40p**	 MH+: 390.2, 1.66 min, B
40q	 MH+: 393.1, 1.86 min, B	**40r**	 MH+: 411.1, 1.79 min, B	**40s**	 MH+: 379.2, 1.64 min, B
40t	 MH+: 390.1, 1.46 min, B	**40u**	 MH+: 443.0, 1.94 min, B	**40v**	 MH+: 379.1, 1.55 min, B
40w	 MH+: 393.1, 1.77 min, D	**40x**	 MH+: 390.2, 1.53 min, B	**40y**	 MH+: 408.0, 1.85 min, B
40z	 MH+: 411.0, 1.69 min, B	**40aa**	 MH+: 408.1, 1.76 min, B	**40ab**	 MH+:382.2, 1.61 min, D
40ac	 MH+:382.2, 1.65 min, D	**40ad**	 MH+:396.1, 1.49 min, F	**40ae**	 MH+:426.2, 1.73 min, D

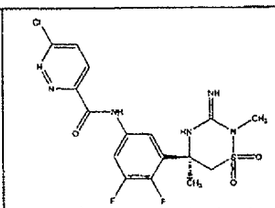
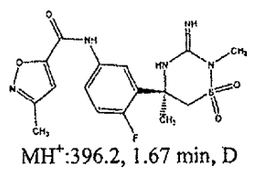
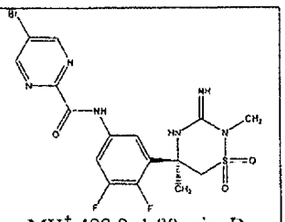
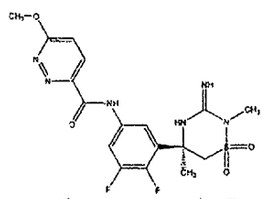
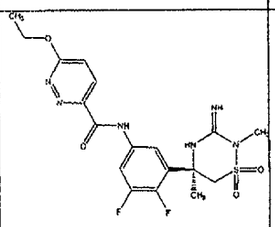
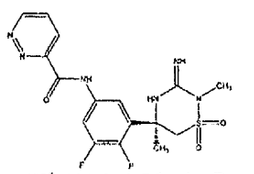
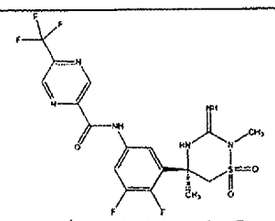
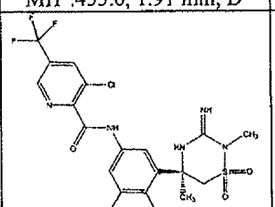
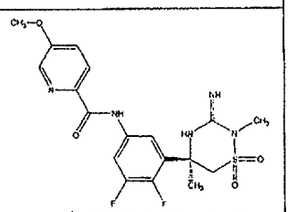
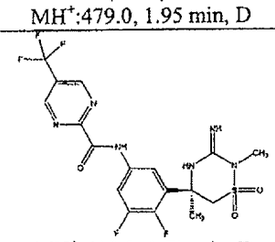
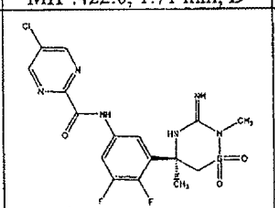
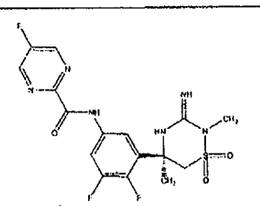
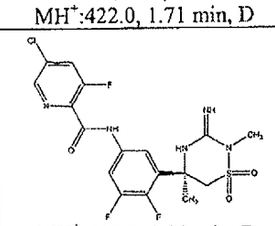
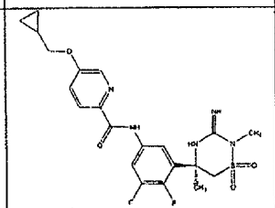
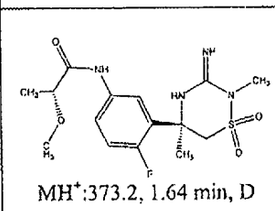
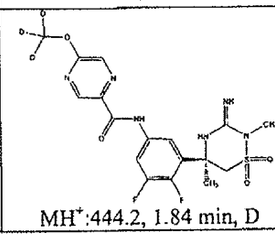
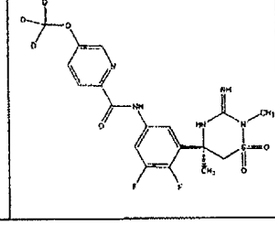
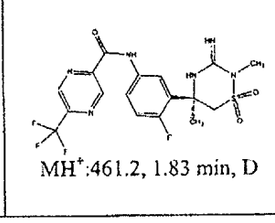
40af	 MH+:410.2, 1.71 min, D	**40ag**	 MH+:460.2, 1.82 min, D	**40ah**	 MH+:444.2, 1.78 min, D
40ai	 MH+:423.2, 1.76 min, D	**40aj**	 MH+:437.2, 1.85 min, D	**40ak**	 MH+:491.2, 1.91 min, D
40al	 MH+:451.3, 1.93 min, D	**40am**	 MH+:467.2, 1.79 min, D	**40an**	 MH+:543.1, 2.01 min, D
40ao	 MH+:395.2, 1.81 min, D	**40ap**	 MH+:465.2, 1.99 min, D	**40aq**	 MH+:426.0, 1.75 min, D
40ar	 MH+:459.0, 1.86 min, D	**40as**	 MH+:527.0, 2.01 min, D	**40at**	 MH+:473.0, 1.93 min, D
40au	 MH+:475.0, 1.93 min, D	**40av**	 MH+:473.0, 1.78 min, D	**40aw**	 MH+:431.2, 1.75 min, D
40ax	 MH+:413.0, 1.81 min, D	**40ay**	 MH+:429.0, 1.78 min, D	**40az**	 MH+:426.0, 1.78 min, D
40ba	 MH+:463.2, 1.91 min, D	**40bb**	 MH+:429.0, 1.87 min, D	**40bc**	 MH+:425.2, 1.84 min, D

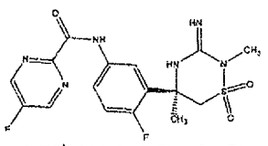
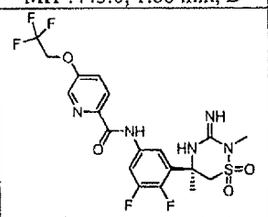
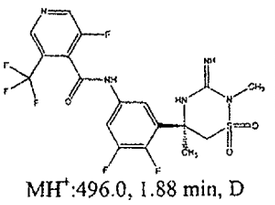
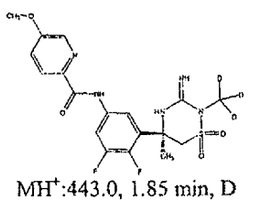
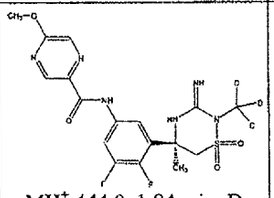
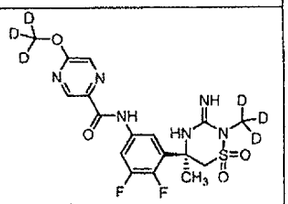
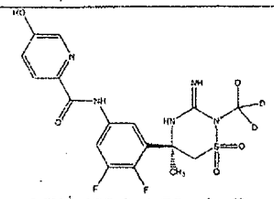
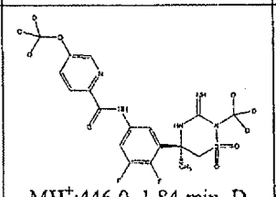
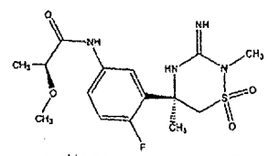
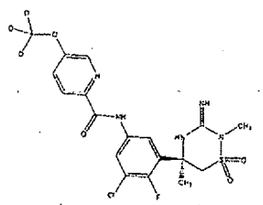
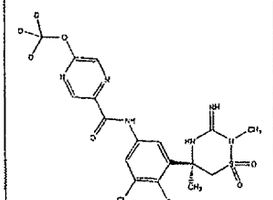
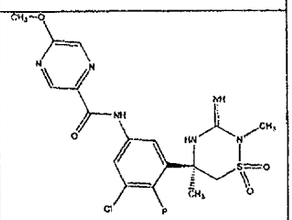
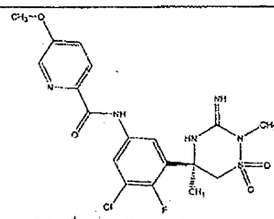
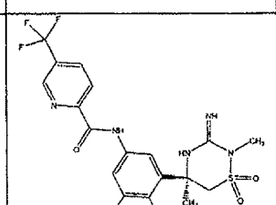
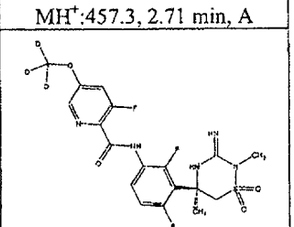
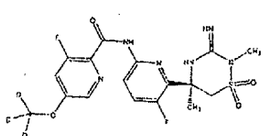
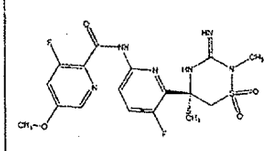
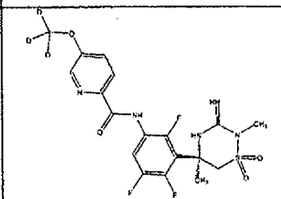
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40bg	 MH^+:437.0, 1.82 min, D	**40bh**	 MH^+:458.0, 1.87 min, D	**40bi**	 MH^+:474.0, 1.87 min, D
40bj	 MH^+: 474.2, 1.95 min, D	**40bk**	 MH^+:436.0, 1.85 min, D	**40bl**	 MH^+:500.0, 1.98 min, D
40bm	 MH^+:466.0, 1.95 min, D	**40bn**	 MH^+:462.0, 1.92 min, D	**40bo**	 MH^+:463.0, 1.90 min, D
40bp	 MH^+:450.0, 1.91 min, D	**40bq**	 MH^+:460.0, 1.87 min, D	**40br**	 MH^+:444.0, 1.81 min, D
40bs	 MH^+:438.0, 1.86 min, D	**40bt**	 MH^+:439.0, 1.83 min, D	**40bu**	 MH^+:453.0, 1.92 min, D
40bv	 MH^+:427.0, 1.79 min, D	**40bw**	 MH^+:478.0, 1.87 min, D	**40bx**	 MH^+:494.2, 1.81 min, D
40by	 MH^+:461.2, 1.73 min, D	**40bz**	 MH^+:442.0, 1.86 min, D	**40ca**	 MH^+:473.0, 1.71 min, D

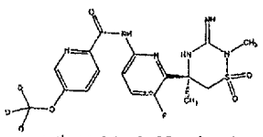
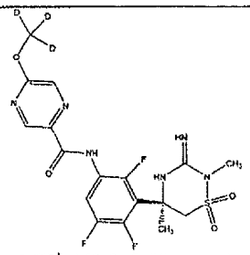
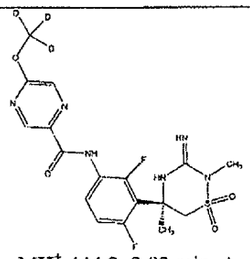
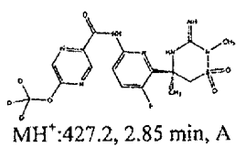
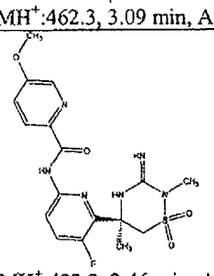
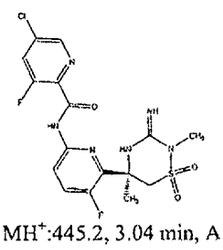
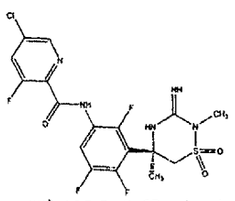
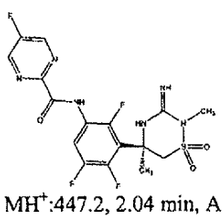
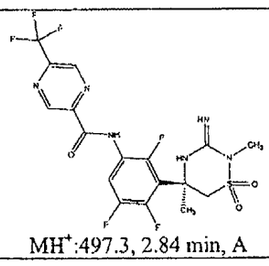
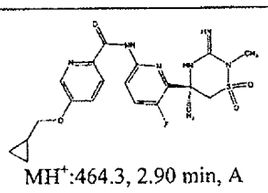
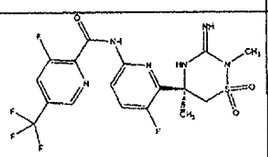
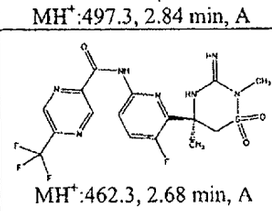
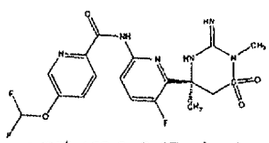
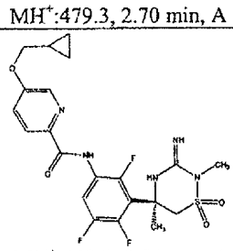
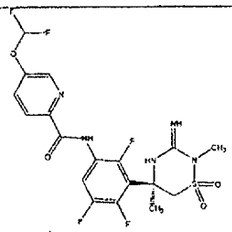
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40ce	 MH+:484.2, 1.90 min, D	**40cf**	 MH+:448.0, 1.88 min, D	**40cg**	 MH+:458.0, 1.59 min, F
40ch	 MH+:480.0, 1.92 min, D	**40ci**	 MH+:459.2, 1.73 min, D	**40cj**	 MH+:443.0, 1.79 min, D
40ck	 MH+:408.2, 1.69 min, D	**40cl**	 MH+:431.0, 1.85 min, D	**40cm**	 MH+:450.2, 1.88 min, D
40cn	 MH-:427.0, 1.67 min, D	**40co**	 MH+:407.0, 1.72 min, D	**40cp**	 MH+:461.0, 1.75 min, D
40cq	 MH+:436.2, 1.84 min, D	**40cr**	 MH+:461.4, 1.83 min, D	**40cs**	 MH+:462.0, 1.92 min, D

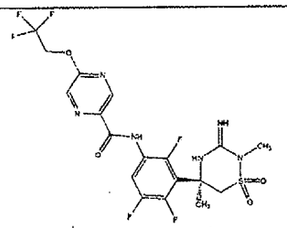
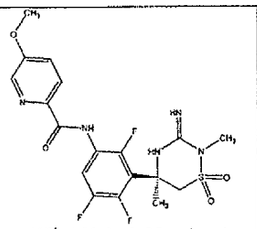
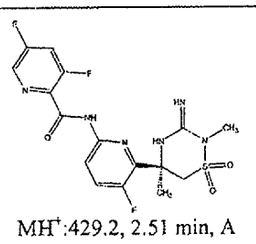
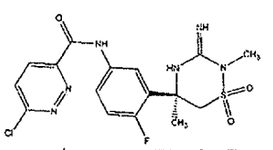
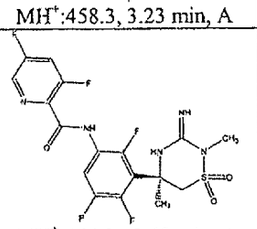
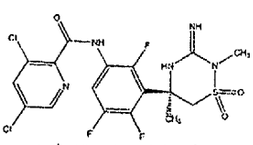
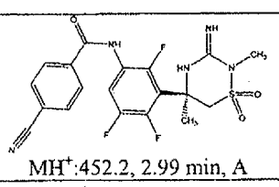
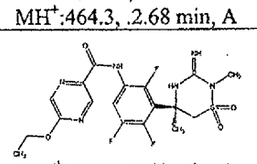
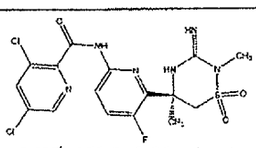
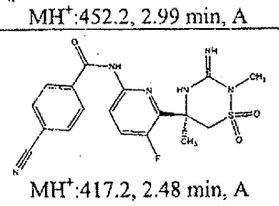
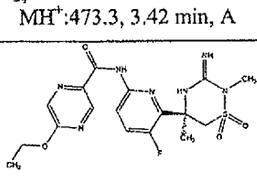
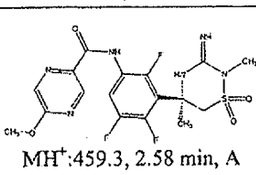
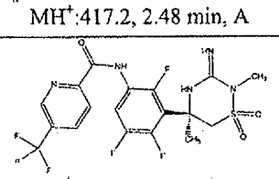
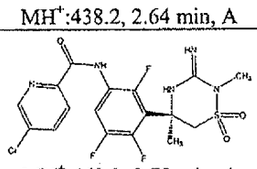
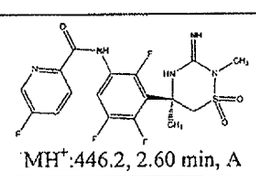
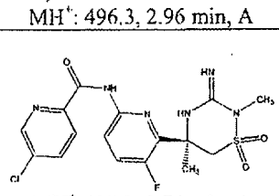
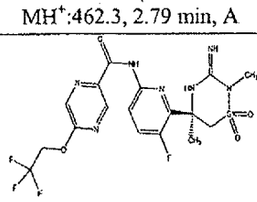
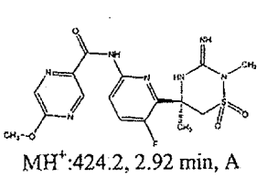
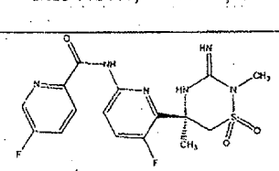
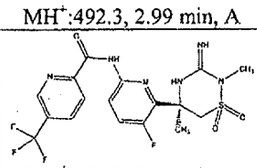
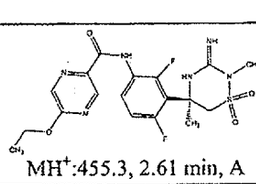
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40cw	 MH+:439.0, 1.79 min, D	**40cx**	 MH+:476.0, 1.72 min, D	**40cy**	 MH+:466.0, 1.82 min, D
40cz	 MH+:425.0, 1.80 min, D	**40da**	 MH+:410, 1.79 min, D	**40db**	 MH+:426.0, 1.83 min, D
40dc	 MH+:422.0, 1.71 min, D	**40dd**	 MH+:444.0, 1.94 min, D	**40de**	 MH+:478.0, 2.04 min, D
40df	 MH+:428.0, 1.89 min, D	**40dg**	 MH+:446.0, 1.85 min, D	**40dh**	 MH+:435.0, 1.87 min, D
40di	 MH+:441.0, 1.85 min, D	**40dj**	 MH+:534.8, 2.04 min, D	**40dk**	 MH+:455.0, 1.95 min, D

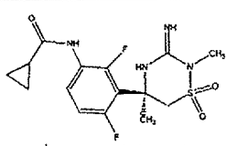
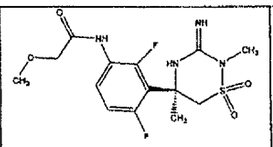
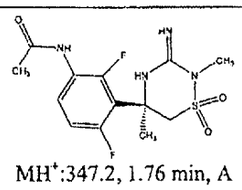
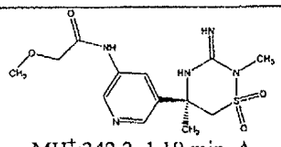
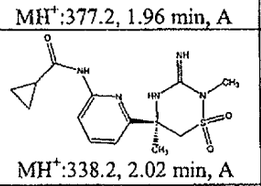
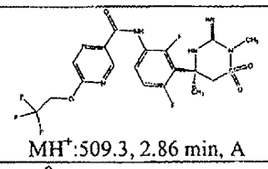
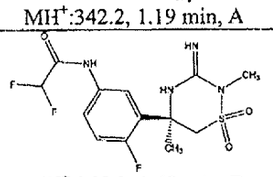
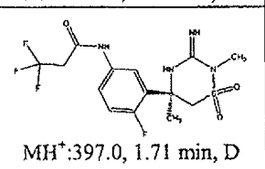
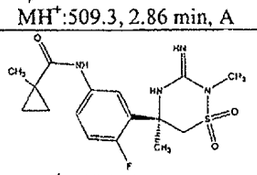
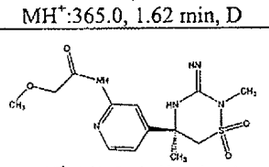
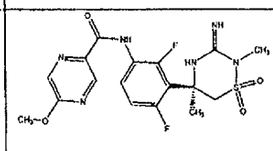
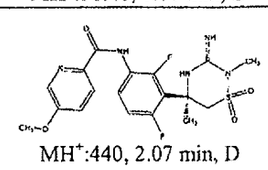
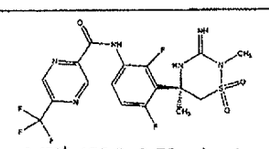
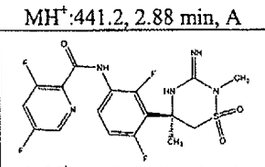
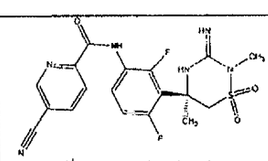
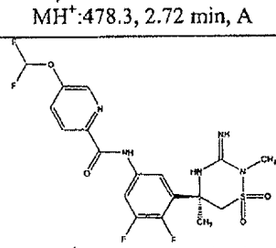
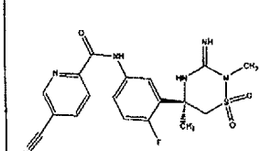
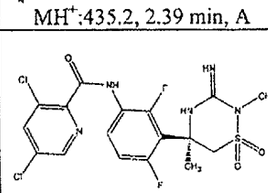
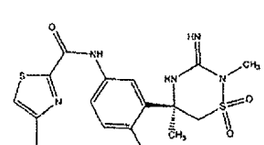
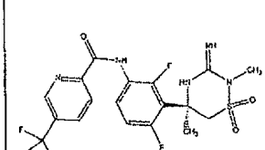
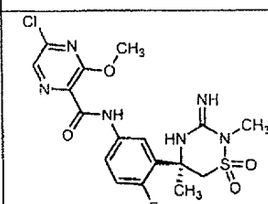
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40do	 MH+:488.0, 1.81 min, D	**40dp**	 MH+:449.0, 1.93 min, D	**40dq**	 MH+:463.0, 2.02 min, D
40dr	 MH+:479.0, 1.94 min, D	**40ds**	 MH+:483.0, 2.01 min, D	**40dt**	 MH+:478.0, 1.97 min, D
40du	 MH+:460, 1.96 min, D	**40dv**	 MH+:509.0, 2.11 min, D	**40dw**	 MH+:455.2, 1.90 min, D
40dx	 MH+:456.2, 1.92 min, D	**40dy**	 MH+:450.2, 1.95 min, D	**40dz**	 MH+:478.0, 1.92 min, D
40ea	 MH+:445.0, 1.87 min, D	**40eb**	 MH+:425.0, 1.81 min, D	**40ec**	 MH+:490.0 1.90 min, D

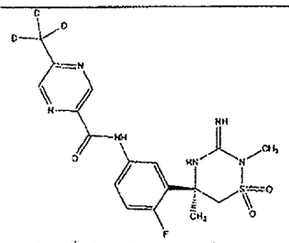
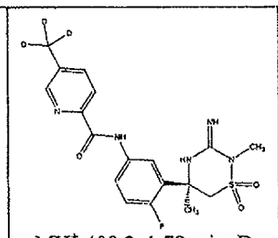
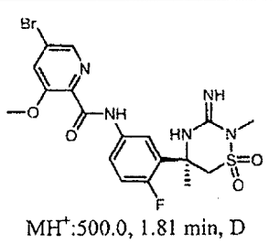
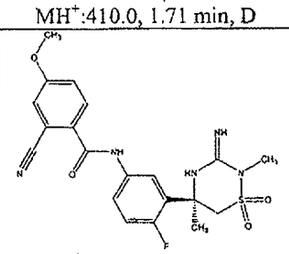
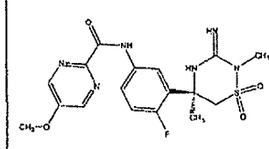
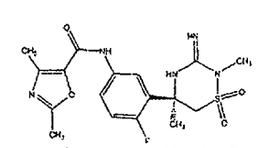
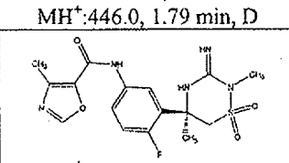
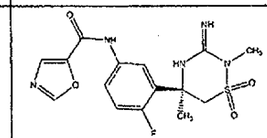
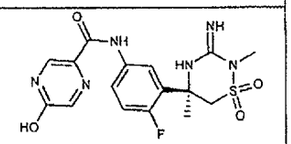
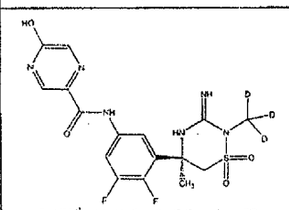
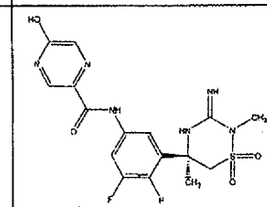
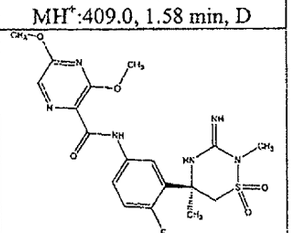
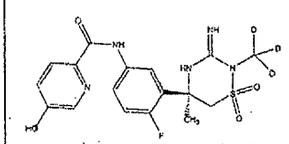
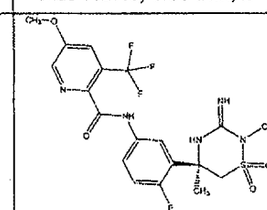
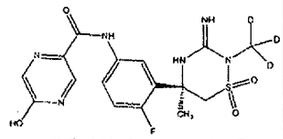
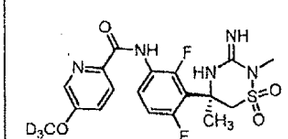
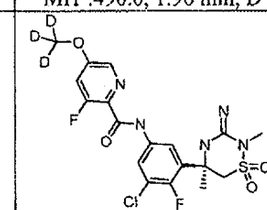
40ed	 MH$^+$:445.0, 1.84 min, D	**40ee**	 MH$^+$:396.2, 1.67 min, D	**40ef**	 MH$^+$:488.8, 1.80 min, D
40eg	 MH$^+$:441.0 1.84 min, D	**40eh**	 MH$^+$:455.0, 1.91 min, D	**40ei**	 MH$^+$:411.0, 1.76 min, D
40ej	 MH$^+$:479.0, 1.95 min, D	**40ek**	 MH$^+$:422.0, 1.71 min, D	**40el**	 MH$^+$:440.0, 1.88 min, D
40em	 MH$^+$:422.0, 1.71 min, D	**40en**	 MH$^+$:445.0, 1.79 min, D	**40eo**	 MH$^+$:429.0, 1.73 min, D
40ep	 MH$^+$:462.0, 1.90 min, D	**40eq**	 MH$^+$:480.0, 1.98 min, D	**40er**	 MH$^+$:373.2, 1.64 min, D
40es	 MH$^+$:444.2, 1.84 min, D	**40et**		**40eu**	 MH$^+$:461.2, 1.83 min, D

			MH^+:443.0, 1.88 min, D		
40ev	 MH^+:411.2, 1.61 min, D	**40ew**	 MH^+:508.0, 1.99 min, D	**40ex**	 MH^+:496.0, 1.88 min, D
40ez	 MH^+:443.0, 1.85 min, D	**40fa**	 MH^+:444.0, 1.84 min, D	**40fb**	 MH^+:447.0, 1.83 min, D
40fc	 MH^+:429.0, 1.75 min, D	**40fd**	 MH^+:446.0, 1.84 min, D	**40fe**	 MH^+:373.4, 1.66 min, D
40ff	 MH^+:459.3, 1.78 min, A	**40fg**	 MH^+:460.3, 2.72 min, A	**40fh**	 MH^+:457.3, 2.71 min, A
40fi	 MH^+:456.3, 2.76 min, A	**40fj**	 MH^+:494.3, 3.08 min, A	**40fk**	 MH^+:461.3, 2.83 min, A
40fl	 MH^+:444.2, 2.87 min, A	**40fm**	 MH^+:441.2, 2.80 min, A	**40fn**	 MH^+:461.3, 2.88 min, A

40fo	 MH+:426.2, 2.68 min, A	**40fp**	 MH+:462.3, 3.09 min, A	**40fq**	 MH+:444.2, 2.82 min, A
40fr	 MH+:427.2, 2.85 min, A	**40fs**	 MH+:423.2, 2.46 min, A	**40ft**	 MH+:445.2, 3.04 min, A
40fu	 MH+:480.3, 2.68 min, A	**40fv**	 MH+:447.2, 2.04 min, A	**40fw**	 MH+:497.3, 2.84 min, A
40fx	 MH+:464.3, 2.90 min, A	**40fy**	 MH+:479.3, 2.70 min, A	**40fz**	 MH+:462.3, 2.68 min, A
40ga	 MH+:459.3, 2.67 min, A	**40gb**	 MH+:498.3, 3.83 min, A	**40gc**	 MH+:494.3, 3.46 min, A

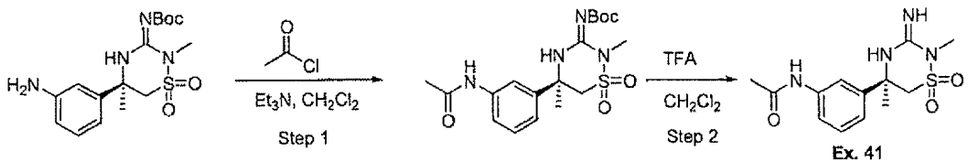
40gd	 MH^+:527.3, 3.75 min, A	**40ge**	 MH^+:458.3, 3.23 min, A	**40gf**	 MH^+:429.2, 2.51 min, A
40gg	 MH^+:427.3, 1.71 min, D	**40gh**	 MH^+:464.3, .2.68 min, A	**40gi**	 MH^+:496.3, 3.04 min, A
40gj	 MH^+:452.2, 2.99 min, A	**40gk**	 MH^+:473.3, 3.42 min, A	**40gl**	 MH^+:461.3, 3.21 min, A
40gm	 MH^+:417.2, 2.48 min, A	**40gn**	 MH^+:438.2, 2.64 min, A	**40go**	 MH^+:459.3, 2.58 min, A
40gp	 MH^+: 496.3, 2.96 min, A	**40gq**	 MH^+:462.3, 2.79 min, A	**40gr**	 MH^+:446.2, 2.60 min, A
40gs	 MH^+:427.2, 2.74 min, A	**40gt**	 MH^+:492.3, 2.99 min, A	**40gu**	 MH^+:424.2, 2.92 min, A
40gv	 MH^+:411.2 2.89 min, A	**40gw**	 MH^+:461.3, 3.40 min, A	**40gx**	 MH^+:455.3, 2.61 min, A

40gy	 MH+:373.2, 2.24 min, A	**40gz**	 MH+:377.2, 1.96 min, A	**40ha**	 MH+:347.2, 1.76 min, A
40hb	 MH+:342.2, 1.19 min, A	**40hc**	 MH+:338.2, 2.02 min, A	**40hd**	 MH+:509.3, 2.86 min, A
40he	 MH+:365.0, 1.62 min, D	**40hf**	 MH+:397.0, 1.71 min, D	**40hg**	 MH+:369.0, 1.71 min, D
40hh	 MH+:342.2, 1.62 min, A	**40hi**	 MH+:441.2, 2.88 min, A	**40hj**	 MH+:440, 2.07 min, D
40hk	 MH+:478.3, 2.72 min, A	**40hl**	 MH+:446.2, 2.33 min, A	**40hm**	 MH+:435.2, 2.39 min, A
40hn	 MH+:476.0, 1.92 min, D	**40ho**	 MH+:417.2, 1.73 min, D	**40hp**	 MH+:478.3, 2.68 min, A
40hq	 MH+:438.0, 1.89 min, D	**40hr**	 MH+:478.3, 1.99 min, A	**40hs**	 MH+:457.0, 1.79 min, D

40ht	 MH^+:410.0, 1.71 min, D	**40hu**	 MH^+:409.2, 1.79 min, D	**40hv**	 MH^+:500.0, 1.81 min, D
40hw	 MH^+:446.0, 1.79 min, D	**40hx**	 MH^+:423.0, 1.68 min, D	**40hy**	 MH^+:410.2, 1.69 min, D
40hz	 MH^+:396.2, 1.65 min, D	**40ia**	 MH^+:382.2, 1.58 min, D	**40ib**[a]	 MH^+:409.0, 1.58 min, D
40ic[a]	 MH^+:430.0, 1.66 min, D	**40id**[a]	 MH^+:427.0, 1.68 min, D	**40ie**	 MH^+:453.2, 1.60 min, D
40if	 MH^+:411.0, 1.83 min, D	**40ig**	 MH^+:490.0, 1.96 min, D	**40ih**[a]	 MH^+:412.0, 1.72 min, D
40ii	 MH^+:443.2, 2.57 min, A	**40ij**	 MH^+:477.3, 2.95 min, A		

[a] The hydroxypyrazine amides were formed using the cyclopropylmethylether pyrazine acid (Entry 5, Table IVb) instead of 1,3-oxazole-4-carboxylic acid in step 1 of Scheme 11b.

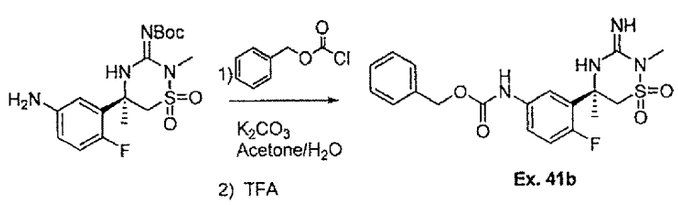
Scheme 12:



Step 1: To a solution of the aniline from Table IV entry 1 (80 mg) and Et_3N (50 μL) in CH_2Cl_2 (2 mL) was added acetyl chloride (1.2 eq.). The resulting solution was stirred at RT for 2 hours. Water was added and the aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via flash chromatography (SiO_2: 0 to 60% EtoAc in hex).

Step 2: Example 41 was prepared as the TFA salt from the product of step 1 using a method similar to that described in Scheme 11b step 2. LCMS data: (method D): t_R = 0.91 min, *m/e* = 311 (M+H).

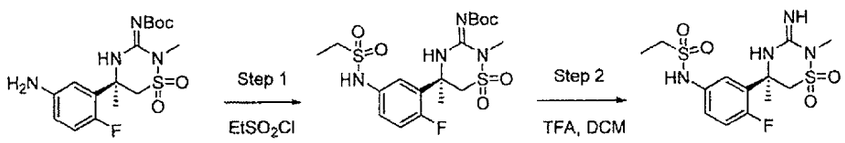
Scheme 12b:



To a mixture of the aniline from Scheme 10 (50 mg, 0.13 mmol) and potassium carbonate (18 mg, 0.13 mmol) in 1:1 acetone:water (4 mL) was added benzyl chloroformate (0.028 mL, 0.19 mmol). The mixture was stirred at RT for 30 min. Water was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2; gradient elution 100:0 to 70:30 hexanes:EtOAc) to afford the carbamate.

Example 41b was prepared as its TFA salt from the above carbamate using a method similar to that described in Scheme 11b step 2. LCMS data: (method D): t_R = 1.88 min, *m/e* = 421.0 (M+H).

Scheme 12c:



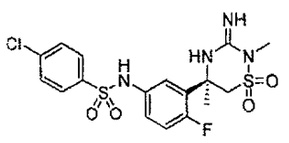
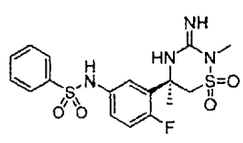
Ex. 41c

Step 1: To a mixture of the aniline (200 mg, 0.517 mmol, Scheme 10) and DIEA (0.36 mL, 2.07 mmol) in CH_2Cl_2 (2 mL) at RT was added dropwise ethylsulfonyl chloride (0.074 mL, 0.775 mmol). After 18 h, the reaction was quenched with 1 M HCl and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

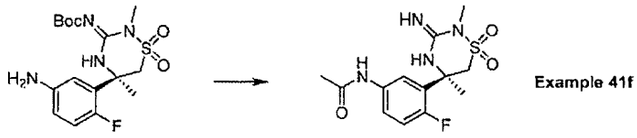
Step 2: Example 41c was prepared from the above material using a method similar to that described in Scheme 11b step 2. After deprotection, the resulting residue was purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Example 41c** as its TFA salt. LCMS (conditions D): t_R = 1.64 min, *m/e* = 379.0 (M+H).

Table Va: The following examples were prepared using a method similar to that described in Scheme 12c.

Examples
(LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)

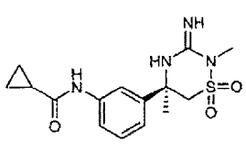
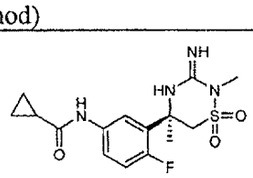
41d	 MH$^+$:460.8, 1.86 min, D	**41e**	 MH$^+$:427.0, 1.78 min, D

Scheme 12d:

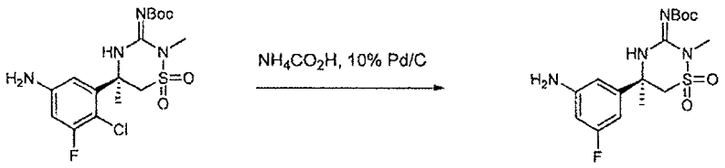


To the aniline (Scheme 10, 70 mg, 0.18 mmol) in 2 mL DCM was added acetic anhydride (19 μL, 0.2 mmol) and triethylamine (29 μL, 0.2 mmol). The reaction was stirred for 3 hours at room temperature, then poured into water. The mixture was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-50% EtOAc/hexanes over 30 minutes) to provide a methyl amide product. This material was stirred in 2 mL 20% TFA/DCM for 1 hr and then concentrated *in vacuo* to provide **Example 41f** as a trifluoroacetate salt (0.041g, 69%). LCMS data: (method A): t_R = 2.96 min, *m/e* = 379.2 (M+H).

Table VI: The following examples were prepared using a method similar to that described in Scheme 12 using the appropriate acid chlorides and aryl amines.

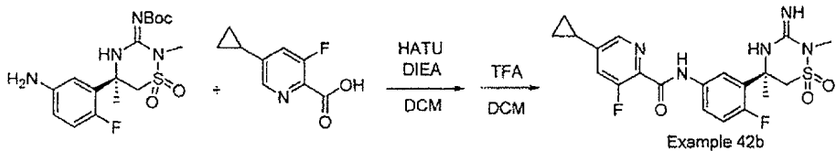
Examples (LCMS data listed with each compound: observed MH$^+$, HPLC retention time and LCMS method)			
42	 MH$^+$:337, 1.57 min, D	**42a**	 MH$^+$:335.0, 1.66 min, D

Scheme 12e:



A mixture of 2-chloro-3-fluoro aniline (252 mg, 0.60 mmol), ammonium formate (5.0 g, 79 mmol) in 25 mL of isopropanol was heated at 70 °C overnight. After filtration and concentration, the residue was purified by silica gel chromatography (elution with 0-30% EtOAc/Hex) to afford the 3-fluoro aniline product (150 mg).

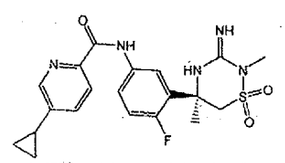
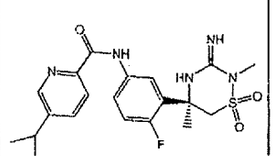
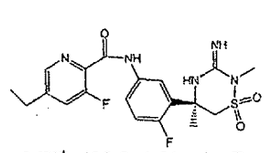
Scheme 12f:

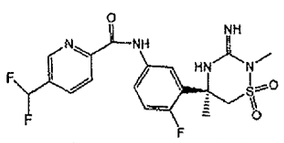
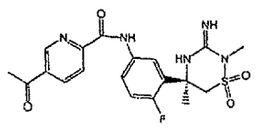
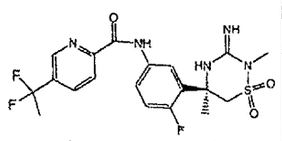
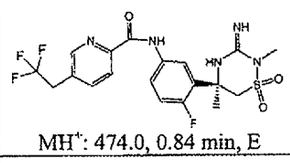
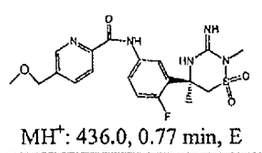
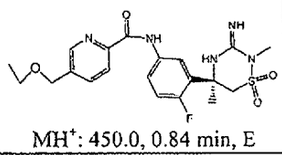
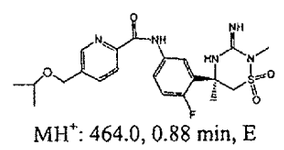
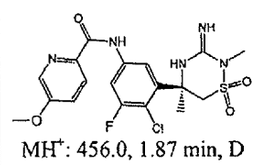
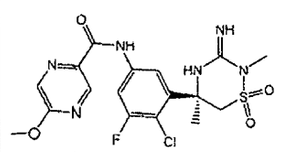
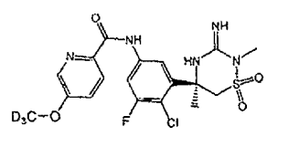
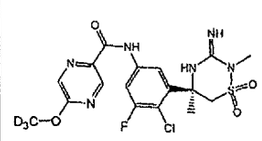
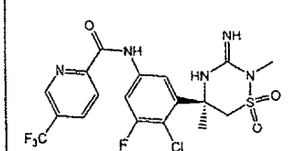
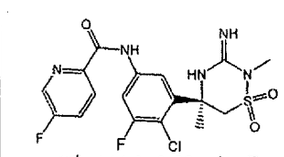
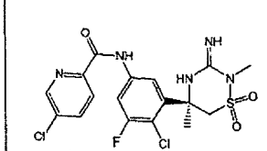
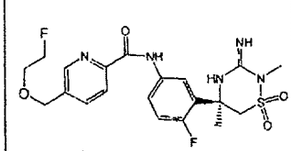
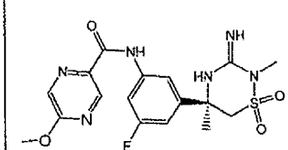
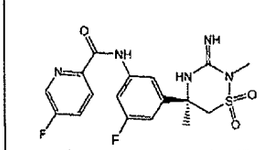


Example 42b

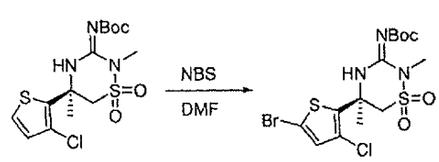
A mixture of aniline (96 mg, 0.25 mmol, Scheme 10), the acid (Scheme 11x, 81 mg, 0.45 mmol), HATU (230 mg, 0.60 mmol), and DIEA (0.36 mL, 2.0 mmol) in 5 mL of DCM was stirred at room temperature overnight. The reaction mixture was diluted with DCM, washed with 5% citric acid, sat. $NaHCO_3$, and brine. After drying ($MgSO_4$) and concentration, the residue was subjected to silica gel chromatograpy (elution with 0-25% EtOAc/Hex). The resulting product was dissolved in 6 mL of 25% of TFA/DCM and stirred at room temperature for 1 h. Concentration and drying *in vacuo* provided **Example 42b** (143 mg) as a TFA salt. LCMS (conditions D): t_R = 1.91 min, *m/e* = 450.2 (M+H).

Table VIb: The following examples were prepared from the corresponding aniline and carboxylic acid using a procedure similar to that described in Scheme 12f.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
42c	 MH^+: 432.2, 1.95 min, D	**42d**	 MH^+: 434.2, 1.99 min, D	**42e**	 MH^+: 438.2, 1.91 min, D

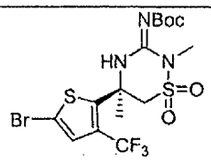
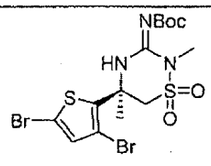
42f	 MH+: 442.2, 0.81 min, E	**42g**	 MH+: 434.2, 0.76 min, E	**42h**	 MH+: 432.2, 1.95 min, D
42i	 MH+: 474.0, 0.84 min, E	**42j**	 MH+: 436.0, 0.77 min, E	**42k**	 MH+: 450.0, 0.84 min, E
42l	 MH+: 464.0, 0.88 min, E	**42m**	 MH+: 456.0, 1.87 min, D	**42n**	 MH+: 457.0, 0.84 min, E
42o	 MH+: 459.0, 0.84 min, E	**42p**	 MH+: 460.0, 0.84 min, E	**42q**	 MH+: 493.9, 0.88 min, E
42r	 MH+: 444.0, 0.82 min, E	**42s**	 MH+: 459.9, 0.88 min, E	**42t**	 MH+: 468.0, 0.79 min, E
42u	 MH+: 432.0, 0.78 min, E	**42v**	 MH+: 410.0, 0.79 min, E		

Scheme 13:

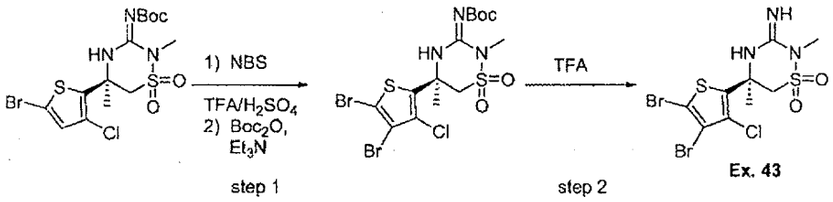


To a solution of the thiophene from Table IIb Entry 3 (2.2 g, 5.6 mmol) in DMF in an aluminum foil wrapped round bottom flask under an atmosphere of N_2 was added NBS (2.7 g, 15 mmol). The resultant solution was heated to 50°C with stirring for 8 hours. The solution was cooled to RT. To the solution was added an aqueous solution of $NaHCO_3$ and $Na_2S_2O_5$. The aqueous layer was extracted with EtOAc. The organic layer was washed with sat $NaHCO_{3\,(aq.)}$ (2x). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 83:17 hexanes:EtOAc) to afford the bromothiophene (1.7 g, 63% yield).

Table VII: The following compounds were prepared using a procedure similar to that described in Scheme 13 using the appropriate starting material.

Entry	2-bromothiophene	Entry	2-bromothiophene
1		2	

Scheme 14:

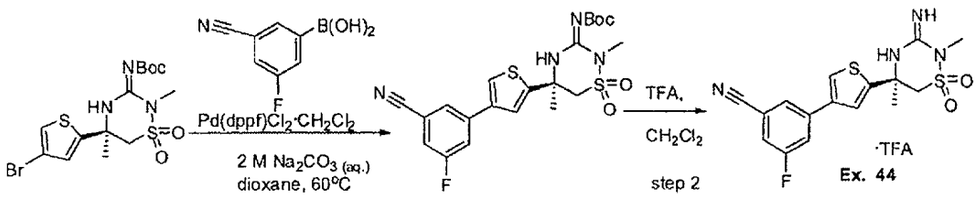


Step 1: To a solution of the thiophene from Scheme 13 (100 mg, 0.21 mmol) in TFA (ca. 2 mL) was added NBS (94 mg, 0.53 mmol) and H_2SO_4 (4 drops). The solution was allowed to stir at RT for 30 min. After that time, additional NBS (80 mg) was added and the solution was stirred for an additional 30 min. The mixture was then quenched with sat. $NaHCO_{3\,(aq.)}$ and $Na_2S_2O_{5\,(s)}$. The aqueous layer was extracted with EtOAc. The organic layer was washed with sat. $NaHCO_{3\,(aq.)}$ (2x), dried over Na_2SO_4, filtered and concentrated. The crude product was slurried in CH_2Cl_2. To this mixture was added di-*tert*-butyldicarbonate (96 mg, 0.21 mmol) and Et_3N (25 mg, 0.23 mmol). The resultant mixture was stirred at RT overnight. The

solution was then concentrated and the crude residue was purified via prep TLC (SiO_2: 3:1 hexanes:EtOAc) to afford the dibromothiophene (49 mg).

Step 2: **Example 43** was prepared using a method similar to that described in Scheme 11b Step 2. LCMS (conditions A): t_R = 3.07 min, *m/e* = 452.2 (M+H).

Scheme 15:

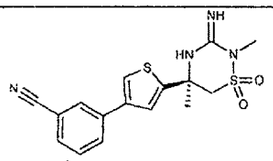
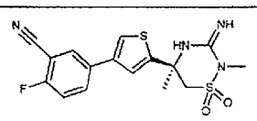
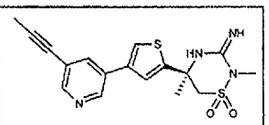
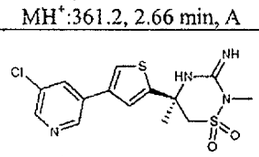
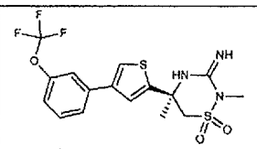
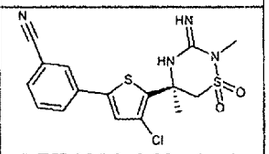
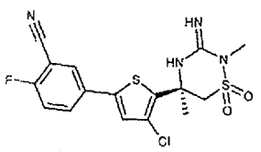
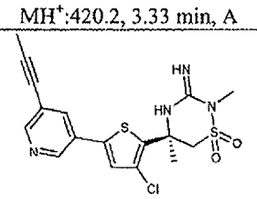
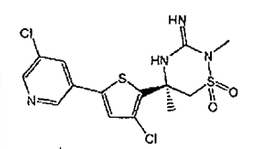
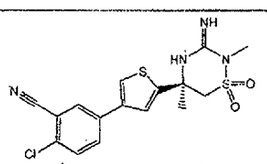
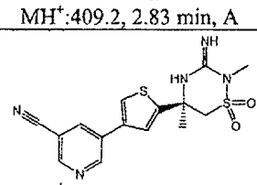
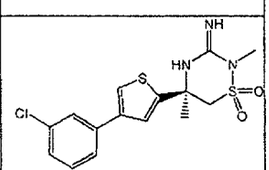
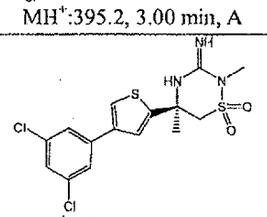
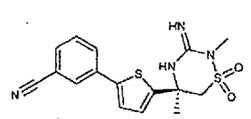
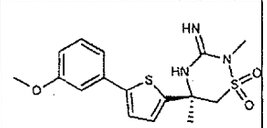
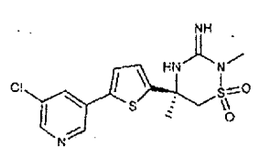
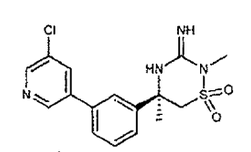
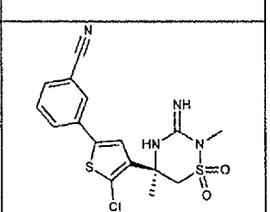
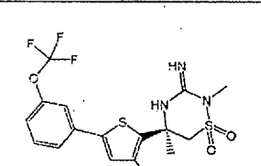
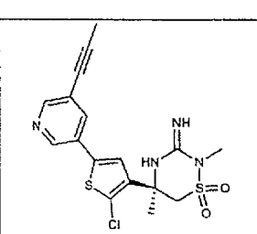
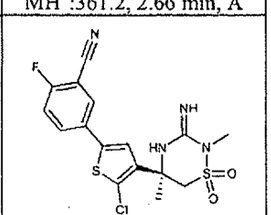


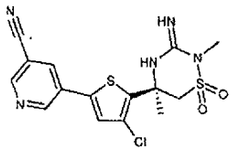
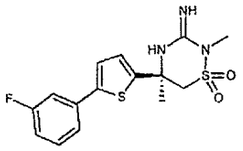
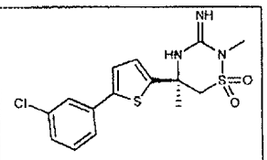
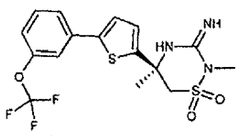
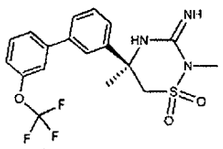
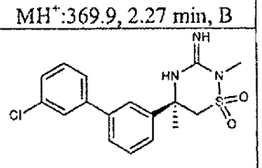
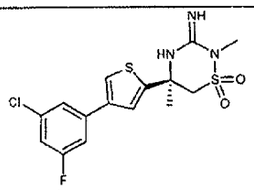
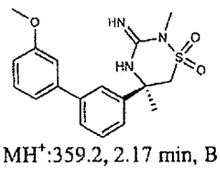
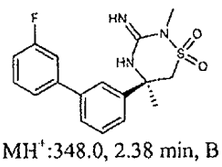
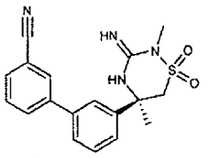
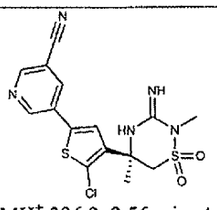
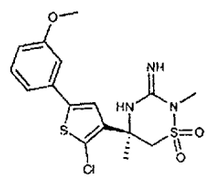
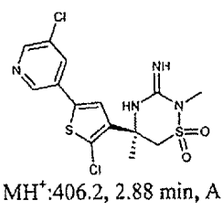
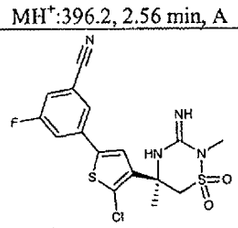
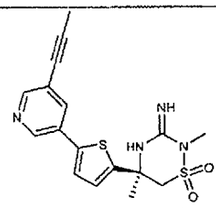
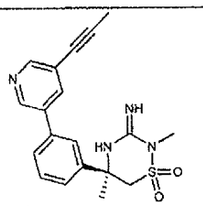
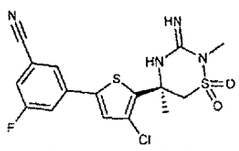
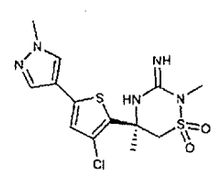
Step 1: To a microwave vial containing the thiophene bromide (Scheme 3) (149 mg, 0.34 mmol) was added 3-cyano-5-fluorophenyl boronic acid (146 mg, 0.88 mmol), 2 M $Na_2CO_{3\,(aq.)}$ (0.31 mL) and dioxane (2.5 mL). The mixture was degassed by bubbling N_2 through it for 5 min. To this mixture was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (60mg, 0.074 mmol). The vial was capped and the atmosphere was purged with nitrogen. The mixture was heated to 60°C with stirring for 2 hours. The mixture was cooled to RT and diluted with EtOAc. The mixture was then filtered through Celite. The organic layer was washed with brine. The aqueous layer was back extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via preperative TLC (SiO_2: 3:1 hexanes:EtOAc) to afford the biaryl compound (105 mg).

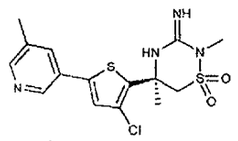
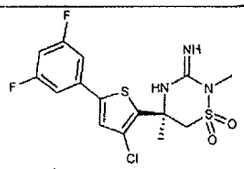
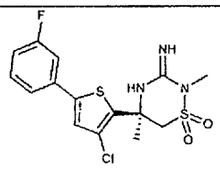
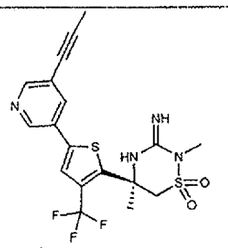
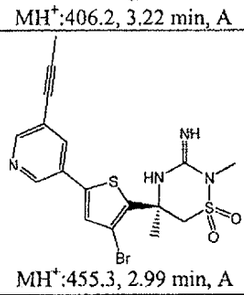
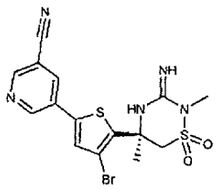
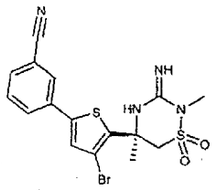
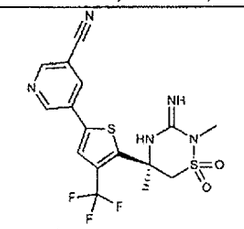
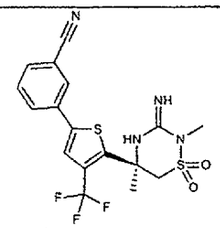
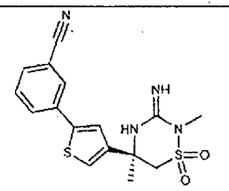
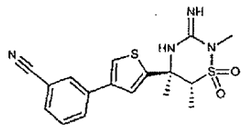
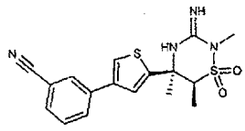
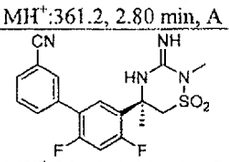
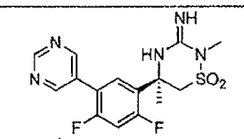
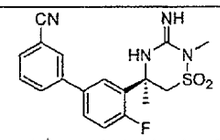
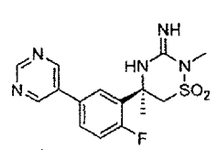
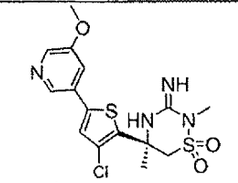
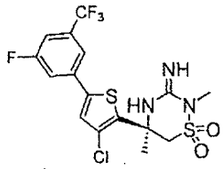
Step 2: To a solution of the biaryl compound from step 1 in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL). The resultant solution was stirred at RT for 1.5 hours. The solvent was removed *in vacuo* to afford **Example 44** as the trifluoroacetate salt. LCMS data: (method A): t_R = 2.96 min, *m/e* = 379.2 (M+H).

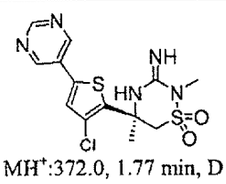
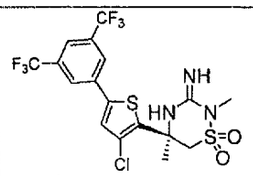
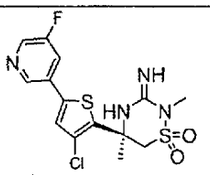
Table VIII: The following examples were prepared using a procedure similar to that described in Scheme 15 using the appropriate aryl bromide and boronic acid/ester.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)

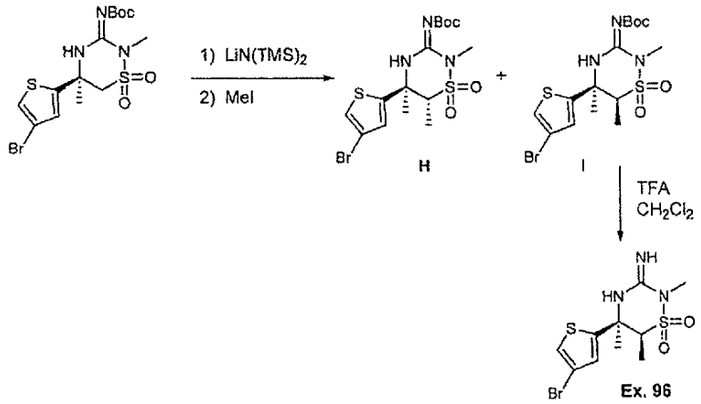
45	 MH^+:361.2, 2.66 min, A	46	 MH^+:379.2, 3.43 min, A	47	 MH^+:375.2, 2.90 min, A
48	 MH^+:371.2, 3.11 min, A	49	 MH^+:420.2, 3.33 min, A	50	 MH^-:395.2, 2.99 min, A
51	 MH^+:413.2, 3.11 min, A	52	 MH^+:409.2, 2.83 min, A	53	 MH^+:405.2, 2.80 min, A
54	 MH^+:395.2, 3.00 min, A	55	 MH^+:362.2, 2.37 min, A	56	 MH^+:370.2, 3.15 min, A
57	 MH^+:404.2, 3.27 min, A	58	 MH^+:360.8, 2.09 min, B	59	 MH^+:365.9, 2.19 min, B
60	 MH^+:370.9, 1.95 min, B	61	 MH^+:364.9, 1.98 min, B	62	 MH^+:361.2, 2.66 min, A
63	 MH^+:454.2, 3.36 min, A	64	 MH^+:409.2, 2.87 min, A	65	 MH^+:413.2, 3.16 min, A

66	 MH^+:396.2, 2.49 min, A	**67**	 MH^+:353.9, 2.20 min, B	**68**	 MH^+:369.9, 2.27 min, B
69	 MH^+:419.9, 2.36 min, B	**70**	 MH^+:413.9, 2.42 min, B	**71**	 MH^+:363.9, 2.28 min, B
72	 MH^+:386.2, 3.09 min, A	**73**	 MH^+:359.2, 2.17 min, B	**74**	 MH^+:348.0, 2.38 min, B
75	 MH^+:355.0, 2.30 min, B	**76**	 MH^+:396.2, 2.56 min, A	**77**	 MH^+:400.2, 3.10 min, A
78	 MH^+:406.2, 2.88 min, A	**79**	 MH^+:413.2, 3.17 min, A	**80**	 MH^+:375.0, 1.94 min, B
81	 MH^+:369.0, 1.95 min, B	**82**	 MH^+:413.2, 2.96 min, A	**83**	 MH^+:374.2, 2.59 min, A

84	 MH^+:385.2, 1.92 min, A	**85**	 MH^+:406.2, 3.22 min, A	**86**	 MH^+:388.2, 3.15 min, A
87	 MH^+:442.9, 2.06 min, B	**88**	 MH^+:455.3, 2.99 min, A	**89**	 MH^+:440.2, 2.77 min, A
90	 MH^+:441.2, 3.10 min, A	**91**	 MH^+:361.2, 2.66 min, B	**92**	 MH^+:428.9, 2.34 min, B
93	 MH^+:361.2, 2.80 min, A	**94**	 MH^+:375.2, 2.84 min, A	**95**	 MH^+:375.2, 2.94 min, A
95a	 MH^+:391.0, 3.09 min, C	**95b**	 MH^+:368.0, 2.32 min, C	**95c**	 MH^+:373.0, 2.98 min, C
95d	 MH^+:350.0, 2.15 min, C	**95e**	 MH^+:401.0, 1.78 min, D	**95f**	 MH^+:456.0, 2.16 min, D

95g	 MH+:372.0, 1.77 min, D	95h	 MH+:506.0, 2.23 min, D	95i	 MH+:389.0, 1.90 min, D

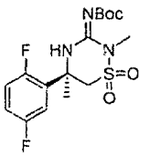
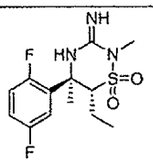
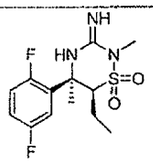
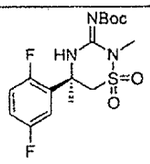
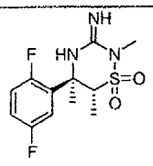
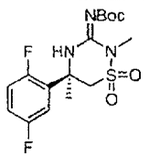
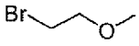
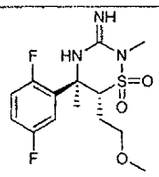
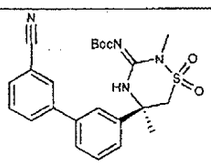
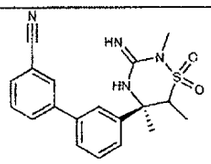
Scheme 16:



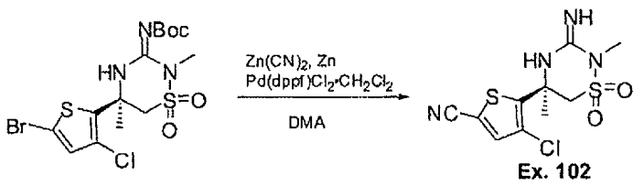
Step 1: To a solution of the thiophene (Scheme 3) (238 mg, 0.54 mmol) in anhydrous THF (2.5 mL) at -78°C was added a solution of LHMDS (1.0 M in THF, 1.63 mL). The resultant solution was stirred at -78°C for 1 hour. To this solution was added methyl iodide (0.086 mL, 1.36 mmol). The resultant solution was stirred at -78°C for an additional 1.25 hours. After that time, water was added and the mixture was allowed to warm to RT. The aqueous layer was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 80:20 hexanes:EtOAc) to afford the faster eluting *trans* isomer **H** (20 mg, 8.1 %) and the slower eluting *cis* isomer **I** (168 mg, 68%).

Step 2: To a solution of **I** (16 mg, 0.035 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL). The resultant solution was stirred at RT for 1.5 hours. The solution was concentrated to afford **Example 96** (15 mg) as the trifluoroacetate salt. LCMS data: (method A): t_R = 2.79 min, *m/e* = 354.2 (M+H).

Table IX: The following examples were prepared using a method similar to that described in Scheme 16 except NaHMDS was used instead of LHMDS in step 1.

Core	Alkyl halide	Examples		LCMS Obser. MH^+	LCMS Ret time (min)	lcms method
		**97**		318.1	2.02	B
		98		318.0	2.44	B
	MeI	**99**		304.0	1.77	B
		**100**		348.1	2.12	B
	MeI	**101**		369.0	2.16	B

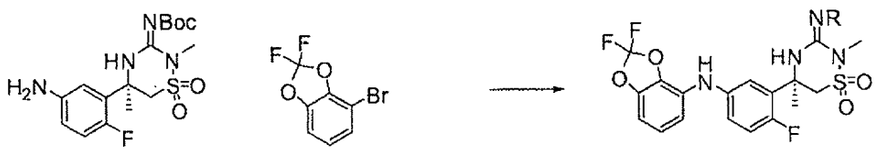
Scheme 17:



Ex. 102

A sealed microwave vial containing a slurry of the thiophene from Scheme 13 (74 mg, 0.16 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (19 mg, 0.023 mmol) , zinc (8.2 mg, 0.12 mmol), zinc cyanide (11 mg, 0.094 mmol) in N,N-dimethylacetamide (2.0 mL) was degassed by bubbling N_2 through the mixture for 5 min. The mixture was then heated to 85°C with stirring for 2 hours. The mixture was cooled to RT and diluted with Et_2O. The organic layer was washed with water (2x), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preperative TLC (SiO_2: 95:5 CH_2Cl_2:MeOH) to afford **Example 102** (15 mg). LCMS data: (method A): t_R = 2.22 min, *m/e* = 319.2 (M+H).

Scheme 18:



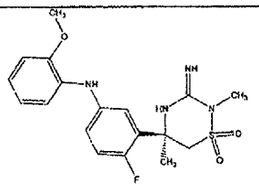
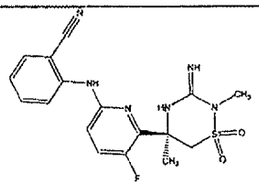
J

K R = Boc
Ex. 103 R = H

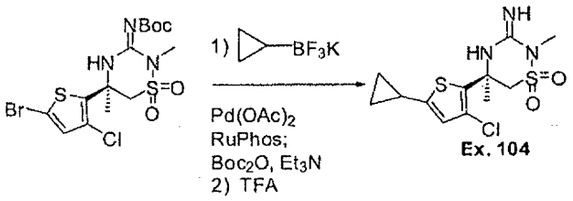
A 20 mL microwave vessel was flame-dried and cooled under vacuum, then backfilled with N_2, followed by two cycles of vacuum/N_2 backfill. The aniline (Scheme 10) (55 mg, 142 µmol), Pd_2dba_3-$CHCl_3$ (17 mg, 19 µmol), di-*tert*-butylphosphinyl-2-biphenyl (15 mg, 50 µmol), sodium *tert*-butoxide (31 mg, 322 µmol) and 4-bromo-2,2-difluorobenzo[d][1,3]dioxole **J** (48 mg, 202 µmol) were suspended in anhydrous toluene (2 mL), the microwave vial was sealed and placed in a preheated 65°C oil bath. After stirring for 18 h, the reaction mixture was diluted with EtOAc, washed with sat. aqueous $NaHCO_3$ (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil, which was subjected to silica-gel chromatography using 0→20 % EtOAc/hexanes as eluent to give intermediate **K** as a film (39 mg). This intermediate was deprotected with TFA (2 mL) in CH_2Cl_2 (3 mL) at RT, then diluted with toluene (5 mL), concentrated under reduced pressure, and subjected to RP-HPLC (C18, 30 ml/min, 10%-100% MeCN/H_2O) with 0.1% TFA) to give

Example 103 in 32% yield (24.9 mg, TFA salt). LCMS (conditions C): t_R = 3.44 min, *m/e* = 443.2 (M+H).

Table IXa: The following Examples were made using methods described in Scheme 18, with the following modification: The coupling reaction was run at 80 °C:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
103a	 MH^+:393, 2.01 min, D	**103b**	 MH^+:389, 1.88 min, D

Scheme 19:

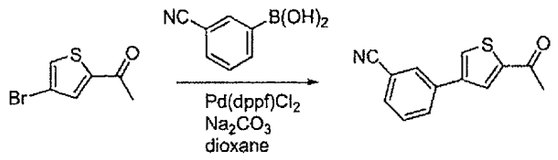


Step 1: To a microwave vial containing 3 mL toluene/water (3:1) was added the bromothiophene from Scheme 13 (50 mg, 0.11 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), RuPhos (21 mg, 0.04 mmol), potassium cyclopropyl trifluoroborate (17 mg, 0.12 mmol) and Cs_2CO_3 (108 mg, 0.33 mmol). The vial was sealed and the vial was purged with N_2. The mixture was then heated at 70°C for 12 hours. Additional $Pd(OAc)_2$ (5 mg, 0.02 mmol), RuPhos (21 mg, 0.04 mmol), potassium cyclopropyl trifluoroborate (17 mg, 0.12 mmol) were added and the mixture was heated under an atmosphere of N_2 to 70°C for an additional 12 hours. The mixture was cooled to RT, filtered through celite and extracted with CH_2Cl_2. The aqueous layer was dried over Na_2SO_4, filtered and concentrated. The crude mixture was then dissolved in CH_2Cl_2. To this solution was added Boc_2O (24 mg, 0.11 mmol) and Et_3N (13 mg, 0.13

mmol). The resultant solution was stirred overnight at RT. The solution was concentrated and the crude product was purified via preparative TLC (SiO_2; 70:30 hexanes:EtOAc).

Step 2: Example 104 was prepared from the above material using a method similar to that described in Scheme 11b step 2. LCMS data: (method A): t_R = 2.85 min, *m/e* = 334.2 (M+H).

Scheme 20:



The biaryl ketone was formed using a method similar to that described in Scheme 15 step 1.

Table X: The following examples were formed using methods similar to that described in Scheme 1a starting from the ketone in Scheme 20 and the appropriate sulfonamide from Table I.

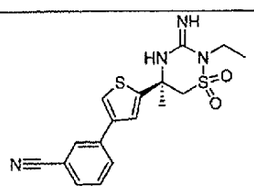
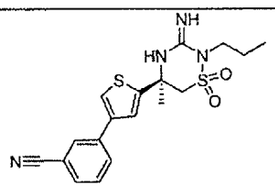
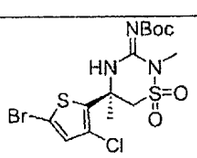
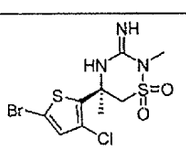
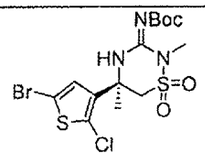
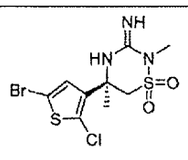
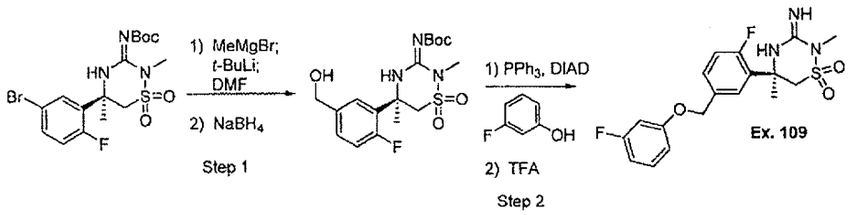
Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
105	 MH^+:374.9, 2.13 min, B	**106**	 MH^+:388.9, 2.22 min, B

Table XI: The following examples were prepared using a method similar to that described in Scheme 11b step 2.

Carbamate	Examples		LCMS Obser. MH^+	LCMS Ret. time (min)	LCMS method
	**107**		374.2	2.81	A

	108		374.2	2.69	A

Scheme 21:



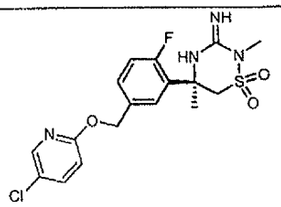
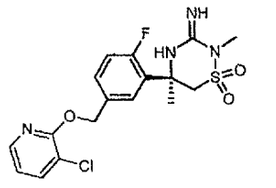
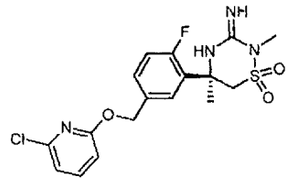
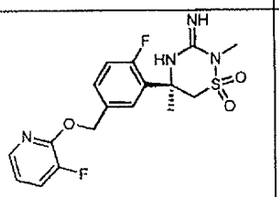
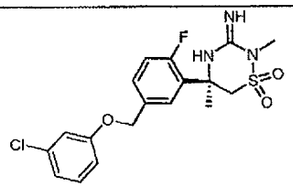
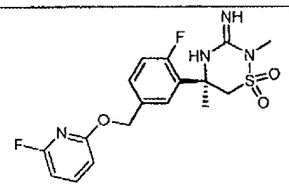
Step 1: To a solution of the bromide (Table IIb, entry 14) (500 mg, 1.11 mmol) in THF (7 mL) at -20°C was added a solution of MeMgBr (3 M in Et_2O, 0.48 mL, 1.4 mmol). The solution was stirred for 30 min at -20°C. The solution was then cooled to -78°C. To the solution was added *t*-BuLi (1.7 M in pentane, 1.6 mL, 2.8 mmol). The solution was stirred for 2 h at -78°C. To the solution was added DMF (0.13 mL, 1.7 mmol). The solution was allowed to slowly warm to RT over 2.5 hours. To the solution was then added sat. NH_4Cl (aq.) (20 mL) and the mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: 3:1 heptane:EtOAc) to afford the aldehyde (237 mg, 54%).

To a solution of the aldehyde (1.04 g, 2.60 mmol) in MeOH (10 mL) at 0°C was added portionwise over 3 min $NaBH_4$ (197 mg, 5.21 mmol). The resultant mixture was stirred for 20 min. To the solution was then added sat. NH_4Cl (aq.) (30 mL) and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: 1:1 heptane:EtOAc) to afford the alcohol (949 mg, 91%).

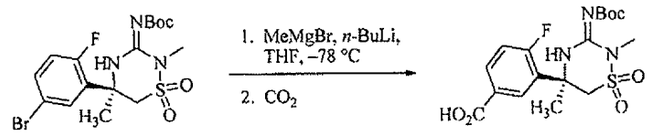
Step 2: To a solution of the alcohol from step 1 (105 mg, 0.26 mmol) and triphenylphosphine (102 mg, 0.39 mmol) in THF (3 mL) was added 3-fluorophenol (0.030 mL, 0.33 mmol). To this solution was added dropwise DIAD (0.075 mL, 0.39 mmol) and the resultant solution was stirred for 2 hours. The reaction was loaded onto a SiO_2 flash column and purified (gradient elution 100:0 to 0:100 heptane:EtOAc) to afford the ether (73 mg, 56%).

Ex. 109 was prepared from the above material using a method similar to that described in Scheme 11b step 2. LCMS (conditions B): t_R = 2.10 min, *m/e* = 396.0 (M+H).

Table XII: The following examples were prepared from the benzylic alcohol described in Scheme 21 step 1 using a method similar to that described in Scheme 21 step 2 using the appropriate aryl alcohol.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
110	 MH^+:412.0, 2.17 min, B	111	 MH^+:413.0, 2.02 min, B	112	 MH^+:397.0, 1.99 min, B
113	 MH^+:396.0, 2.06 min, B	114	 MH^+:397.1, 1.96 min, B	115	 MH^+:412.9, 2.08 min, B

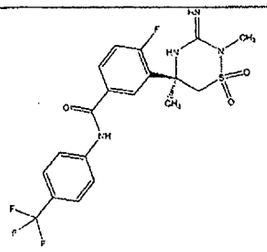
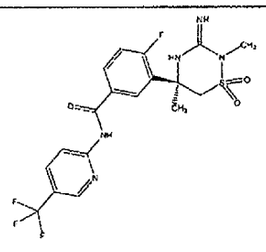
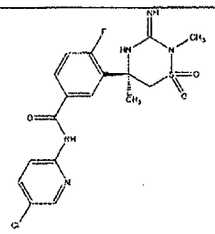
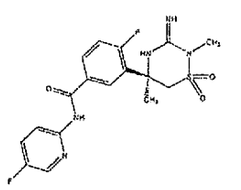
Scheme 22:



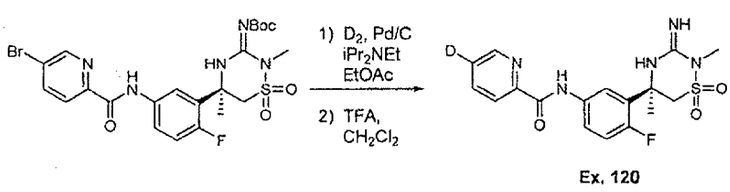
To a stirred solution of the bromide (Table IIb, entry 14, 2.55 g, 5.66 mmol) in anhydrous THF (45 mL) was added a MeMgBr solution (3 M in Et_2O, 2.4 mL, 7.20 mmol) at -78 °C under nitrogen. After addition was completed, the reaction mixture was stirred for 20 min. After that time, a solution of *n*-BuLi solution (2.5 M in hexanes, 5.1 mL, 12.8 mmol) was added dropwise over 5 min. The reaction mixture was then stirred for 50 min at –78 °C and the cooling bath was removed. CO_2 gas was bubbled into the reaction mixture for 50 min. After this time, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and 1 N

hydrochloric acid (aq) (100 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 10% methanol/methylene chloride) to afford the carboxylic acid (1.49 g, 53%).

Table XIII: The following examples were prepared using a procedure similar to that described in Scheme 11b using the acid from Scheme 22 and the appropriate aryl amine. The molar ratios used for the acid, amine and BOPCl were 1:1.3:1.5 respectively.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
116	 MH^+:459.0, 2.35 min, B	**117**	 MH^+:460.1, 2.02 min, B
118	 MH^+:426.1, 1.86 min, B	**119**	 MH^+:410.1, 1.74 min, B

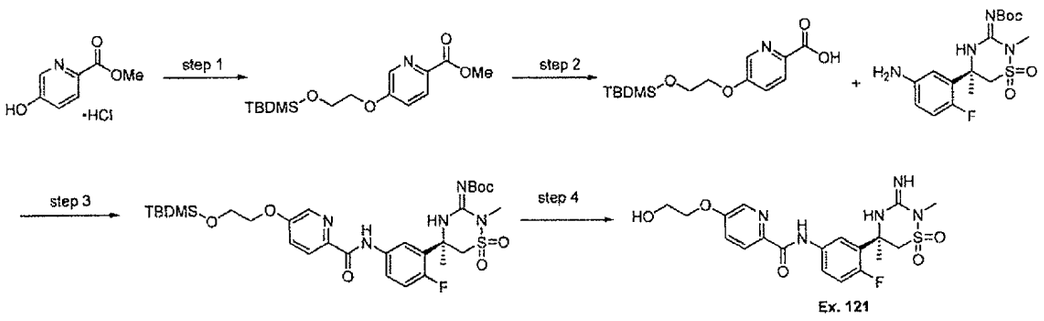
Scheme 23:



Ex. 120

To a sealed round bottom flask containing a solution of the bromide (Table V: Boc intermediate for Ex. 29) (48 mg, 0.084 mmol) in EtOAc (4 mL) under an atmosphere of N_2 was added iPr_2NEt (22 μL, 0.13 mmol) and 10% Pd/C, Degussa type (9.0 mg, 0.0042 mmol). The flask was evacuated and backfilled with D_2 (3x). The mixture was stirred under an atmosphere of D_2 for 4.5 hours. The mixture was purged with N_2, filtered and concentrated. The residue was partitioned between EtOAc and 1/2 sat. $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford the deuterate (38 mg, 92%) as a white solid. **Example 120** was prepared as its TFA salt from the above material using a procedure similar to that described in Scheme 11b step 2. LCMS data: (method D): t_R = 1.76 min, *m/e* = 393.0 (M+H).

Scheme 24:



Step 1: To the methyl 5-hydroxypicolinate hydrochloride prepared in scheme 11h (0.40 g, 2.1 mmol) in DMF (1 mL) was added potassium carbonate (0.88 g, 6.3 mmol) and (2-bromoethoxy)-*tert*-butyldimethylsilane (0.68 mL, 3.2 mmol). The reaction was warmed to 70 °C and stirred for 18 h. Another equivalent of (2-bromoethoxy)-*tert*-butyldimethylsilane was added and the reaction stirred for an additional 1.5 h at 90 °C. The reaction was cooled to room temperture and water was added. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex) over 30 minutes to provide product (0.31 g, 47%).

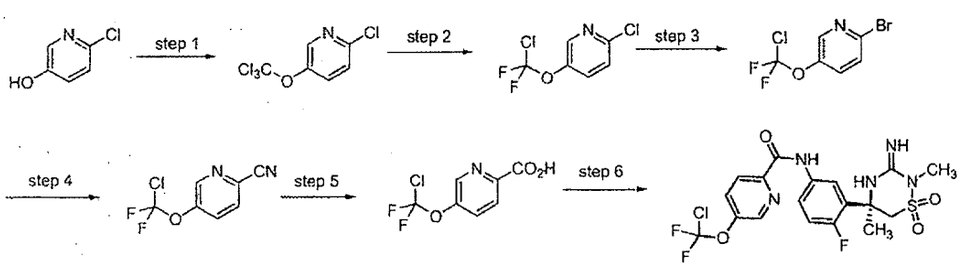
Step 2: To the compound prepared in step 1 (0.31 g, 1.0 mmol) in THF (1.5 mL) was added 2N LiOH (1.5 mL, 3 mmol). The reaction was stirred at room temperature for 4 h. The reaction pH was adjusted to pH~4 using saturated aqueous citric acid. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the carboxylic acid (0.18 g, 60%).

Step 3: To the aniline prepared in scheme 10 (0.15 g, 0.39 mmol) in pyridine (1.5 mL) was added the carboxylic acid prepared in step 2 (0.17 g, 0.58 mmol) followed by BOP Cl (0.23 g, 0.89 mmol). The reaction was stirred at room temperature for 4.5 h. The reaction was then concentrated *in vacuo* and the residue was taken up into EtOAc and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide the amide product (0.14 g, 54%).

Step 4: To the product from step 3 (0.20 g, 0.30 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.33 mL, 0.33 mmol). The reaction was stirred at room temperature for 24h. EtOAc was added to the reaction mixture and the mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-70% EtOAc/hex over 30 minutes) to yield the alcohol (0.14 g, 85%).

To that product (0.14 g, 0.25 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 1 h and concentrated *in vacuo*. The reaction was then stirred for 1 h with methanol (1 mL) and 7N NH_3/MeOH (0.5 mL). The reaction was then concentrated *in vacuo* and taken up into EtOAc. The mixture was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **Example 121** (0.10 g, 88%). LCMS data: (method D): t_R = 1.68 min, *m/e* = 452.0 (M+H).

Scheme 25



Ex. 122

Step 1: To 2-chloro-5-hydroxypyridine (10 g, 80 mmol) in 1.5 M $NaOH_{(aq)}$ (67 mL) at 0 °C was added thiophosgene (6.0 mL, 79 mmol) in chloroform (46 mL) dropwise. After addition, the reaction was stirred for 2 h. The mixture was then extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed with 1N HCl (aq) and water, dried ($MgSO_4$), and filtered. Into this solution was bubbled Cl_2 gas until the reaction became warm (~1 minute). The reaction was stirred at room temperature for 2h and then Cl_2 gas was bubbled through the mixture again. The reaction was then stirred for 18 h. Nitrogen gas was then bubbled through the reaction mixture to remove residual Cl_2 gas. The reaction was then concentrated *in vacuo*. The residue was purified by reverse phase chromatography [C18 (800g) 5% (2 column volumes (CV), 5-100% (10 CV), 100 (2 CV); 0.1% formic acid/water//0.1% formic acid/acetonitrile] to provide the trichloromethyl ether (4.0 g, 21%).

Step 2: To antimony trifluoride (4.1 g, 22.7 mmol) and antimony pentachloride (0.22 mL, 1.7 mmol) at 120 °C was added the trichloromethylether prepared in step 1 (2.8 g, 11.3 mmol). The mixture was warmed to 150 °C, stirred for 1 h and then cooled to room temperature. DCM and saturated $NaHCO_3$ (aq) were added and the aqueous laywer was extracted with DCM. The combination was washed with 20% $KF_{(aq)}$, water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide product (2.0 g, 83%).

Step 3: To the chlorodifluoromethylether prepared in step 2 (2.0 g, 9.3 mmol) in propanenitrile (11 mL) was added bromotrimethylsilane (2.8 mL, 21 mmol). The reaction was warmed to 100 °C and stirred for 6.5 h. The reaction was cooled to room temperature and saturated $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a product (2.1 g) which was used in the next step without further purification.

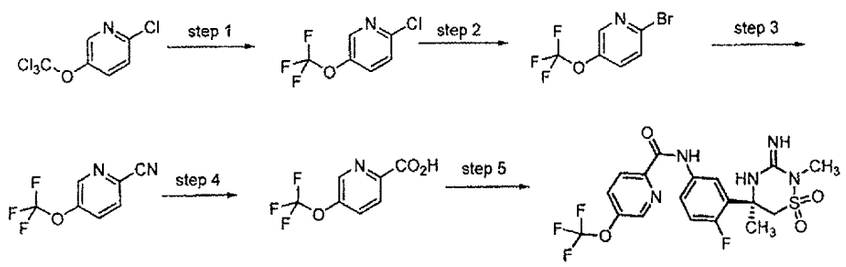
Step 4: To the bromopyridine prepared in step 3 (0.33 g, 1.3 mmol) in DMF (2.7 mL) in a microwave reaction vial was bubbled N_2 gas for 5 minutes. $Zn(CN)_2$ (0.22 g, 1.9 mmol) was added and nitrogen was bubbled through the reaction mixture for 5 minutes. $Pd(PPh_3)_4$ (0.078 g, 0.07 mmol) was added and nitrogen was bubbled through the reaction for 5 minutes. The reaction vessel was capped and warmed to 100 °C, then stirred for 2.5 h and cooled to room temperature. Water and EtOAc were added and the combination was then filtred through a

pad of Celite washing with EtOAc. The filtrate was then extracted with EtOAc. The organics were then combined and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, then purified by silica gel chromatography (0-8% EtOAc/hex over 30 minutes) to provide product (0.21 g, 81%).

Step 5: To the nitrile prepared in step 4 (0.21 g, 1.0 mmol) in ethanol (2 mL) was added 2N $LiOH_{(aq)}$ (2.7 mL). The reaction was warmed to 100 °C and stirred for 2 h. The reaction was cooled to room temperature and the ethanol removed *in vacuo*. The pH of the aqueous was adjusted to pH~4 using saturated aqueous citric acid. Solid sodium chloride was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a white solid (0.14 g, 62%).

Step 6: To the aniline prepared in scheme 10 (0.20 g, 0.52 mmol) in THF (0.84 mL) at 0 °C was added the carboxylic acid prepared in step 5 (0.14 g, 0.63 mmol), *N,N*-diisopropylethylamine (0.27 mL, 1.6 mmol), and 50% 1-propanephosphonic acid cyclic anhydride in ethyl acetate (0.42 mL, 0.71 mmol), respectively. The reaction mixture was then stirred for 1h at 0 °C and then another hour at room temperature. Water was added to the reaction and the mixture was stirred vigorously for 20 minutes. The mixture was then extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide the amide (0.26 g, 84%). To the amide (0.26 g, 0.44 mmol) in DCM (1 mL) at room temperature was added TFA (0.68 mL, 8.8 mmol). The reaction was stirred for 18 h and then concentrated *in vacuo*. The residue was taken up into DCM and stirred with saturated $NaHCO_3$ (aq). The mixture was extracted with DCM. The combined DCM layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **Example 122**. LCMS data: (method D): t_R = 2.06 min, *m/e* = 492 (M+H).

Scheme 26



Ex. 123

Step 1: To antimony trifluoride (4.05 g, 23 mmol) and antimony pentachloride (0.22 mL, 1.7 mmol) at 120 °C was added the trichloromethyl ether prepared in step 1 of scheme 25 (2.80 g, 11 mmol). The reaction was warmed to 165 °C under nitrogen and stirred for 14 h and then warmed to 175 °C and stirred for an additional 4h. The reaction was cooled to room temperature. The resulting solid mass was stirred vigorously with saturated $NaHCO_{3\,(aq.)}$ [Gas evolution!] and EtOAc. The mixture was filtered through a plug of Celite washing with EtOAc. The filtrate was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hex over 30 minutes) (0.90 g, 40%).

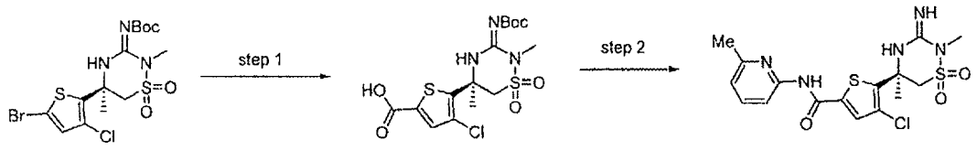
Step 2: The trifluoromethylether prepared in step 1 was converted to the bromopyridine according to the procedure in step 3 of scheme 25.

Step 3: The bromopyridine prepared in step 2 was converted to the cyanopyridine according to the procedure in step 4 of scheme 25.

Step 4: The cyanopyridine prepared in step 3 was converted to the pyridylcarboxylic acid according to the procedure in step 5 of scheme 25.

Step 5: The pyridylcarboxylic acid prepared in step 4 was converted to **Ex. 123** according to the procedures in step 6 of scheme 25. LCMS (conditions D): t_R = 2.04 min, *m/e* = 476.0 (M+H).

Scheme 27



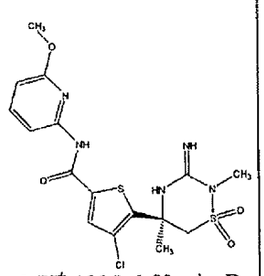
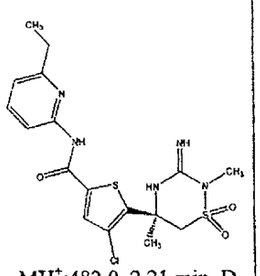
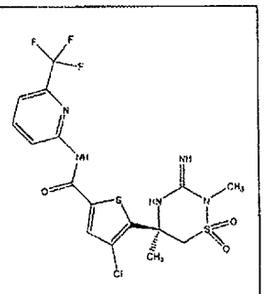
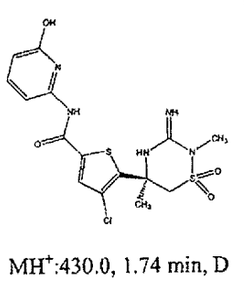
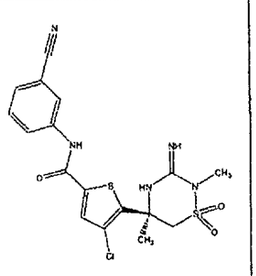
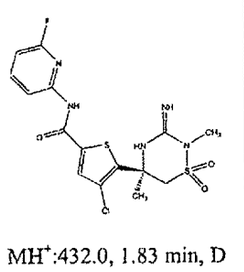
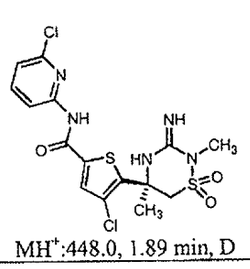
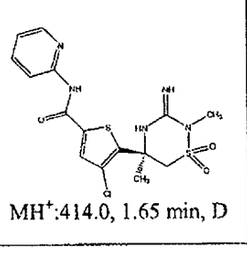
Scheme 13

Step 1: To the bromothiophene prepared in scheme 13 (1.34 g, 2.83 mmol) in THF (9.2 mL) at 0 °C was added methylmagnesium chloride (3.0 M in THF, 1.18 mL, 3.54 mmol). The reaction was stirred for 30 minutes at 0 °C and then cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 2.55 mL, 6.38 mmol) was added over 10 minutes. The reaction was stirred for 1 hour at -78 ° and then CO_2 gas was bubbled through the reaction. The cold bath was taken away and the reaction allowed to warm to room temperature while continuing to bubble CO_2 gas through the mixture. To the mixture was added 1N HCl $_{(aq.)}$ and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-80% EtOAc/hex over 30 minutes) to provide the carboxylic acid (0.97 g, 78%).

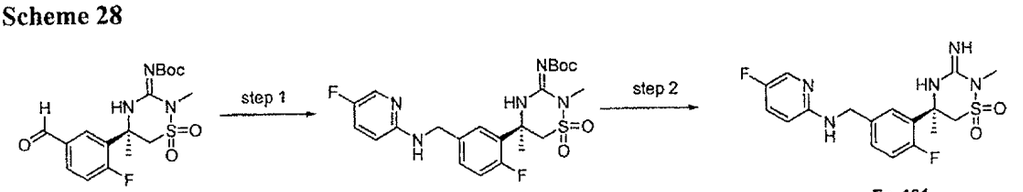
Step 2: To the carboxylic acid prepared in step 1 (0.027 g, 0.06 mmol) in pyridine (0.25 mL) was added 2-amino-6-methylpyridine (0.013 g, 0.12 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.024 g, 0.09 mmol). The reaction was stirred for 18 h at room temperature and then concentrated *in vacuo*. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative silica gel TLC (1000 μm SiO_2, 30% EtOAc/hexane) to provide product (13 mg, 40%). To the amide (0.065 g, 0.14 mmol) in DCM (0.4 mL) was added TFA (0.2 mL). The reaction was stirred for 20 h at RT and then concentrated in vacuo to provide **Ex. 124** as the TFA salt. LCMS data: (method D): t_R = 1.59 min, *m/e* = 428.0 (M+H).

Table XIV: The following examples were prepared using procedures similar to those described in Scheme 27 using the appropriate aryl amines.

Examples
(LCMS data: observed MH^+, HPLC retention time and LCMS method)

125  MH^+:466.0, 1.82 min, D	**126**  MH^+:482.0, 2.21 min, D	**127**  MH^+:442.0, 1.70 min, D
128  MH^+:430.0, 1.74 min, D	**129**  MH^+:438.0, 1.84 min, D	**130**  MH^+:432.0, 1.83 min, D
130a  MH^+:448.0, 1.89 min, D	**130b**  MH^+:414.0, 1.65 min, D	

Scheme 28



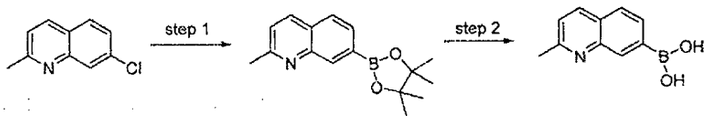
Ex. 131

Step 1: To the aldehyde (intermediate from scheme 21 step 1 prior to treatment with $NaBH_4$) (0.10 g, 0.2 mmol) in methanol (1.5 mL) and pyridine (0.5 mL) was added 4 Å mol sieves (100 mg), 2-amino-5-fluoropyridine (0.056 g, 0.5 mmol), and acetic acid (0.02 mL, 0.35 mmol). The reaction was warmed to 50 °C and stirred for 18 h. After cooling to room temperature, saturated sodium bicarbonate (0.5 mL) was added and the mixture was stirred for

10 minutes. The mixture was then filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-35% EtOAc/hex over 30 minutes) to provide product (0.077 g, 78%).

Step 2: To the material prepared in step 1 (0.077 g, 0.16 mmol) in DCM (0.4 mL) was added TFA (0.24 mL, 3.1 mmol). The reaction was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was taken up into DCM and washed with saturated $NaHCO_3$ (aq) water, and brine. The DCM layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was then taken up into DCM and excess 2N HCl/ether was added. The mixture was concentrated to provide **Ex. 131** (57 mg) as the HCl salt. LCMS data: (method D): t_R = 1.56 min, *m/e* = 396.2 (M+H).

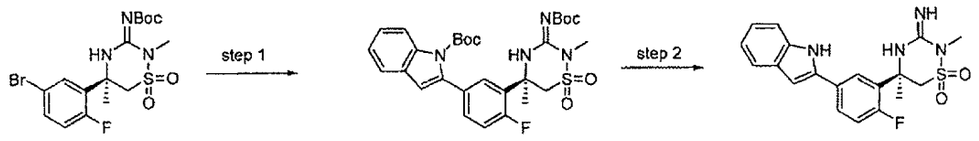
Scheme 29:



Step1: To 7-chloroquinaldine (1.2 g, 6.5 mmol) in THF (80 mL) was added bis(pinacolato)diboron (1.9 g, 7.6 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene hydrochloride (0.17 g, 0.4 mmol), and potassium acetate (1.6 g, 16 mmol). Nitrogen was bubbled through the reaction for 10 minutes. Palladium acetate (0.044 g, 0.20 mmol) was added and the reaction was warmed to reflux and stirred for 6 hours. The reaction was filtered through a plug of silica gel washing with EtOAc. The filtrate was concentrated *in vacuo*. The filtrate was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide the boronic ester (0.97 g, 55%).

Step 2: To the boronic ester prepared in step 1 (0.78 g, 2.9 mmol) in THF (6 mL) was added water (24 mL) and sodium metaperiodate (0.93 g, 4.4 mmol). The reaction was stirred for 1 h and then 3M $HCl_{(aq)}$ (19 mL) were added. The mixture was stirred for 45 minutes and then extracted with EtOAc. The aqueous layer was then basified with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the boronic acid (0.34 g, 63%).

Scheme 30:

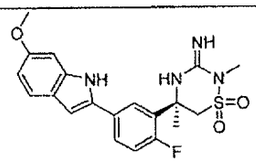
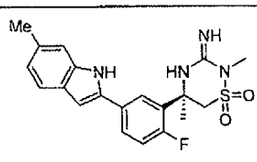
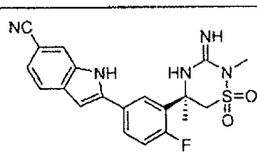


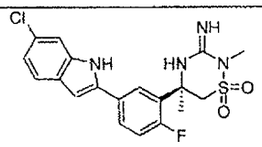
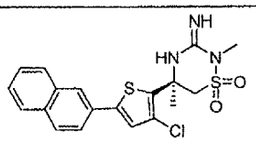
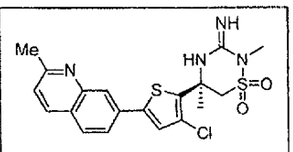
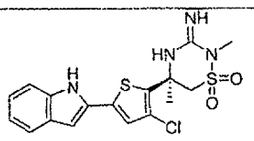
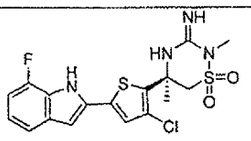
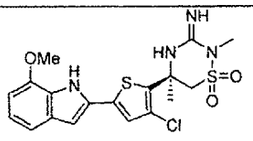
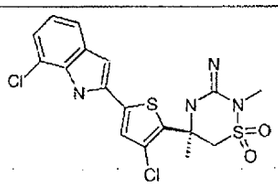
Ex.132

Step 1: To the bromide (Table IIb, entry 14) (0.15 g, 0.33 mmol) in a microwave reaction vial was added *t*-butanol (1.5 mL), 1-(*t*-butoxycarbonyl)-indole-2-boronic acid (0.16 g, 0.60 mmol) and aqueous potassium carbonate (2M, 0.25 mL, 0.50 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes. $PdCl_2(dppf)$ (0.054 g, 0.066 mmol) was added and nitrogen was bubbled through the reaction for 5 minutes. The reaction vessel was capped, warmed to 65 °C, and stirred for 3 h. The reaction was cooled to room temperature and EtOAc was added. The mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hex over 30 minutes) to provide the biaryl product (0.12 g, 60%).

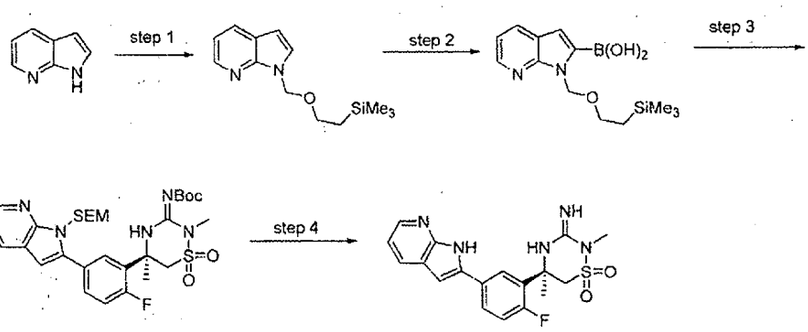
Step 2: To the product prepared in step 1 (0.12 g, 0.20 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 1 h and then concentrated *in vacuo* to provide **Ex. 132** as a TFA salt (0.078 g, 78%). LCMS data: (method D): t_R = 1.96 min, *m/e* = 387.0 (M+H). The residue was further purified as needed by reverse phase chromatography [C18 5% (2 column volumes (CV), 5-100% (10 CV), 100 (2 CV); 0.1% formic acid/water//0.1% formic acid/acetonitrile].

Table XV: The following examples were prepared using procedures similar to those described in Scheme 30 using the appropriate aryl bromides and boronic acids.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
133	 MH^+:417.0, 1.93 min, D	**134**	 MH^+:401.0, 2.01 min, D	**135**	 MH^+:412.0, 1.93 min, D

136	 MH+:421.0, 2.03 min, D	**137**	 MH+:420.0, 2.07 min, D	**138**	 MH+:435.0, 1.68 min, D
139	 MH+:409.0, 1.95 min, D	**140**	 MH+:428.0, 1.99 min, D	**141**	 MH+:439.0, 1.96 min, D
141a	 MH+:443.0, 2.13 min, D	**	**	**	**

Scheme 31:



Ex. 142

Step 1: To 7-azaindole (1.5 g, 12.7 mmol) in DMF (30 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.56 g, 14 mmol). The reaction was stirred for 15 minutes at room temperature then cooled to -40 °C (EtOAc/CO_2 cooling bath). (2-(Chloromethoxy)ethyl) trimethylsilane (2.5 mL, 14 mmol) was then added and the reaction allowed to warm to room temperature. The reaction was stirred at room temperature for 18 h. EtOAc was added and the mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

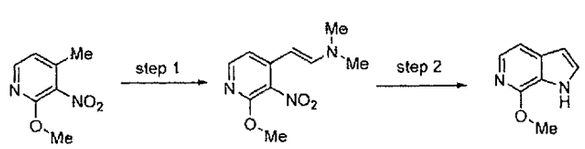
The residue was purified by silica gel chromatography (0-10% EtOAc/hex over 30 minutes) to provide the SEM-protected indole (2.9 g, 91%).

Step 2: To the SEM-protected indole prepared in step 1 (0.99 g, 4.0 mmol) in THF (10 mL) at -40 °C was added *n*-BuLi (2.5 M in hexanes, 1.9 mL, 4.8 mmol). The mixture was stirred at -40 °C for 1 h and then triisopropyl borate (1.2 mL, 5.2 mmol) was added. The mixture was allowed to warm to room temperature while stirring for 18 h. To the reaction mixture was added 1N HCl (aq). The mixture was stirred at room temperature for 30 minutes. The mixture was then adjusted to pH~5 using saturated $NaHCO_3$ (aq) The mixture was extracted with ether. The combined ether extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-50% EtOAc/hex over 30 minutes) to provide the indole boronic acid (0.20 g, 17%).

Step 3: To the bromide (Table IIb, entry 14) (0.21 g, 0.46 mmol) in *t*-butanol (3 mL) a microwave reaction vial was added the boronic acid prepared in step 2 (0.20 g, 0.68 mmol) and 2M $K_2CO_{3\,(aq)}$ (0.34 mL, 0.68 mmol). Nitrogen was bubbled through the reaction for 10 minutes. $PdCl_2$(dppf) (0.075 g, 0.092 mmol) was added and the reaction was sealed and heated to 65 °C. After 3 h, the reaction was cooled to room temperature and EtOAc was added. The mixture was washed with water and brine ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hex over 30 minutes) to provide the coupling product (0.21 g, 74%).

Step 4: To the coupling product prepared in step 3 (0.086 g, 0.14 mmol) was added 4M HCl in ethanol (6 mL). The reaction was warmed to 60 °C and stirred for 20 h. The reaction was concentrated *in vacuo* and then purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid) to provide **Ex. 142** (0.030 g). LCMS data: (method D): t_R = 1.67 min, *m/e* = 388.0 (M+H).

Scheme 32:

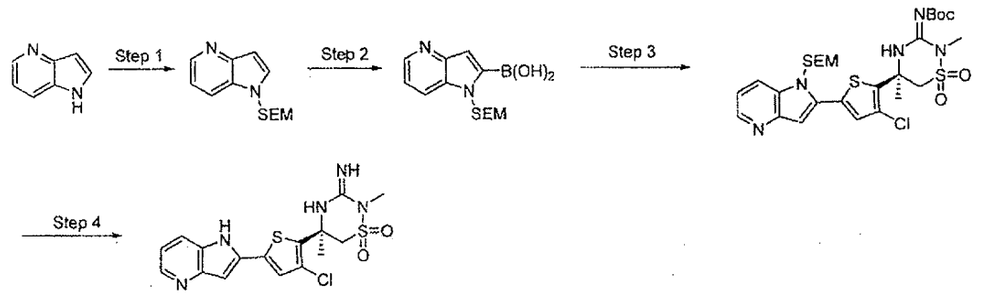


Step 1: To the nitropyridine (5.1 g, 30 mml) in DMF (5 mL) was added 1,1-methoxy-*N,N*-dimethylmethanamine (15 mL, 110 mmol). The reaction was warmed to 130 °C and stirred

for 16 h. The reaction was cooled to room temperature and then added to a beaker of ice. The resulting solid was isolated by filtration to give product (5.9 g, 88%).

Step 2: To the enamine prepared in step 1 (5.9 g, 26 mmol) in ethanol (275 mL) was added 10% palladium on carbon, Degussa type (1.5 g). The reaction mixture was shaken under a hydrogen atmosphere (15 psi) for 15 minutes. The reaction was filtered through a bed of celite washing with DCM. The filtrate was concentrated *in vacuo* to provide the indole (4.3 g, 61%).

Scheme 33:



Ex. 143

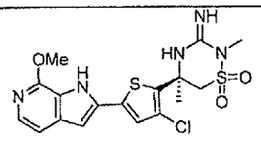
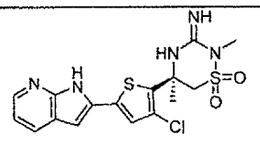
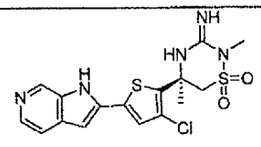
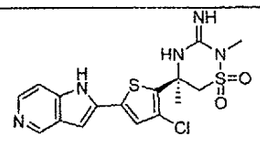
Step 1: The 4-azaindole was protected with the SEM group according to the procedure described in step 1 of Scheme 31.

Step 2: The SEM protected indole prepared in step 1 was converted to the 2-boronic acid according to the procedure described in step 2 of Scheme 31.

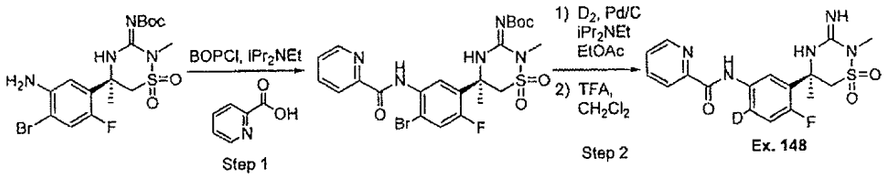
Step 3: To SEM-protected indole 2-boronic acid prepared in step 2 (0.40 g, 1.37 mmol) in a microwave reaction vial in *t*-butanol (3 mL) was added potassium carbonate (2M, 0.6 mL, 1.1 mmol) and the bromothiophene prepared in scheme 13 (0.36 g, 0.76 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes after which $PdCl_2(dppf)$ (0.12 g, 0.15 mmol) was added. The reaction vessel was capped and warmed to 65 °C. The reaction was stirred for 16 h and then cooled to room temperature. EtOAc was added and the mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was taken up into DCM (2 mL) and $(Boc)_2O$ (166 mg) was added. The reaction was stirred at room temperature for 18 h. The reaction was concentrated *in vacuo* to provide a residue that was purified by silica gel chromatography (0-40% EtOAc/hex) to provide a mixture of desired product and bis-boc product (360 mg). The mixture was carried on directly to the next step

Step 4: The biaryl prepared in step 3 (0.28 g, 0.43 mmol) was heated in 4N HCl in ethanol (12 mL) to 65 °C for 12 h. The reaction was concentrated *in vacuo* to provide desired material and the indole *N*-hydroxymethyl intermediate. The mixture was taken up into acetone (2 mL) and ethanol (1 mL) and potassium carbonate was added (0.15 g, 1.1 mmol). The mixture was stirred at room temperature for 1 h and then added to saturated $NH_4Cl_{(aq)}$. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative silica gel TLC (10% MeOH/DCM) to provide **Ex. 143** (0.10 g, 57%). LCMS data: (method D): t_R = 1.67 min, *m/e* = 410.0 (M+H). (Alternatively, the residue could be purified by reverse phase chromatography [C18 5% (2 column volumes (CV), 5-100% (10 CV), 100 (2 CV); 0.1% formic acid/water//0.1% formic acid/acetonitrile]).

Table XVI: Using the conditions described in Scheme 33, the following examples were prepared from the appropriate aryl bromides and aryl boronic acids.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
144	 MH^+:440.0, 1.65 min, D	**145**	 MH^+:410.0, 1.78 min, D
146	 MH^+:410.0, 1.70 min, D	**147**	 MH^+:410.0, 1.67 min, D

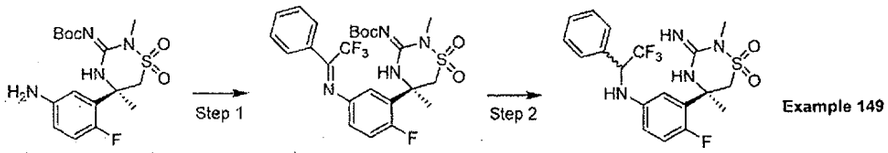
Scheme 34:



Step 1: To a slurry of the aniline from Scheme 10a (95 mg, 0.20 mmol), picolinic acid (30 mg, 0.25 mmol) and BOPCl (78 mg, 0.31 mmol) in CH_2Cl_2 (4 mL) at 0°C was added iPr_2NEt (89 µL, 0.51 mmol). The resultant mixture was warmed to RT and stirred for 16 hours. The mixture was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via preparative TLC (SiO_2: 1:1 hexanes:EtOAc) to afford the amide (47 mg, 40%) as a white solid.

Step 2: **Ex. 148** was prepared as its TFA salt from the above material using a procedure similar to that described in Scheme 23. LCMS data: (method D): t_R = 1.75 min, *m/e* = 393.0 (M+H).

Scheme 35:



Step 1: To a RT mixture of aniline (Scheme 10, 0.1 g, 0.26 mmol), 2 mL DCM, diisopropylethylamine (45 µL, 0.26 mmol), and trifluoroacetophenone (0.045 g, 0.26 mmol) was slowly added dropwise titanium tetrachloride (1.0 M in DCM, 0.26 mL, 0.26 mmol). The reaction was stirred for 2 hours. Saturated aqueous sodium bicarbonate was then poured into the reaction, forming a white precipitate, which was then filtered through celite. The celite was washed with DCM and the filtrate was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hexanes over 20 minutes) to provide the imine compound (0.051 g, 36%).

Step 2: To the imine prepared in Step 1 (0.051 g, 0.09 mmol) stirring in 2 mL MeOH was added sodium borohydride (0.007 g, 0.18 mmol). The reaction was stirred at room temperature for 1 hour, then concentrated to dryness *in vacuo*. The reaction was purified by preparative RP HPLC (10-100% acetonitrile with 0.1% formic acid/water with 0.1% formic acid over 22 minutes) to provide the amine product. This material was treated with 2 mL 20% TFA/DCM for 1 hour, and then concentrated *in vacuo* to provide **Example 149** (1:1 mixture of

diastereomers) as a trifluoroacetate salt (39 mg, 75%). LCMS data: (method D): t_R = 1.97 min, *m/e* = 445.0 (M+H).

Table XVII: The following examples were made according to the methods described in Scheme 35:

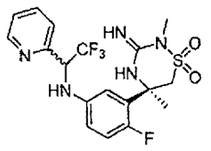
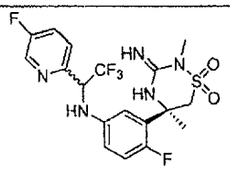
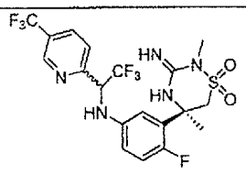
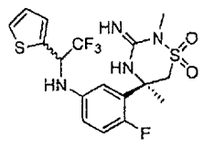
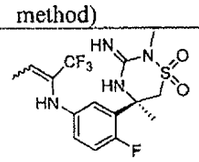
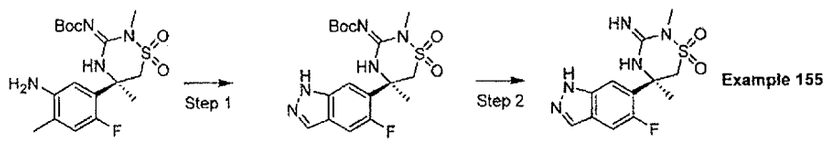
Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
150	 MH^+:446.0, 1.87 min, D	**151**	 MH^+:464.0, 1.93 min, D
152	 MH^+:514.0, 1.99 min, D	**153**	 MH^+:451.0, 1.93 min, D

Table XVIII: The following Example was made as a mixture of diastereomers using the following sequence: (1) Scheme 35, Step 1, (2) Scheme 11b, Step 2:

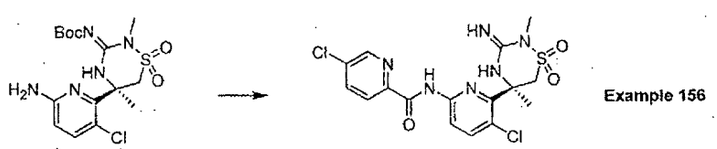
Example (LCMS data: observed MH^+, HPLC retention time and LCMS method)	
154	 MH^+:395.0, 1.89 min, D

Scheme 36:



Step 1: To the aniline (Table IV, entry 5 0.2 g, 0.5 mmol) stirring at room temperature in glacial acetic acid (5 mL) was added dropwise a solution of sodium nitrite (0.035 g, 0.5 mmol) in water (0.25 mL). The reaction was stirred at room temperature 6 hrs, then concentrated to dryness *in vacuo*. The residue was purified by silica gel chromatography (0-100% EtOAc/hexanes over 30 minutes) to provide the indazole compound as a solid (0.060 g, 29%). **Step 2:** The material from step 1 (0.005g, 0.012 mmol) was treated according to Scheme 11b, step 2 to afford **Example 155** as the TFA salt (0.005 g, 97%). LCMS data: (method D): t_R = 1.63 min, *m/e* = 312.0 (M+H).

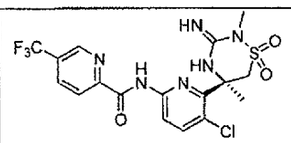
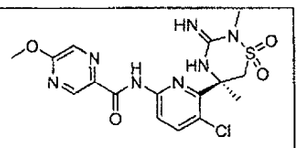
Scheme 37:



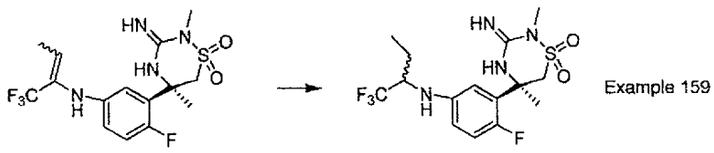
To the aminopyridine compound (Table IIIb, 0.068 g, 0.17 mmol) stirring in 1.68 mL 4:1 DMF:diisopropylethylamine at room temperature was added 5-chloropicolinoyl chloride (Scheme 11p) and 1 crystal of DMAP. The reaction was heated to 50°C and stirred for 48 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes over 20 minutes, then 60-100% EtOAc/hexanes 20-30 minutes) to provide an amide product (0.014 g, 15%). This material was treated according to Scheme 11b, step 2 to provide **Example 156** (0.014 g, 97%) as a trifluoroacetate salt. LCMS data: (method D): t_R = 1.91 min, *m/e* = 443.0 (M+H).

Table XIX: The following examples were made according to the methods described in Scheme 37 using acid chlorides from Table IVj:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)

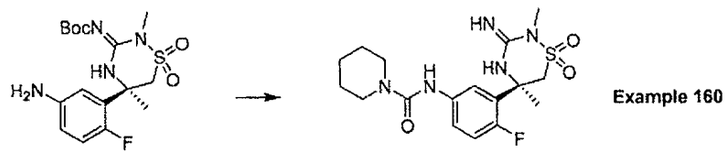
157	 MH+:477.0, 1.93 min, D	**158**	 MH+:440.0, 1.84 min, D

Scheme 38:



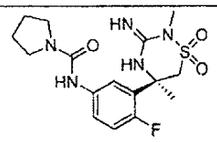
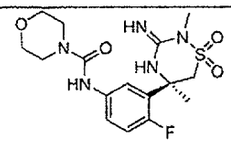
To **Example 154** (0.020 g, 0.04 mmol) stirring in 2 mL EtOH was added 10% palladium on carbon (0.010 g). This solution was subjected to a hydrogen atmosphere (balloon) and stirred 16 hours. The reaction was filtered through celite and washed with MeOH. The filtrate was concentrated to dryness *in vacuo* and purified by preparative RP HPLC (10-100% acetonitrile with 0.1% formic acid/water with 0.1% formic acid over 22 minutes) to provide **Example 159** as a mixture of diastereomers as a formate salt (0.013 g, 65%). LCMS data: (method D): t_R = 1.92 min, *m/e* = 397.0 (M+H).

Scheme 39:

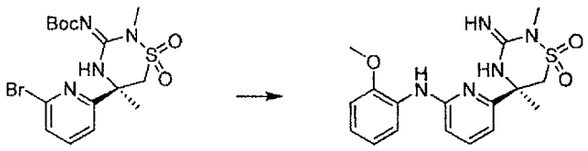


Step 1: To the aniline (Scheme 10, 0.1 g, 0.26 mmol) stirring in 3 mL DCM was added triethylamine (54 µL, 0.39 mmol) and 1-piperidinecarbonyl chloride (34 µL, 0.27 mmol), and the mixture was allowed to stir for 3 days at room temperature. The reaction was poured into water and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-80% EtOAc/hexanes over 20 minutes) to provide a urea product (0.093 g, 72%). This compound was then treated according to Scheme 11b, Step 2 to provide **Example 160** (0.094 g, 98%) as a trifluoroacetate salt. LCMS data: (method D): t_R = 1.75 min, *m/e* = 398.2 (M+H).

Table XX: The following examples were made according to the methods described in Scheme 39 using the appropriate carbonl chloride:

Example (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
161	 MH^+:384.2, 1.61 min, D	161a	 MH^+:400.0, 1.47 min, D

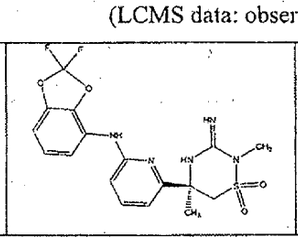
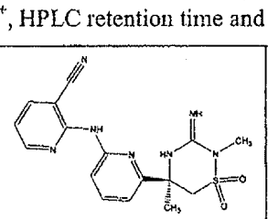
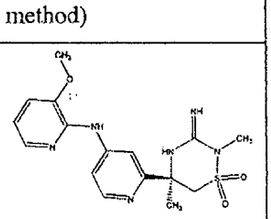
Scheme 40:

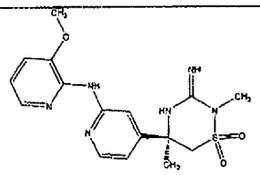
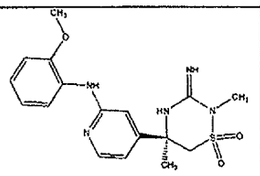


Ex. 162

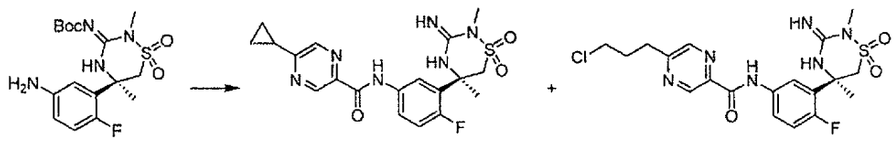
The bromopyridine compound (Scheme 7a , step 6) 0.07 g, 0.16 mmol) along with *O*-anisidine (22 μL, 0.19 mmol), tris(dibenzylideneacetone)dipalladium (0.003 g, 0.003 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.004 g, 0.006 mmol), and sodium *t*-butoxide (0.022 g, 0.22 mmol) were stirred in a flame-dried, sealed microwave vial flushed with nitrogen in 2 mL anhydrous toluene at 80°C for 3.5 hours. The reaction mixture was cooled to room temperature, poured into water, and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes over 20 minutes) to provide biarylamine product (0.007 g, 9%). This material was treated according to Scheme 11b, Step 2 to provide **Example 162** as a trifluoroacetate salt (0.007 g, 97%). LCMS data: (method D): t_R = 1.80 min, *m/e* = 376.2 (M+H).

Table XXI: The following Examples were made according to the methods in Scheme 40:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
163		164		165	

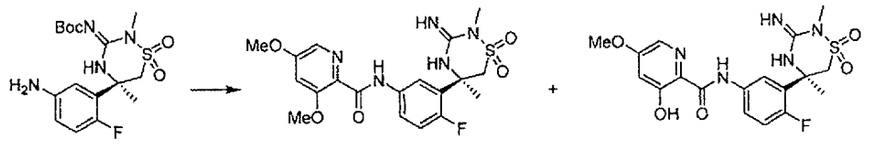
	MH^+:426.0, 2.05 min, D		MH^+:372.0, 1.83 min, D		MH^+:377.0, 1.65 min, D
166	 MH^+:377.0, 1.18 min, D	**167**	 MH^+:376.0, 1.38 min, D		**

Scheme 41:



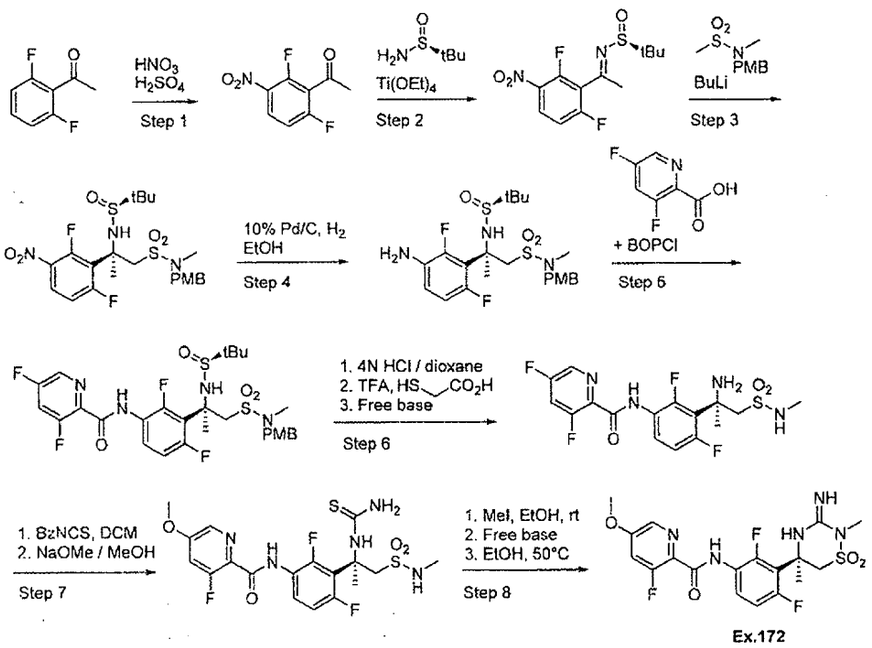
The aniline shown (Scheme 10) was treated according to Scheme 11b using 5-cyclopropylpyrazine-2-carboxylic acid (Table IVg, entry 4) to afford, after separation, both **Example 169** [LCMS data: (method D): t_R = 1.80 min, *m/e* = 433.0 (M+H)] and **Example 168** [LCMS data: (method D): t_R = 1.83 min, *m/e* = 469.0 (M+H)] both as TFA salts.

Scheme 42:



The aniline shown (Scheme 10) was treated according to Scheme 11b using 3,5-dimethoxypyridine-2-carboxylic acid (Scheme 11q) to afford, after separation, both **Example 170** [LCMS data: (method D): t_R = 1.73 min, *m/e* = 452.0 (M+H)] and **Example 171** [LCMS data: (method D): t_R = 1.85 min, *m/e* = 438.0 (M+H)] both as TFA salts.

Scheme 43:



Ex.172

Step 1: To a -40 °C mixture of concentrated H_2SO_4 (100 mL) and fuming HNO_3 (100 mL) was added 1-(2,6-difluorophenyl)ethanone (20 g, 128 mmol) dropwise. The resulting mixture was stirred at -40 °C for 2h then poured slowly onto ice. That mixture was diluted with DCM and the phases were separated. The aqueous layer was neutralized with sat. aq. $NaHCO_3$ and then extracted with DCM. All organic portions were combined, dried over $MgSO_4$, filtered, and concentrated to give 1-(2,6-difluoro-3-nitrophenyl)ethanone (26.3 g, 131 mmol, > theoretical) that was used without further purification.

Step 2: The nitrophenyl ketone from the previous step was treated according to Scheme 1a, Step 1 [substituting (S)-2-methyl-2-propanesulfinamide for (R)-2-methyl-2-propanesulfinamide] to give a ketimine product (17.1 g, 44% based on 1-(2,6-difluorophenyl)ethanone from Step 1).

Step 3: The ketimine from step 2 (17.1 g, 56.2 mmol) was treated according to Scheme 1a, Step 3 to give desired syn addition product (6 g, 20%) as well as a mixture of syn and anti diastereomers (6 g, 3:1, 20%).

Step 4: To a solution of the syn addition product from Step 3 (2.71 g, 5.1 mmol) in 25 mL of ethanol was added 10% Pd/C (298 mg). The mixture was placed under H_2 balloon atmosphere

overnight. After filtration through Celite, the filtrate was concentrated. The crude residue was purified by flash silica column (60%-100% EtOAc/hexanes) to give the aniline product (1.75 g, 68% yield).

Step 5: A mixture of the aniline from Step 4 (453 mg, 0.9 mmol), 3,5-difluoropicolinic acid (215 mg, 1.4 mmol), and BOPCl (527 mg, 2.07 mmol) in 4 mL of pyridine was stirred overnight. After it was quenched with 1N HCl (aq), the mixture was extracted with ethyl acetate. The organic portions were combined, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash silica column (40% EtOAc/hexane) to give an amide product (431 mg, 74% yield).

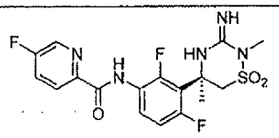
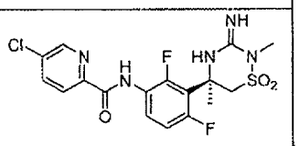
Step 6: To a solution of the above material (431 mg, 0.67 mmol) in 3 mL of DCM and 1 mL of methanol was added 4N HCl in dioxane (1 mL, 4.0 mmol). After the mixture was stirred for 1 h, it was concentrated. This sample was treated with a mixture of TFA (4 mL) and thioglycolic acid (0.46 mL, 6.7 mmol). After the mixture was stirred for 4 h, it was concentrated. The crude residue was neutralized by carefully adding saturated sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate, the organic portions were combined, dried over magnesium sulfate, and concentrated to an amine product that was used in the subsequent step without further purification.

Step 7: To the material from step 6 (assumed to be 0.67 mmol) in 5 mL of DCM was added benzoyl isothiocyanate (0.12 mL, 0.87 mmol). The mixture was stirred overnight at RT. After it was concentrated, the residue was dissolved in 5 mL of methanol, and sodium methoxide (25% in methanol, 0.37 mL) was added. The mixture was stirred for 2 h at RT. It was quenched with 2 drops of acetic acid. After the mixture was concentrated, the crude was diluted with saturated sodium carbonate, and extracted with DCM. The combined organic portions were dried over magnesium sulfate and concentrated to give an isothiourea product that was used in the subsequent step without purification.

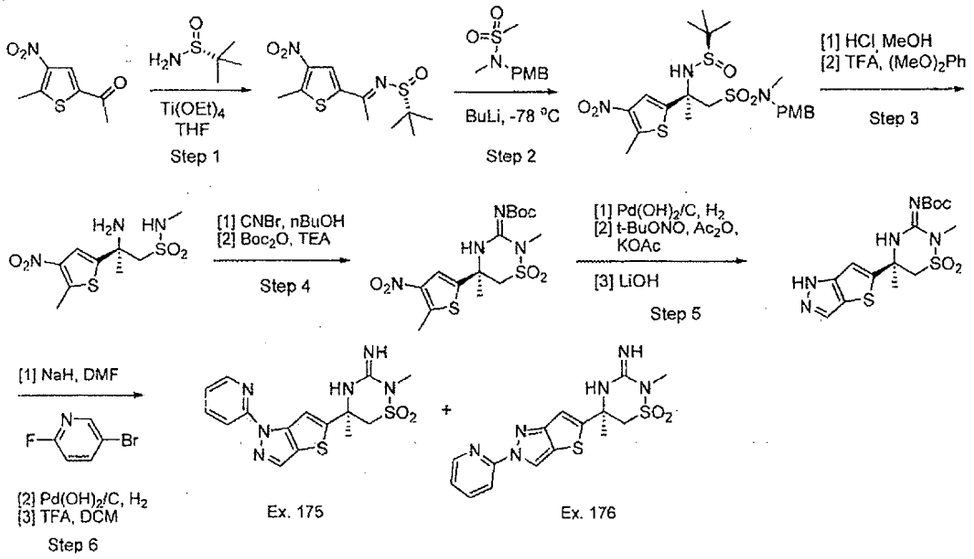
Step 8: To a solution of the material from step 7 (assumed to be 0.67 mmol) in 5 mL of ethanol was added methyl iodide (0.05 mL, 0.8 mmol). The mixture was stirred overnight at room temperature and then diluted with saturated sodium bicarbonate. After the mixture was extracted with ethyl acetate, the organic layers were combined, dried over magnesium sulfate, and concentrated. The crude residue was dissolved in 5 mL of ethanol, and the mixture was heated at 50°C for 2 h. The mixture was then diluted with saturated sodium bicarbonate, and

extracted with ethyl acetate. The organic portions were combined, dried over magnesium sulfate, and concentrated. The crude residue was purified by reverse phase HPLC (C18 radial compression, 10% to 100% MeCN/water with 0.1% TFA) to give **Example 172** as a TFA salt (40.3 mg, 14% from the product of Step 5). LCMS (conditions A): t_R = 2.43 min, *m/e* = 458.3 (M+H).

Table XXII: The following examples were made from 1-(2,6-difluorophenyl)ethanone using methods similar to those described in Scheme 43, substituting the appropriate acid in Step 5:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
173	 MH^+:428.2, 2.46 min, A	174	 MH^+:442.2, 3.17 min, A

Scheme 44:



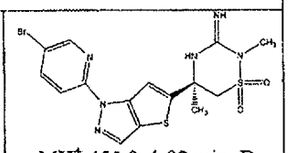
Steps 1-4: 1-(5-Methyl-4-nitrothiophen-2-yl)ethanone, obtained by nitration from 1-(5-methylthiophen-2-yl)ethanone according to the literature procedure (E. Campaigne, J. L. Diedrich, *J. Am. Chem. Soc.* **1951**, *73*, 5240-5243), was converted into the product of step 4 using similar procedures in the following sequence: (i) Scheme 1a, steps 1-4, (ii) Scheme 3b.

Step 5: To a solution of the product of step 4 (570 mg, 1.37 mmol) in MeOH (25 mL) was added 10% $Pd(OH)_2/C$ (250 mg), and the reaction was stirred in a Parr-shaker under an atmosphere of H_2 (50 psi) for 18 h. The reaction was filtered over a pad of celite, the filter residue rinsed with MeOH and the combined organic layers concentrated under reduced pressure to give a residue (423 mg, 80%). To a solution of this residue (423 mg, 1.08 mmol) in toluene (3 mL) was added KOAc (85 mg, 0.86 mmol), acetic anhydride (0.205 mL, 2.16 mmol) and *tert*-butylnitrite (0.145 mL, 1.2 mmol). The reaction was stirred at 90 °C for 4.5 h, then cooled to RT and diluted with EtOAc. After filtration through celite, the filtrate was concentrated under reduced pressure to give a residue that was subjected to silica gel chromatography (gradient elution 100:0 to 70:30 hexanes:EtOAc). The resulting mixture of acetylated and deacetylated materials (298 mg) was dissolved in THF (5 mL) and treated with aqueous 1 M LiOH (2 mL) for 30 min at RT. The reaction was diluted with EtOAc, the layers separated and the aqueous layer extracted with EtOAc (1 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give the product of step 5 (282 mg, 65%).

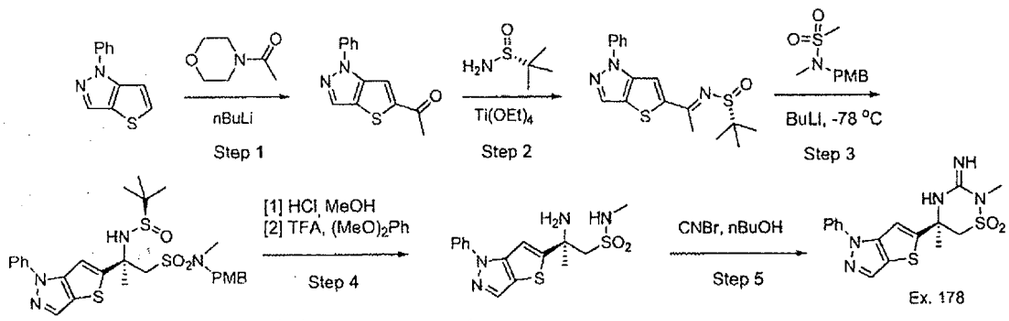
Step 6: Sodium hydride (60% in mineral oil, 20 mg, 0.5 mmol) was added to a solution of the product from step 5 (78 mg, 0.195 mmol) in DMF (2 mL) at RT. After 5 min, 2-fluoro-5-bromopyridine (54 mg, 0.306 mmol) was added and the reaction stirred for 19 h at RT, then quenched with water and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_{3\ (aq.)}$, brine, and then dried over $MgSO_4$, and concentrated under vacuum. To a solution of this residue in MeOH was added 10% $Pd(OH)_2/C$ (110 mg), and the reaction was stirred under a balloon-atmosphere of H_2 for 72 h. The catalyst was removed by filtration over celite, and the filtrate concentrated under reduced pressure to give a mixture of regioisomeric intermediates that were separated by silica gel chromatography (gradient elution with hexanes:EtOAc). Each regioisomer was deprotected according to the procedure described in Scheme 11b, Step 2, then subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Example 175** and **Example 176** as their

TFA salts. LCMS for **Ex. 175** (conditions D): t_R = 1.80 min, *m/e* = 377.0 (M+H); LCMS for **Ex. 176** (conditions D): t_R = 1.78 min, *m/e* = 377.0 (M+H).

Table XXIII: The following examples were prepared using a procedure similar to that described in Scheme 44 omitting the hydrogenation portion of step 6.

Example	
177	 MH$^+$:455.0, 1.92 min, D

Scheme 45:

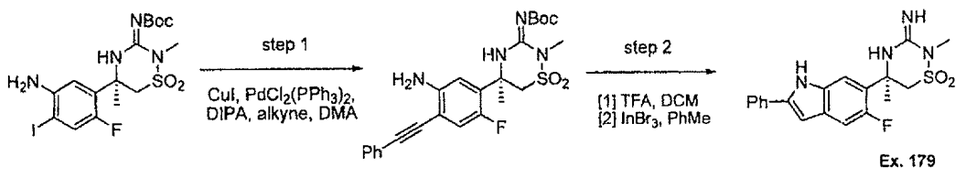


Step 1: To a -78°C solution of 1-phenyl-1H-thieno[3,2-c]pyrazole (1.94 g, 9.68 mmol), obtained from 3-bromothiophene-2-carbaldehyde according to the literature procedure (Lebedev et al., *J. Org. Chem.* **2005**, *70*, 596-602), was added nBuLi (4.25 mL of a 2.5 M solution in hexanes, 10.65 mmol) over 5 min. After 30 min at -78°C, N-acetylmorpholine (2.3 mL, 20 mmol) was added and the reaction was stirred for 60 min at -78°C, then stirred for 6 h while slowly warming to RT. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was washed with sat. aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (gradient elution 100:0 to 85:15 hexanes:EtOAc) to give 1-(1-phenyl-1H-thieno[3,2-c]pyrazol-5-yl)ethanone (682 mg, 2.81 mmol, 29%) along with recovered starting material (823 mg, 4.13 mmol, 43%).

Steps 2-5: These steps were performed using similar procedures to the following sequence: (i) Scheme 1a, steps 1-4, (ii) Scheme 3b, omitting the coversion to the *t*-butyl carbamate. The

final intermediate was subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 178** as its TFA salt. LCMS for **Ex. 178** (conditions D): t_R = 1.82 min, *m/e* = 376.0 (M+H).

Scheme 46:

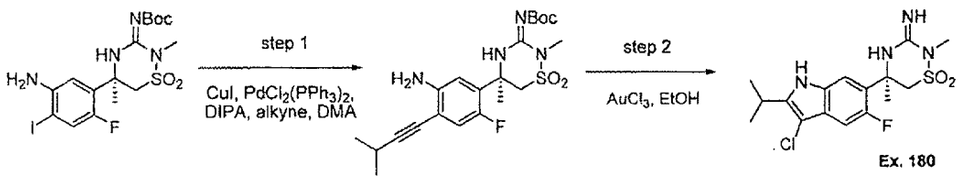


Ex. 179

Step 1: CuI (7.6 mg, 0.04 mmol) was added to a solution of iodoaniline (200 mg, 0.39 mmol, Scheme 10a), diisopropylamine (0.169 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and phenyl acetylene (0.132 mL, 1.2 mmol) in dimethylacetamide (2 mL), and the reaction was stirred at 40°C for 6 h. The reaction was diluted with sat. aqueous $NaHCO_3$ solution and EtOAc, then filtered reaction over celite. After rinsing the residue with EtOAc, the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue that was subsequently subjected to silica gel chromatography (10→20 % EtOAc/hexanes) to provide the anilino acetylene intermediate (181 mg, 95%).

Step 2: Trifluoroacetic acid (0.2 mL) was added to a solution of the product from step 1 (181 mg, 0.37 mmol) in DCM (1 mL) at RT. After 2 h, the reaction was concentrated under vacuum. To part of the residue (50 mg, 0.13 mmol) in toluene (1 mL) was added $InBr_3$ (46 mg, 0.13 mmol.), and the reaction was heated to 115°C for 2 h. After removing volatiles under reduced pressure, the residue was suspended in MeOH, filtered through a PTFE-filter and the filtrate subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 179** as its TFA salt (11.7 mg, 30%). LCMS for **Ex. 179** (conditions D): t_R = 1.98 min, *m/e* = 387.2 (M+H).

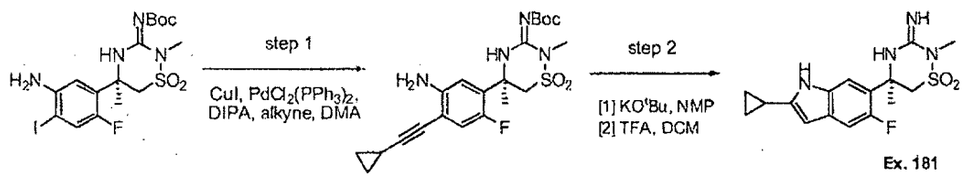
Scheme 47:



Step 1: The anilino acetylene intermediate was prepared in the same manner as in Scheme 46, Step 1 except that isoproylacetylene was used instead of phenylacetylene.

Step 2: To the anilino acetylene intermediate from Step 1 (100 mg, 0.22 mmol) in EtOH (1 mL) was added $AuCl_3$ (133 mg, 0.44 mmol), and the reaction was heated to 70°C for 3 h. After removing volatiles under reduced pressure, the residue was suspended in MeOH, filtered through a PTFE-filter and the filtrate subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Example 180** as its TFA salt (17.2 mg, 20%). LCMS for **Example 180** (conditions D): t_R = 2.04 min, *m/e* = 387.0 (M+H).

Scheme 48:

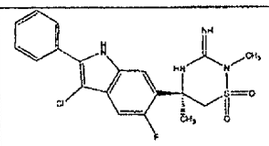
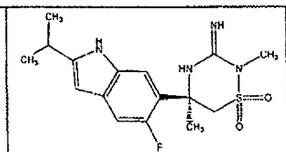
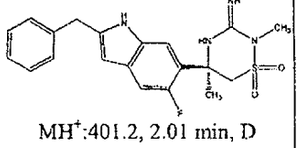
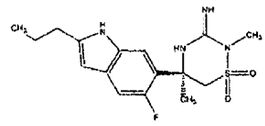
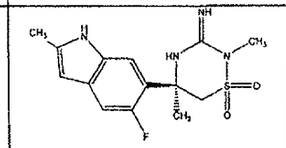
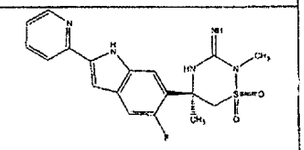
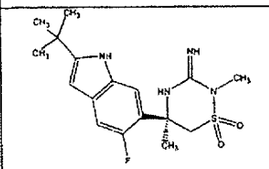
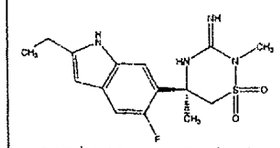


Step 1: The anilino acetylene intermediate was prepared in the same manner as in Scheme 46, Step 1 except that cycloproylacetylene was used instead of phenylacetylene.

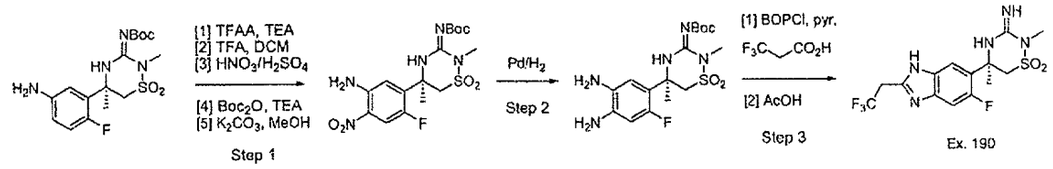
Step 2: To the anilino acetylene intermediate from Step 1 (54 mg, 0.11 mmol) in NMP (1 mL) was added potassium *tert*-butoxide (37 mg, 0.33 mmol), and the reaction was stirred for 18 h at RT. The mixture was then diluted with water and EtOAc, the organic layer was dried over Na_2SO_4, filtered, and concentrated to give a residue that was subsequently subjected to silica gel chromatography (10→25 % EtOAc/hexanes) to provide the Boc-protected indole intermediate (35 mg, 70%). This intermediate was deprotected according to the procedure described in Scheme 11b, Step 2, then subjected to reverse phase chromatography (C_{18}:

gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 181** as its TFA salt. LCMS for **Ex. 181** (conditions D): t_R = 1.91 min, *m/e* = 351.2 (M+H).

Table XXIV: The following examples were prepared using a procedure similar to that described in Schemes 46, 47 and 48.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
182	 MH^+:421.2, 2.07 min, D	**183**	 MH^+:353.2, 1.96 min, D	**184**	 MH^+:401.2, 2.01 min, D
185	 MH^+:353.0, 1.98 min, D	**186**	 MH^+:325.0, 1.85 min, D	**187**	 MH^+:388.0, 1.74 min, D
188	 MH^+:367.0, 2.02 min, D	**189**	 MH^+:339.0, 1.87 min, D		

Scheme 49:



Step 1: Trifluoroacetic anhydride (2.34 mL, 16.85 mmol) was added dropwise to a solution of aniline (5.5 g, 14.24 mmol, Scheme 10) and triethylamine (2.39 mL, 17.1 mmol) in DCM (30 mL) at 0°C. After stirring at RT for 2h, the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a solid (6.0 g), which was dissolved in DCM (10 mL) and

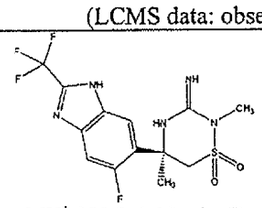
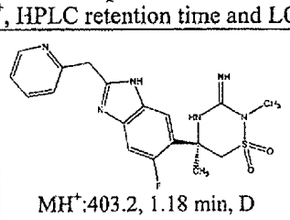
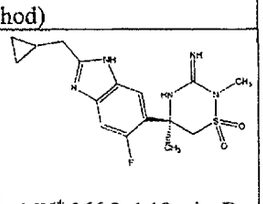
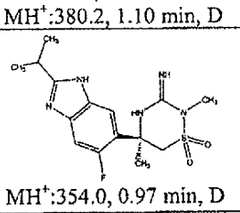
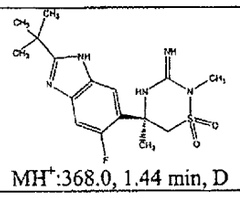
stirred with TFA (2 mL) for 1 h at RT. The reaction was concentrated under reduced pressure, and the residue dissolved in concentrated H_2SO_4 (9 mL). After cooling to 0°C, a mixture of fuming HNO_3/conc. H_2SO_4 (1.26 mL / 3 mL) was slowly added via addition funnel. After 40 min, the reaction was carefully quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x), and the combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was dissolved in DCM (100 mL), and triethylamine (7.93 mL, 56.56 mmol) and di-*tert*-butylcarbonate (3.09 g, 28.28 mmol) were added. After stirring for 18 h at RT, the reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the resulting residue was subjected to silica gel chromatography (gradient elution 80:20 to 75:25 hexanes:EtOAc) to give a mixture of acetylated and deacetylated material. To a solution of this mixture in MeOH (100 mL) at RT was added a solution of K_2CO_3 (5 g, 36 mmol) in water (20 mL), and the reaction stirred for 2h at RT. The reaction was quenched with 1 M HCl (aq) and diluted with EtOAc. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to give product (3.3 g, 54%).

Step 2: To a solution of the product from step 1 (600 mg, 1.39 mmol) in EtOAc/EtOH (10 mL / 10 mL) was added 5% Pd/C (300 mg) and the resulting mixture agitated in a Parr Shaker for 4 h under a 45-psi atmosphere of H_2. The catalyst was filtered off over celite, the residue rinsed with EtOAc, and the organic layer was concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography (gradient elution 95:5 to 90:10 hexanes:EtOAc) to give product (377 mg, 68%).

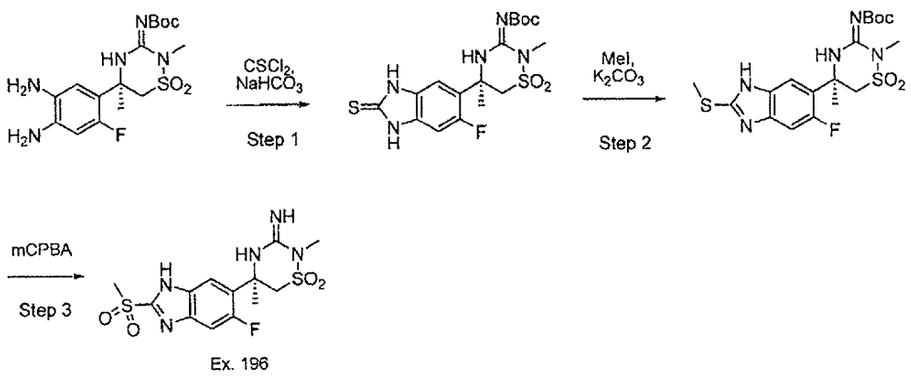
Step 3: To a solution of the product from step 2 (150 mg, 0.37 mmol) in pyridine (3 mL) was added 3,3,3-trifluoropropionic acid (0.032 mL, 0.37 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (188 mg, 0.74 mmol). After stirring for 18 h at RT, the volatiles were removed under vacuum, and the residue was subjected to silica gel chromatography (gradient elution 60:40 to 30:70 hexanes:EtOAc) to give a mixture of amides (102 mg, 54%). This mixture was dissolved in glacial AcOH (2 mL) and heated to 130°C for 1 h. The volatiles were removed under reduced pressure, and the resulting residue purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1

water:MeCN:TFA) to provide **Ex. 190** as its TFA salt. LCMS for **Ex. 190** (conditions D): t_R = 1.29 min, *m/e* = 394.2 (M+H).

Table XXV: The following examples were prepared using a procedure similar to that described in Scheme 49.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
191	 MH^+:380.2, 1.10 min, D	**192**	 MH^+:403.2, 1.18 min, D	**193**	 MH^+:366.2, 1.18 min, D
194	 MH^+:354.0, 0.97 min, D	**195**	 MH^+:368.0, 1.44 min, D		

Scheme 50:



Ex. 196

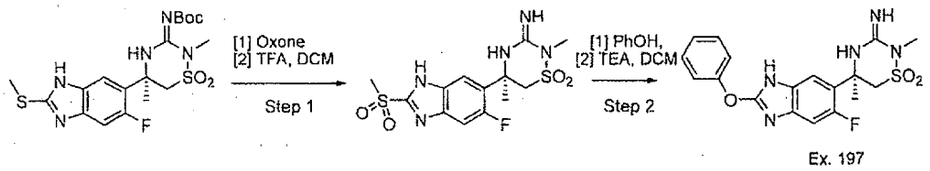
Step 1: Thiophosgene (0.320 mL, 4.21 mmol) was slowly added to a biphasic mixture of saturated aqueous $NaHCO_3$ and a solution of dianiline (1.566 g, 3.90 mmol, Scheme 49, Step 2) in DCM (15 mL). After 1 h at RT, the phases were separated and the aqueous layer extracted with DCM. The combined organic layers were washed with saturated aqueous

$NaHCO_3$, brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the thiourea (1.604 g, 93%).

Step 2: Potassium carbonate (750 mg, 5.43 mmol) was added to a solution of the thiourea from Step 1 (1.604 g, 3.62 mmol) in DMF (18 mL) at RT. After 10 min, a solution of methyl iodide (0.23 mL, 3.68 mmol) in DMF (2 mL) was added over 10 min, and the reaction was stirred for 90 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure (1.725 g). The residue was subjected to silica gel chromatography (gradient elution 100:0 to 60:40 hexanes:EtOAc) to give the thiomethylurea (846 mg, 51%).

Step 3: Meta-chloroperoxybenzoic acid (72%, 150 mg, 0.63 mmol) was added at RT to a solution of the thiomethylurea from step 2 (100 mg, 0.21 mmol) in DCM (5 mL). After 1 h, the mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ (2 x), brine, and dried over $MgSO_4$ and concentrated under reduced pressure to give a residue (150 mg) that was further subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 196** as its TFA salt. LCMS for **Ex. 196** (conditions D): t_R = 1.41 min, *m/e* = 390.0 (M+H).

Scheme 51:

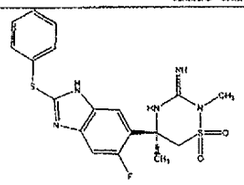
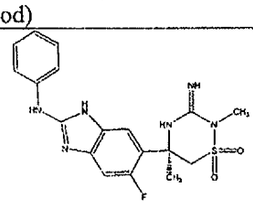


Step 1: A solution of oxone (potassium peroxymonosulfate, 3.2 g, 5.20 mmol) in water (10 mL) was added at RT to a solution of the thiomethylurea from Scheme 50, step 2 (755 mg, 1.65 mmol) in MeOH (10 mL). After 1 h, the mixture was filtered over celite, the filter cake rinsed with EtOAc, and the filtrate diluted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure to give the intermediate (681 mg) in 84% yield.

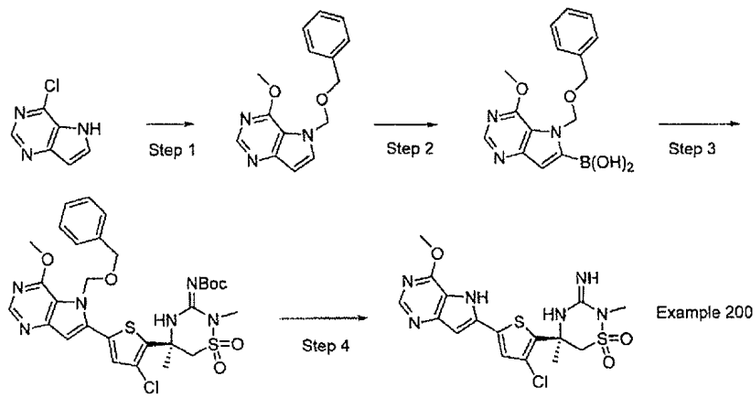
Step 2: The product of Step 1 (93 mg, 0.19 mmol) was deprotected using a method similar to that described in Scheme 11b step 2. After deprotection, the resulting residue was concentrated under vacuum, and triethylamine (0.132 mL, 0.95 mmol) and phenol (90 mg, 0.95 mmol) were

added. The mixture was heated at 120°C for 22 h, then cooled to RT. The residue was subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 197** as its TFA salt. LCMS for **Ex. 197** (conditions D): t_R = 1.78 min, *m/e* = 404.2 (M+H).

Table XXVI: The following examples were prepared using a procedure similar to that described in Scheme 51, replacing phenol in Step 2 with thiophenol or aniline, respectively.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)			
198		**199**	
MH^+:420.0, 1.76 min, D		MH^+:403.2, 1.64 min, D	

Scheme 52:



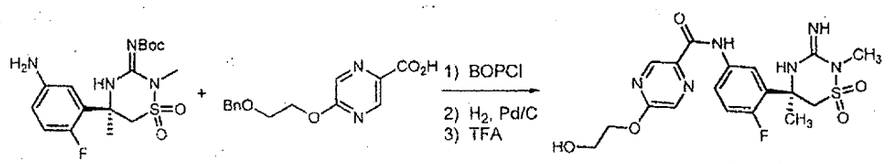
Step 1: To a suspension of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (1.53 g, 10.0 mmol) in 30 mL of THF was added NaH (560 mg, 14.0 mmol, 60% in mineral oil) by portion under N_2. After the mixture was cooled to 0 °C, benzyl chloromethyl ether (1.71 mL, 13.0 mmol) was added. Then the mixture was stirred at RT for 1 h (monitored by TLC 40% EtOAc/Hex). 8 mL of anhydrous MeOH was added into the reaction mixture followed by NaH (400 mg, 10.0 mmol, 60% mineral oil) by portion. The resulting mixture was stirred at RT overnight. After being quenched with sat. NH_4Cl, the mixture was extracted with EtOAc (3x). The organic

layer was washed with sat.$NaHCO_3$ (aq), brine, then dried ($MgSO_4$) and concentrated. Silica gel chromatography (elution with 0-30% EtOAc/Hex) afforded product 5-(benzyloxymethyl)-4-methoxy-5H-pyrrolo[3,2-d]pyrimidine (2.36 g).

Step 2 and 3: 5-(Benzyloxymethyl)-4-methoxy-5H-pyrrolo[3,2-d]pyrimidine was treated according to Scheme 31, Steps 2 and 3 to afford a biaryl product.

Step 4: To a solution of the material from step 3 (26 mg, 0.039 mmol) in 8 mL of DCM was added a suspension of $AlCl_3$ (52 mg, 0.39 mmol) in 4 mL of DCM. After the mixture was stirred at RT for 1.5 h, 3 mL of water was added. The reaction mixture was basified with $NaHCO_3$ and extracted with DCM (3x). The organic layer was washed with brine and dried (Na_2SO_4), and concentrated. The crude residue was purified by preparative TLC (10% 2N NH_3 MeOH in DCM) to provide **Example 200** (10 mg). LCMS (conditions E): t_R = 0.60 min, *m/e* = 441.0 (M+H).

Scheme 53:



Ex. 201

Step 1: The aniline from Scheme 10 and the acid (Entry 3, Table IVb) were coupled using a procedure similar to that described in Scheme 11b step 1.

Step 2: To a pressure vessel containing a solution of the amide from step 1 (181 mg, 0.28 mmol) in EtOH (15 mL) was added 10% Pd/C (50% water-Degussa Type). The vessel was sealed, evacuated and backfilled with N_2 (3x). The vessel was then evacuated and backfilled with H_2 (3x). The vessel was pressurized with H_2 to 50 psi and shaken at RT for 6 hours. The mixture was purged with N_2, filtered through Celite and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 1:1 hex.: EtOAc) to afford the hydroxy compound (24 mg, 15%).

Step 3: **Example 201** was prepared from the product of step 2 (24 mg) using a procedure similar to that described in Scheme 11b step 2. The crude product was purified via reverse phase flash chromatography (C_{18}; gradient elution 95:5:0.1 to 0:100:0.1 H_2O:MeCN:formic acid) to afford **Example 201** (11 mg, 51%) as the formate salt.

LC/MS Conditions

Method A:

Column: Gemini C-18, 50 x 4.6 mm, 5 micron, obtained from Phenomenex.

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 to 5:95 (A:B) over 5 min.

Flow rate: 1.0 mL/min

UV detection: 254 nm

ESI-MS: Electro Spray Ionization Liquid chromatography-mass spectrometry (ESI-LC/MS) was performed on a PE SCIEX API-150EX, single quadrupole mass spectrometer.

Method B:

Column: Waters SunFire C-18 4.6mm x 50 mm

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 1 min, 90:10 to 0:100 (A:B) over 4 min, 0:100 (A:B) for 2 min.

Flow rate: 1.0 mL/min

UV detection: 254 nm

Mass spectrometer: Finnigan LCQ Duo electrospray.

Method C:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 0.3 min, 90:10 to 5:95 (A:B) over 5.1 min, 5:95 (A:B) for 1.2 min.

Flow rate: 1.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

Method D:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 0.3 min, 90:10 to 5:95 (A:B) over 1.2 min, 5:95 (A:B) for 1.2 min.

Flow rate: 1.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

Method E:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 0.1 min, 90:10 to 5:95 (A:B) over 1.0 min, 5:95 (A:B) for 0.36 min.

Flow rate: 2.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

Method F:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Formic acid in water

B: 0.05% Formic acid in acetonitrile

Gradient: 90:10 to 5:95 (A:B) over 1.5 min, 5:95 (A:B) for 1.2 min.

Flow rate: 1.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

ASSAYS

The protocol that was used to determine the recited values is described as follows.

BACE1 HTRF FRET Assay

Reagents

Na^+-Acetate pH 5.0

1% Brij-35

Glycerol

Dimethyl Sulfoxide (DMSO)

Recombinant human soluble BACE1 catalytic domain (>95% pure)

APP Swedish mutant peptide substrate (QSY7-APP^{swe}-Eu): QSY7-EISEVNLDAEFC-Europium-amide

A homogeneous time-resolved FRET assay was used to determine IC_{50} values for inhibitors of the soluble human BACE1 catalytic domain. This assay monitored the increase of 620 nm fluorescence that resulted from BACE1 cleavage of an APPswedish APP^{swe} mutant peptide FRET substrate (QSY7-EISEVNLDAEFC-Europium-amide). This substrate contained an N-terminal QSY7 moiety that served as a quencher of the C-terminal Europium fluorophore (620 nm Em). In the absence of enzyme activity, 620 nm fluorescence was low in the assay and increased linearly over 3 hours in the presence of uninhibited BACE1 enzyme. Inhibition of BACE1 cleavage of the QSY7-APP^{swe}-Eu substrate by inhibitors was manifested as a suppression of 620 nm fluorescence.

Varying concentrations of inhibitors at 3x the final desired concentration in a volume of 10ul were preincubated with purified human BACE1 catalytic domain (3 nM in 10 µl) for 30 minutes at 30° C in reaction buffer containing 20 mM Na-Acetate pH 5.0, 10% glycerol, 0.1% Brij-35 and 7.5% DSMO. Reactions were initiated by addition of 10 µl of 600 nM QSY7-APP^{swe}-Eu substrate (200 nM final) to give a final reaction volume of 30 µl in a 384 well Nunc HTRF plate. The reactions were incubated at 30° C for 1.5 hours. The 620nm fluorescence was then read on a Rubystar HTRF plate reader (BMG Labtechnologies) using a 50 µs delay followed by a 400 millisecond acquisition time window. Inhibitor IC_{50} values were derived from non-linear regression analysis of concentration response curves. K_i values were then calculated from IC_{50} values using the Cheng-Prusoff equation using a previously determined µm value of 8µM for the QSY7-APP^{swe}-Eu substrate at BACE1.

All of the example compounds of the invention were tested (except for Examples 8, 9, 10, 14b, 14c, 14d, 14e, and 14f) in this BACE-1 assay and exhibited K_i values of less than about 7.5 µM and greater than about 0.5 nM in this assay. All of the example compounds except for examples 19, 40x, 98, 101, and 189 exhibited K_i values of less than about 5 µM in this assay. Some of the example compounds exhibited K_i values of less than about 4 µM in this assay; others less than about 3 µM in this assay; others less than about 2 µM in this assay;

others less than about 1 μM in this assay; others less than about 500 nM in this assay; others less than about 300 nM in this assay; others less than about 200 nM in this assay; others less than about 100 nM in this assay; others less than about 50 nM in this assay; others less than about 10 nM in this assay; others less than about 5 nM in this assay. The compound of Example 45 exhibited a Ki value of about 26 nM in this assay. The compound of Example 47 exhibited a Ki value of about 6.5 nM in this assay.

BACE-2 Assay

Inhibitor IC_{50s} at purified human autoBACE-2 were determined in a time-resolved endpoint proteolysis assay that measures hydrolysis of the QSY7-EISEVNLDAEFC-Eu-amide FRET peptide substrate (BACE-HTRF assay). BACE-mediated hydrolysis of this peptide results in an increase in relative fluorescence (RFU) at 620 nm after excitation with 320 nm light. Inhibitor compounds, prepared at 3x the desired final concentration in 1x BACE assay buffer (20 mM sodium acetate pH 5.0, 10% glycerol, 0.1% Brij-35) supplemented with 7.5% DMSO were pre-incubated with an equal volume of autoBACE-2 enzyme diluted in 1x BACE assay buffer (final enzyme concentration 1 nM) in black 384-well NUNC plates for 30 minutes at 30°C. The assay was initiated by addition of an equal volume of the QSY7-EISEVNLDAEFC-Eu-amide substrate (200 nM final concentration, K_m=8 μM for 4 μM for autoBACE-2) prepared in 1x BACE assay buffer supplemented with 7.5% DMSO and incubated for 90 minutes at 30°C. DMSO was present at 5% final concentration in the assay. Following laser excitation of sample wells at 320 nm, the fluorescence signal at 620 nm was collected for 400 ms following a 50 μs delay on a RUBYstar HTRF plate reader (BMG Labtechnologies). Raw RFU data was normalized to maximum (1.0 nM BACE/DMSO) and minimum (no enzyme/DMSO) RFU values. IC_{50s} were determined by nonlinear regression analysis (sigmoidal dose response, variable slope) of percent inhibition data with minimum and maximum values set to 0 and 100 percent respectively. Similar IC_{50s} were obtained when using raw RFU data. The K_i values were calculated from the IC_{50} using the Cheng-Prusoff equation.

All of the example compounds of the invention were tested in this BACE-2 assay except for the following examples: 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14b, 14c, 14d, 14e, 14f, 15, 16, 17, 19, 40a, 40b, 40ea, 40h, 40o, 40p, 40q, 40u, 40w, 40x, 40y, 40aa, 40au, 40cc, 40co, 40cp, 40cy, 40dj, 40gy, 40gz, 40ha, 40hb, 40hc, 40ih, 41, 43, 45, 49, 60, 61, 67, 68, 69,

70, 71, 73, 74, 75, 77, 85, 86, 88, 89, 90, 91, 96, 97, 98, 99, 100, 101, 102, 103, 105, 108, 109, 109, 115, 116, 117, 122, 123, 125, 130b, 137, 138, 143, 145, 161b, 176, 179, 182, 189, 192, 194, 195, 199. Of the example compounds of the invention that were tested in this BACE-2 assay, all exhibited K_i values of less than about 900 nM and greater than about 0.04 nM in this assay. All of the example compounds that were tested in this assay, except for examples 40ex, 40do, 160, 161a, 164, and 197 exhibited K_i values of less than about 500 nM in this assay. Some of the example compounds exhibited K_i values of less than about 200 nM in this assay; others less than about 100 nM in this assay; others less than about 50 nM in this assay; others less than about 25 nM in this assay; others less than about 10 nM in this assay; others less than about 5 nM in this assay; others less than about 1 nM in this assay; others less than about 0.5 nM in this assay. The compound of Example 47 exhibited a Ki value of about 1 nM in this assay.

The novel iminothiadiazine dioxide compounds of the invention have surprisingly been found to exhibit properties which are expected to render them advantageous as BACE inhibitors and/or for the various methods of used herein.

Cortical $A\beta_{40}$

The iminothiadiazine dioxide compounds of the invention have been found, surprisingly and advantageously, to exhibit improved efficacy in lowering $A\beta_{40}$ production in the cerebral cortex than their iminopyrimidone analogs. The following procedures were used. Results are shown in the table below.

Rat Tissue Collection

Male CD rats (~100 g; Crl:CD(SD); Charles River Laboratories, Kingston, NY) were group housed and acclimated to the vivarium for 5-7 days prior to use in a study. Compounds were formulated in 20% hydroxypropyl-β-cyclodextrin and administered orally with a dosing volume of 5 ml/kg for rats. Three h after drug administration, rats were euthanized with excess CO_2. The brain was removed from the skull and immediately frozen on dry ice. All tissues were stored at -70°C until Aβ quantification.

Determination of $A\beta_{40}$ Levels in Rat Cortex by ELISA

The measurement of endogenous rat Aβ1-40 (Aβ40) in cortex relied on the 585 antibody (Ab585, BioSource), catalogue no. NONO585), which specifically recognizes the N-

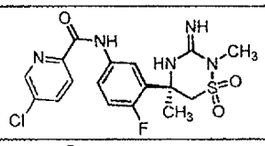
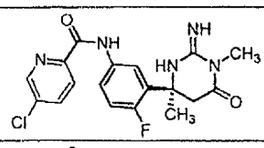
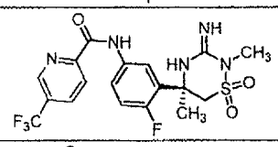
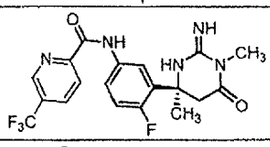
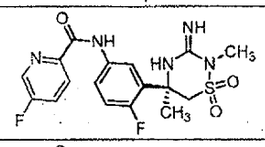
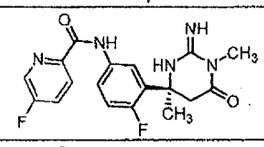
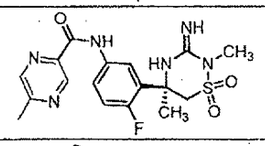
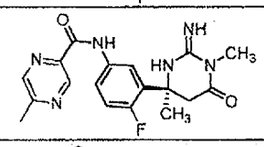
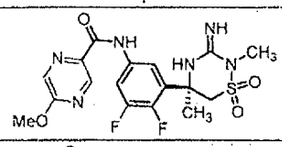
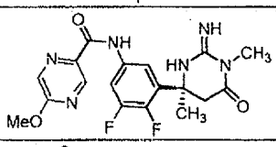
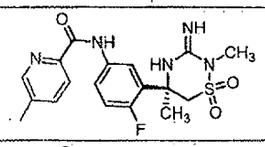
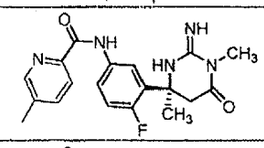
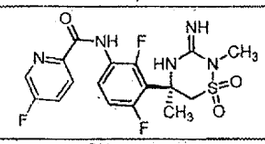
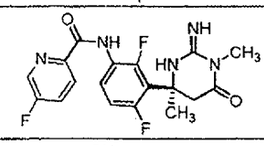
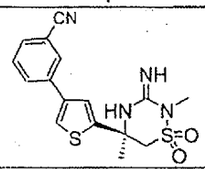
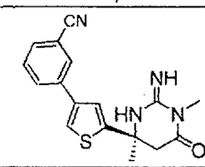
terminal sequence of rodent Aβ40, and the monoclonal antibody, G2-10, which specifically recognizes the free C-terminus of Aβ40. Ab585 was labeled with biotin (b-Ab585) by first dialyzing the antibody sample extensively versus PBS (pH 7.8) to remove impurities, followed by dilution to between 1 and 2 mg/mL protein concentration. EZ-Link Sulfo-NHS-LC-Biotin (Pierce) was dissolved in PBS (pH 7.8) at a concentration of 1 mg/mL immediately prior to use. Ab585 was labeled with EZ-Link Sulfo-NHS-LC-biotin using a 10:1 biotin:antibody ratio by incubation at room temperature for 1 hour. The labeling reaction was quenched by addition of 1.0 M glycine to a final concentration of 0.1 M followed by 10 minute incubation at room temperature. Glycine was removed by extensive dialysis versus PBS.

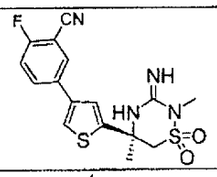
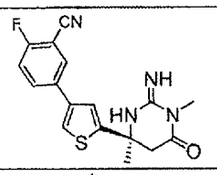
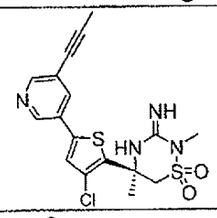
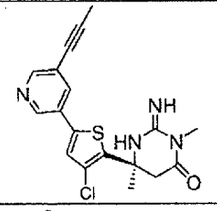
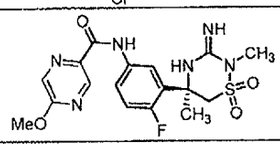
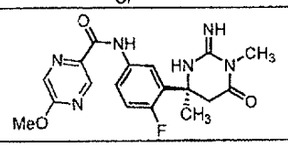
The use of the Luminex based immunoassay for measurement of rat cortical Aβ40 required that the G2-10 antibody be labeled with Bio-Plex COOH Bead 25 (Bio-Rad laboratories catalogue no. 171506025). The antibody was coupled to the beads using the Bio-Plex Amine Coupling Kit (Bio-Rad) as per the manufacturer's recommendations.

Rat cortex Aβ40 levels were measured from guanidine HCl extracts of individual rat cortices using a Luminex-based immunodetection assay. Rat brains were thawed briefly at 37° C and both mid- and hindbrain regions were removed. The remaining material, consisting primarily of cortex (~800 mg) was carried through the guanidine extraction procedure. Cortices were added to a 2 ml BioPur tube (Eppendorf) along with a 6.35 mm chrome-coated steel ball and 1.0 ml of sucrose homogenization buffer (20 mM HEPES [pH 7.5], 50 mM KCl, 50 mM sucrose, 2 mM EDTA, 2 mM EGTA supplemented with complete protease inhibitors [Roche, EDTA-free]). Samples were then homogenized by agitation for 1.5 min at 30 cylces/sec in a MM300 tissue mixer (Retsch®). The resulting cortical homogenate was extracted with guanidine-HCl by mixing 67 µl of homogenate with 133 µl of 5 M Guanidine HCl, 50 mM Tris HCl (pH 8.0). To maximize the efficiency of Aβ extraction, samples were vortexed and then sonicated for 2 minutes in an ice bath using an Ultrasonics XL cup horn sonicator at a power setting of 8 (Heat Systems, Inc.). Insoluble material was removed by ultracentrifugation using a using a TLA-55 rotor in a TL-100 benchtop centrifuge (Beckman) at 100,000xg for 30 minutes. The resulting supernatant was then either diluted 1:10 in 5 M guanidine HCl, 0.05 M Tris HCl (pH 8.0) for protein analysis (BCA protein assay, Pierce Biochemicals) or assayed neat for Aβ40 levels. The Luminex rodent Aβ40 assay was

performed as follows. First, 96 well filter binding plates (Millipore, catalogue # MSBVN12) were wetted with 100 µl of 1x LAβ40 buffer (0.05 M HEPES [pH 7.5], 0.2% BSA, 0.2% Tween-20, 0.15 M NaCl) by vacuum filtration on a Millipore 96-well manifold. The plate bottom was sealed and 100 µl of 1x LAβ40 buffer was added to each well followed by addition of 50 µl each of G2-10:COOH beads (1000 beads/well) and 50 µl b-Ab585 at 0.5 µg/ml in 1 x LAβ40 buffer. Guanidine HCl was added to synthetic rodent Aβ40 standards in order to control for the effect of guanidine in brain extracts on the assay performance. Ten microliters of cortical extract, rodent Aβ40 standards or cortical extract from amyloid precursor protein knockout mice (to define background immunoreactivity) was added to each well. Plates were covered and incubated overnight at 4°C. Following the incubation, wells were cleared by vacuum and washed twice with 100 µl of 1x LAβ40 buffer on a Millipore manifold. Phycoerythrin-conjugated streptavidin (PE-strepavidin, BioRad) for detection of bound b-Ab585 was diluted 100-fold in 1x LAβ40 buffer and 50 µl was added to each well and incubated for 1 hour at room temperature with shaking. Unbound PE-streptavidin was removed by three 100 µl washes with cytokine assay buffer (BioRad). Washed beads were resuspended in 125 µl of cytokine assay buffer by shaking on a microplate shaker. Plates were read on a BioPlex suspension array system (BioRad) with target region beads set to 40 beads/region and the upper end of the DD gate set to 10,000. Raw fluorescence data was analyzed using nonlinear regression analysis and absolute Aβ40 levels were extrapolated from the standard curve using GraphPad Prism 4.0.2. Absolute amounts of $A\beta_{1-40}$ are expressed as picograms per micrograms protein. Percent change values for each compound were calculated by normalization of the average absolute cortical Aβ1-40 level in each compound treated cohort to the average absolute cortical Aβ1-40 levels in the vehicle cohort. Comparative results are shown in the table below. "NT" means not tested.

Change in Cortical $A\beta_{40}$ in Rats 3 h After a 10 mg/kg Oral Dose of Compound					
Iminothiadiazine Dioxide				**Iminopyrimidinone**	
Ex. #	**Structure**	**BACE-1 Ki (nM) / BACE-2 Ki (nM)**	**Change in rat cortex $A\beta_{40}$**	**Structure**	**Change in rat cortex $A\beta_{40}$**

Change in Cortical $A\beta_{40}$ in Rats 3 h After a 10 mg/kg Oral Dose of Compound					
Iminothiadiazine Dioxide				Iminopyrimidinone	
Ex. #	Structure	BACE-1 Ki (nM) / BACE-2 Ki (nM)	Change in rat cortex $A\beta_{40}$	Structure	Change in rat cortex $A\beta_{40}$
34		0.949 / 0.22	-51%		-19%
26		1.261 / 2.46	-33%		0%
25		1.753 / 0.37	-49%		-11%
36		10 / 4.85	-25%		NT
40di		1.05 / 2.15	-38%		+5%
35		3.0 / 0.45	NT		NT
173		4.88 / 0.47	-27%		-3%
45		25.6 / NT	NT		-5%

Change in Cortical $A\beta_{40}$ in Rats 3 h After a 10 mg/kg Oral Dose of Compound					
Iminothiadiazine Dioxide				Iminopyrimidinone	
Ex. #	Structure	BACE-1 Ki (nM) / BACE-2 Ki (nM)	Change in rat cortex $A\beta_{40}$	Structure	Change in rat cortex $A\beta_{40}$
46		46 / 8.23	NT		NT
52		2.387 / 0.37	-53%		-54%
40ai		1.64 / 1.99	-51%		

Caco-2 Bi-Directional Permeability

It has been found that compounds of the invention exhibit unexpectedly reduced susceptibility to efflux by P-glycoprotein (P-gp) versus compounds having an iminopyrimidinone moiety that are otherwise structurally identical. P-gp is found, among other locations, at the blood-brain barrier, and reduced susceptibility to efflux by this protein is a desirable characteristic of centrally acting compounds (A. Schinkel *Advanced Drug Delivery Reviews* **1999**, *36*, 179-194). The following procedures were used. Results are shown in the table below.

Caco-2 Bi-directional Permeability

The bi-directional permeability with efflux potential of selected compounds of the invention vs. otherwise structurally identical iminopyrimidinones (collectively referred to as test compounds, shown in the table below) were assessed using Caco-2 cell line. The Caco-2 cells were maintained in DMEM (Dulbecco's Modified Eagle Medium) containing 10% fetal bovine serum, 1% non-essential amino acids, 2 mM L-glutamine, and 1% penicillin-streptomycin in an incubator at ~37°C in an atmosphere of 5% CO_2 and about 90%

relative humidity. The cell culture medium was changed three times weekly. Caco-2 cell monolayers were grown on polyethylene terephthalate filters using 24-well BD Falcon™ Cell Culture Insert Plates (0.33 cm^2 insert area, 1 μm pore size; BD BioSciences, Bedford, MA). The culture medium of the plate was changed every other day until used for the transport experiment (21-28 days post seeding).

The transport buffer (TM) was Hank's balanced salt solution (HBSS) with 10 mM HEPES and 25 mM glucose (pH 7.4) for dosing and TM with 4% bovine serum albumin for receiver (pH 7.4). The bi-directional permeability of the test compounds were tested at concentrations of 1, 10 and 100 μM was measured in triplicate with 2-hr incubation. The cell monolayer integrity was monitored with pre- and post-experimental trans-epithelial electrical resistance and post-experimental Lucifer Yellow (LY) permeability with 1 hr incubation. Test article samples were analyzed using LC-MS/MS and the concentration of LY was measured using a Perkin Elmer HTS 7000 Plus Bio Assay Reader (Waltham, MA) with an excitation and emission wavelength of 485 nm and 538 nm, respectively.

The apparent permeability, recovery and efflux ratio values were calculated using the following equations:

$$P_{app}\,(nm/s) = \frac{dM/dt}{S * C_0} = \frac{dC_R/dt * V_R}{S * C_0} * 10^7$$

$$\text{Efflux Ratio} = \frac{P_{app\_BLtoAP}}{P_{app\_APtoBL}}$$

$$\text{Total Recovery (\%)} = \frac{C_{D,final}}{C_0} \times 100 + \frac{\text{Receiver Accumulated Amount}}{C_0 * V_D} \times 100$$

where,

dC_R/dt: The slope of the accumulative concentration in the receiver compartment versus time incubation ($\mu M \cdot s^{-1}$)

C_{0hr}: Donor concentration (μM) immediately after dosing

$C_{D,final}$: Donor concentration (μM) at the end of incubation

S: Membrane surface area (cm^2)

V_D: Volume of donor compartment (mL)

V_R: Volume of receiver compartment (mL)

P_{app_BLtoAP}: Permeability from basolateral (BL) to apical (AP) transport

P_{app_APtoBL}: Permeability from AP to BL transport

Evaluation of P-gp efflux inhibition using Caco-2 bi-directional permeability assay

A preliminary study to assess the compounds in the table below as potential P-gp substrates were performed using the Caco-2 bi-directional transport assay. Digoxin was used as a probe P-gp substrate. The ^{3}H-digoxin dosing solution was prepared by diluting a digoxin DMSO stock with TM and/or the inhibitor solutions and titrating with ^{3}H-digoxin (final digoxin concentration was 5 μM with 0.5 μCi/mL radioactivity). Two concentrations of test compounds (5 and 50 μM) were prepared by diluting a DMSO stock solution with TM (pH 7.4). The Caco-2 bi-directional permeability of ^{3}H-digoxin with or without test compound as inhibitor was measured as described in the Caco-2 bi-directional permeability section. The total radioactivity for each sample was counted using a Packard 2250CA Tri-Carb Liquid Scintillation Analyzer.

The percentage of digoxin efflux inhibition was calculated using the following equation:

$$\%\_Inhibition = (1 - \frac{P_{app\_BLtoAP}^{inhibitor} - P_{app\_APtoBL}^{inhibitor}}{P_{app\_BLtoAP} - P_{app\_APtoBL}}) * 100$$

where,

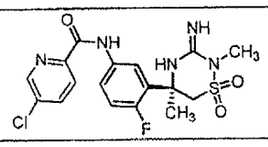
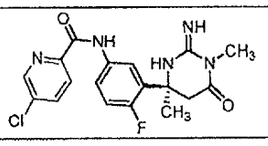
P_{app_BLtoAP}: Digoxin permeability from BL to AP transport

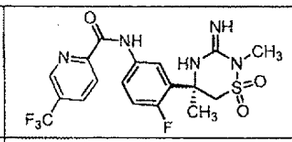
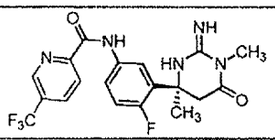
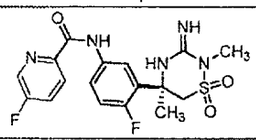
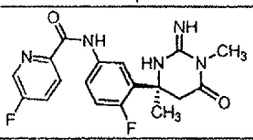
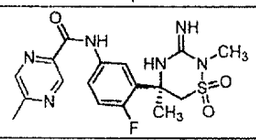
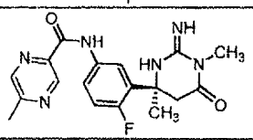
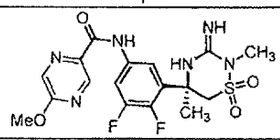
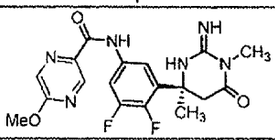
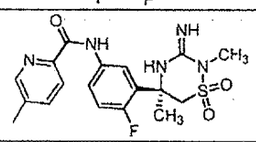
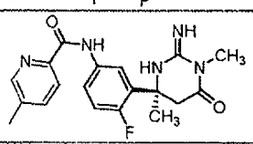
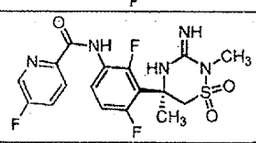
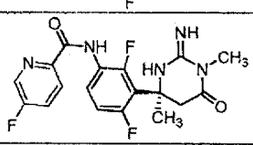
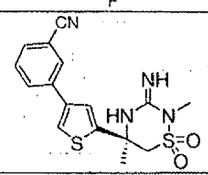
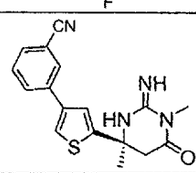
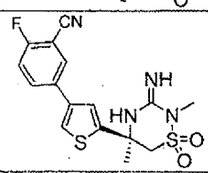
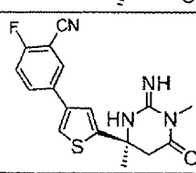
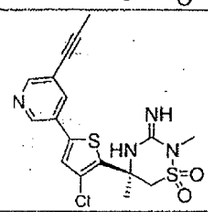
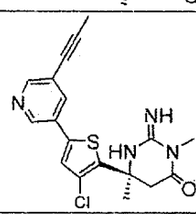
P_{app_APtoBL}: Digoxin permeability from AP to BL transport

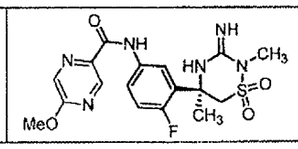
$P_{app\_BLtoAP}^{inhibitor}$: Digoxin permeability with inhibitor from BL to AP transport :

Digoxin permeability with inhibitor from AP to BL transport

Permeability (AP→BL) and efflux ratio in Caco-2 cells
(AP = apical, BL = basolateral)

Iminothiadiazine Dioxide				Iminopyrimidinone		
Ex. #	**Structure**	**Caco-2 AP→BL (nm/s)**	**Caco-2 Efflux ratio**	**Cmpd. #**	**Caco-2 AP→BL (nm/s)**	**Caco-2 Efflux ratio**
34		118	3.1		0	NA

26		89	2.9		17	11.3
25		128	2.4		22	10.6
36		54	3.3		11	12.9
40di		136	2.0		65	3.2
35		151	2.1		0	NA
173		126	2.2		25	6.1
45		226	1.4		174	2.6
46		189	1.9		136	2.6
52		278	1.6		153	2.4

40ai		133	1.8	NA		

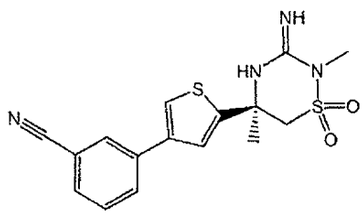
Solution Stability

The iminothiadiazine dioxide compounds of the invention have been found, surprisingly and advantageously, to exhibit improved solution stability (e.g., by resistence to hydrolysis) compared with structurally similar iminopyrimidinones. The following comparative procedures were used. Results are reported as Examples A and B below.

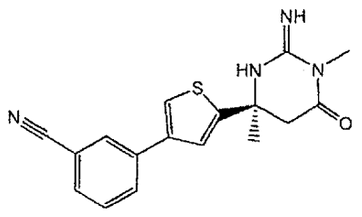
A 1.05 mg/mL stock solution (5 mL) of **Ex. 45** in MeOH was prepared. From the stock solution was taken out 1.25 mL and diluted to 25 mL with the addition of 23.75 mL of 10 mM phosphate buffer (pH 7.4)/MeOH (70/30 v/v). This new solution was split into three. One solution was incubated at 4°C, another incubated at 25°C and the third incubated at 40°C. Each solution was analyzed by LC/MS after day 1, day 2 and day 6 and compared to a standard calibration curve for **Ex. 45.**

Example A: Stability Studies Comparing Example 45 With Compound Z:

In the following study, the solution stability of the compound of Example 45 was measured and compared to that of Compound Z. The compound of Example 45 is an iminothiadiazine dioxide compound of the invention. Compound Z is the corresponding iminopyrimidinone compound. The structures of the compound of Example 45 and of Compound Z are shown below. Studies were performed in aqueous pH 7.4 buffer containing methanol at 4 °C, 25°C and 40°C. At 4°C, the compound of Example 45 showed 0.93% degredation after 6 days while Compound Z showed 18.3% degredation after 1 day. At 25°C, the compound of Example 45 showed 7.4 % degredation after 6 days while Compound Z showed 53.87% degredation. At 40°C, the compound of Example 45 showed 30.71% degredation after 6 days while Compound Z showed 79.93% degredation after 1 day.



Example 45



Compound Z
(US20060111370)

Solution Stability for Ex. 45 in pH 7.4					
Condition	**4°C**				
Batch Number	**7**				
Time, days	**Initial**	**1**	**2**	**6**	
Assay (Area %)	99.82	99.69	99.04	98.89	
Condition	**25°C**				
Assay (Area %)	99.82	98.45	96.07	92.43	
Condition	**40°C**				
Assay (Area %)	99.82	96.32	89.70	69.11	-
a: Results by area normalization ND = Not Detected. (-) stands for > 20 % degradation					

Solution Stability for Compound Z in pH 7.4					
Condition	**4°C**				
Batch Number	**7**				
Time, days	**Initial**	**1**	**2**	**6**	
Assay (Area %)	88.15	69.84	-	-	-

Condition	**25°C**				
Assay (Area %)	88.15	34.28	-	-	-
Condition	**40°C**				
Assay (Area %)	88.15	8.22	-	-	-
a: Approximate RRT for related compounds. Results by area normalization ND = Not Detected. (-) stands for > 20 % degradation					

Stock solutions of the tested compounds were prepared by dissolving about 3 mg of each compound in 3 mL of acetonitrile. Standards for test compounds were prepared by diluting 1 mL of the stock solution with an additional 4 mL of acetonitrile. These standards were stored at 4°C. Samples were prepared by diluting 1 mL of the stock solution with 4 mL of 50 mM pH 7.4 phosphate buffer. These samples were stored at 25°C in the absence of light. Standards and samples were analyzed by LC/MS initially and at day 1, day 4, and day 6.

HPLC conditions:
Mobile phase A: 10 mM pH 5 ammonium acetate buffer : methanol (90 : 10)
Mobile phase B: 10 mM pH 5 ammonium acetate buffer : methanol (10 : 90)
Column: Zorbax SB-Phenyl 4.6 x 50 mm, 1.8 µm
Column temperature: 40°C
Flow: 0.8 mL/min.
Gradient:

Time (min.)	% B
0	40
9	100
11	100

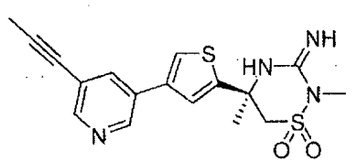
Detectors: UV at 220 nm and 236 nm
MS, ES ionization, positive mode, for identification only at final time point.
The terms reported in the tables below have the following meanings:
Area % is the integration of peak from HPLC as reported by Waters Empower II software.
RRT is the relative retention time of new product compared to the standard of the test compound.
Formula for RRT is:

$$\frac{\text{Retention time of new product}}{\text{Retention time of standard}}$$

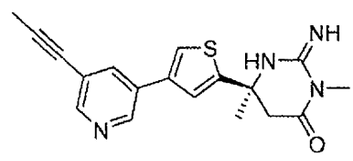
M + 1 is the mass observed including protonation (+ 1 mass unit).
ND stands for no peak detected by the UV detector.
* stands for no ion detected by the mass spectrometer.

Example B: Stability Studies Comparing Example 47 With Compound Y:

In the following study, the solution stability of the compound of Example 47 was measured and compared to that of Compound Y. The compound of Example 47 is an iminothiadiazine dioxide compound of the invention. Compound Y is the corresponding iminopyrimidinone compound. The structures of the compound of Example 47 and of Compound Y are shown below. Studies were performed in pH 7.4 buffer at 25°C. Under these conditions, the compound of Example 47 showed *0*% hydrolysis product after 6 days while Compound Z showed 12.45% hydrolysis product.



Example 47



Compound Y
(US 20070287692)

Example 20: Free base MW = 374.09

	Peak Description	RRT	M + 1	Area %, Initial	Area %, Day 1	Area %, Day 4	Area %, Day 6
Standard	Example 47	1.00	375.10	98.53	98.55	98.52	98.52
	Unknown	1.49	*	1.47	1.45	1.48	1.48
Sample at pH 7.4	Example 47	1.00	375.10	98.55	98.56	98.53	98.53
	Unknown	1.49	*	1.45	1.44	1.47	1.47

Compound Y: Free Base MW = 338.12

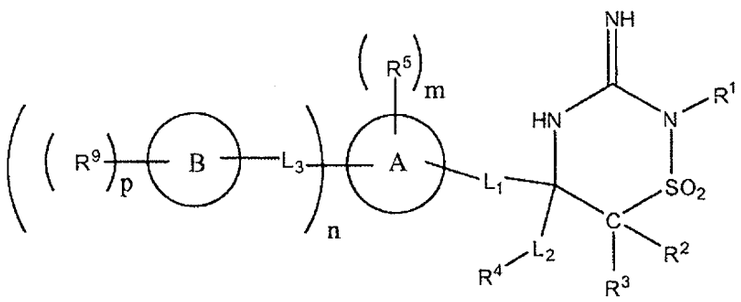
	Peak Description	RRT	M + 1	Area %, Initial	Area %, Day 1	Area %, Day 4	Area %, Day 6
Standard	Compound Y	1.00	339.15	100.0	100.0	100.0	100.0
Sample at pH 7.4	Compound Y	1.00	339.10	99.36	96.89	93.02	87.55
	Hydrolysis product	0.76	357.10	0.64	3.11	6.98	12.45

While the present invention has been described in view of the specific embodiments set forth above, many alternatives, modifications and other 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.

WE CLAIM:

1. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound having the structural Formula (I):



(I)

wherein:

$-L_1-$ represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, and -alkynyl-;

$-L_2-$ represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, and -alkynyl-;

each $-L_3-$ independently represents a bond or a divalent moiety independently selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, -alkynyl-, $-N(R^7)-$, –NHC(O)-, -C(O)NH-, $-NHS(O)_2-$, $-S(O)_2NH-$, -O-alkyl-, -alkyl-O-, $-N(R^7)$-alkyl-, -alkyl-$N(R^7)$-, -haloalkyl-NH-, and –NH-haloalkyl-;

m, n, and p are each independently selected integers, wherein:

m is 0 or more;

n is 0 or more; and

p is 0 or more,

wherein the maximum value of the sum of m and n is the maximum number of available substitutable hydrogen atoms on ring A, and wherein the maximum value of p is the maximum number of available substitutable hydrogen atoms on ring B;

R^1 is selected from the group consisting of: H, alkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein each of said alkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl- of R^1 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^2 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^3 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^4 is selected from the group consisting of alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl,

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl of R^4 is unsubstituted or substituted with one or more independently selected R^{10} groups;

ring A is selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each ring B (when present) is independently selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each R^5 (when present) is independently selected from the group consisting of halo, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^5 (when present) is optionally

independently unsubstituted or further substituted with one or more independently selected groups selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, halo, -CN, -SF_5, -OSF_5, -NO_2, -$N(R^8)_2$, -OR^7, -$C(O)N(R^8)_2$, and cycloalkyl;

each R^6 (when present) is independently selected from the group consisting of alkyl, aryl, arylalkyl-, haloalkyl, cycloalkyl, cycloalkylalkyl-, heteroaryl, and heteroarylalkyl-;

each R^7 (when present) is independently selected from the group consisting of H, alkyl, alkenyl, heteroalkyl, haloalkyl, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, and heterocycloalkylalkyl-;

each R^8 (when present) is independently selected from the group consisting of H, alkyl, alkenyl, heteroalkyl, haloalkyl, haloalkenyl, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, and heterocycloalkylalkyl-;

each R^9 (when present) is independently selected from the group consisting of: halogen, -CN, -SF_5, -OSF_5, -NO_2, -$Si(R^6)_3$, -$P(O)(OR^7)_2$, -$P(O)(OR^7)(R^7)$, -$N(R^8)_2$, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$NR^8C(O)N(R^8)_2$, -$NR^8C(O)OR^7$, -$C(O)R^7$, -$C(O)_2R^7$, -$C(O)N(R^8)_2$, -$S(O)R^7$, -$S(O)_2R^7$, -$S(O)_2N(R^8)_2$, -OR^7, -SR^7, alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl;

each R^{10} (when present) is independently selected from the group consisting of halo, -CN, -NO_2, -$Si(R^6)_3$, -$P(O)(OR^7)_2$, -$P(O)(OR^7)(R^7)$, -$N(R^8)_2$, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$NR^8C(O)N(R^8)_2$, -$NR^8C(O)OR^7$, -$C(O)R^7$, -$C(O)_2R^7$, -$C(O)N(R^8)_2$, -$S(O)R^7$, -$S(O)_2R^7$, -$S(O)_2N(R^8)_2$, -OR^7, -SR^7, alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl,

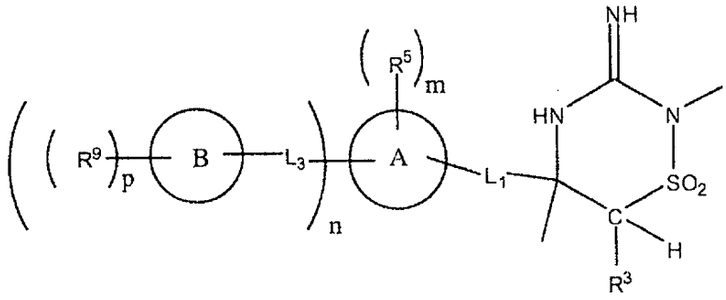
wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl of R^{10} (when present) is optionally independently unsubstituted or further substituted with one or more independently selected groups selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, halo, -CN, -NO_2, -$N(R^8)_2$, -OR^7, and -$C(O)N(R^8)_2$.

2. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:
R^1 is selected from the group consisting of H, lower alkyl, and cyclopropyl.

3. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:
R^2 is H.

4. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:
R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl.

5. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound having a structural Formula (II):



(II).

6. A compound of claim 5, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl;

m is 0 or more;

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$N(R^8)_2$, -OR^7, -SR^7, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl;

n is 1;

-L_3- represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-;

ring B is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridyl, and pyrrolopyrimidinyl;

p is 0 or more; and

each R^9 group (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$N(R^8)_2$, -OR^7, -SR^7, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cycloalkyl.

7. A compound of claim 5, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:

n is 0;

m is 1 or more;

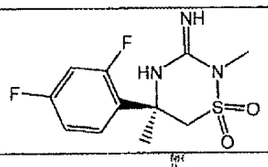
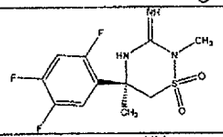
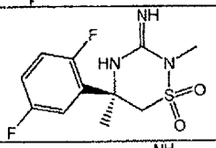
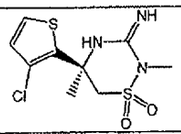
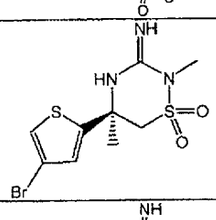
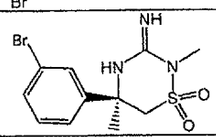
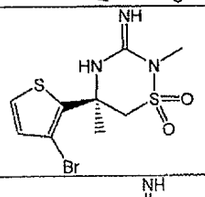
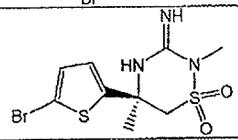
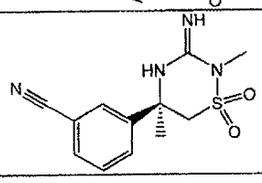
-L_1- represents a bond, –CH_2-, or –CH_2CH_2-;

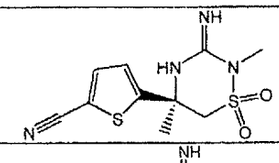
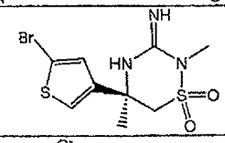
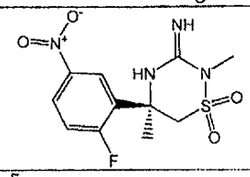
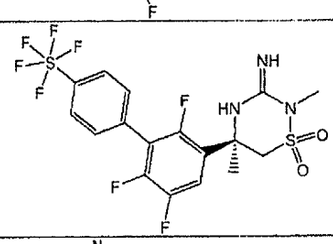
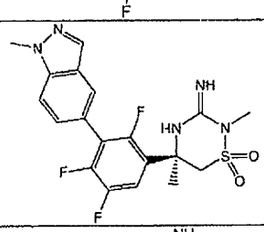
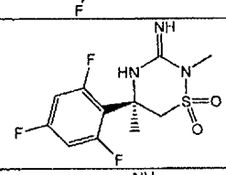
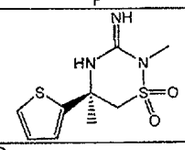
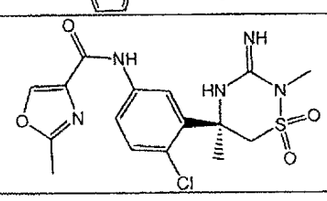
ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, quinazolinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, naphthyl, quinolyl, isoquinolyl, indazolyl, indolyl, and thienopyrazolyl; and

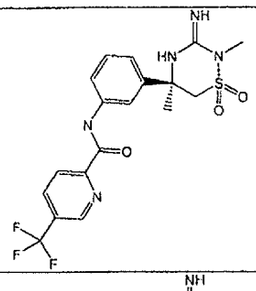
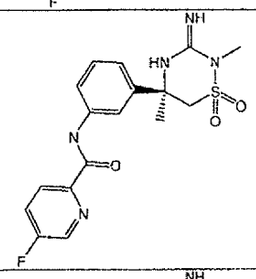
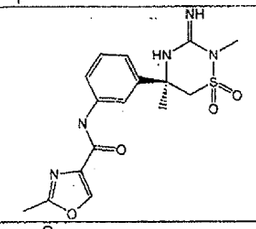
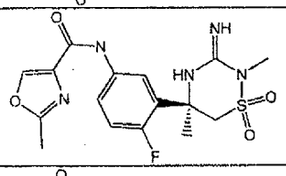
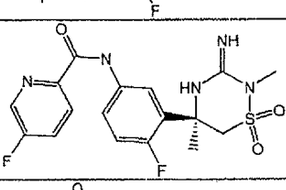
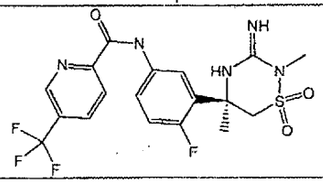
each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$N(R^8)_2$, -OR^7, -SR^7, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl.

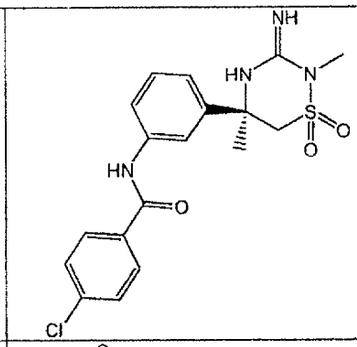
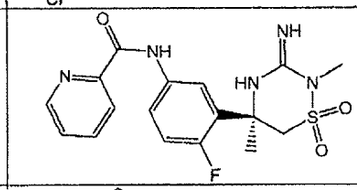
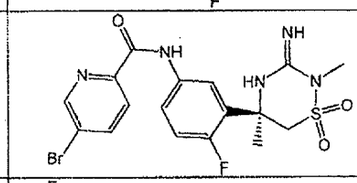
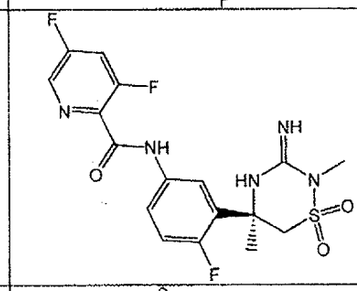
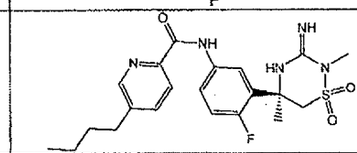
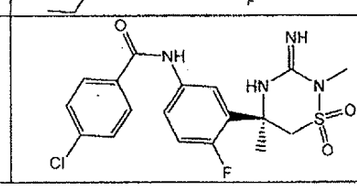
8. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of:

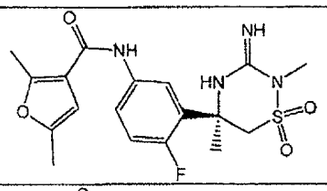
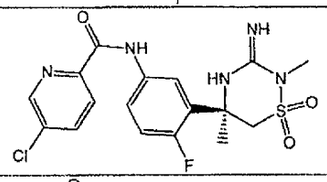
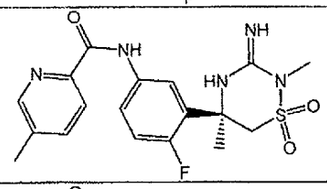
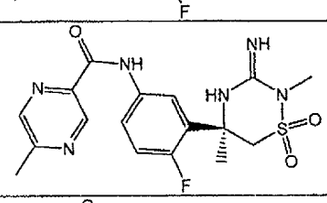
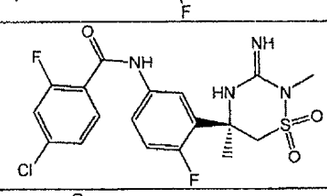
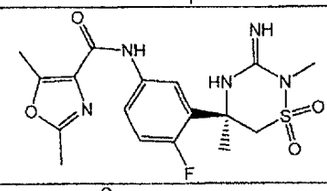
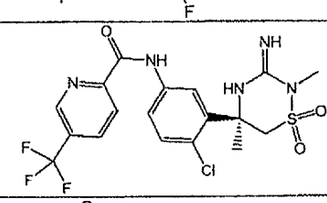
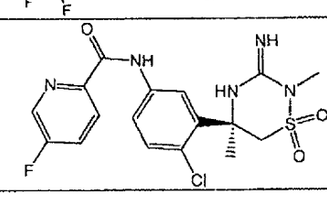
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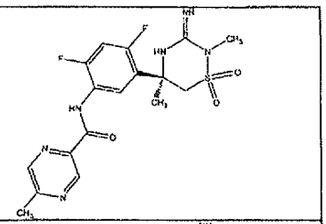
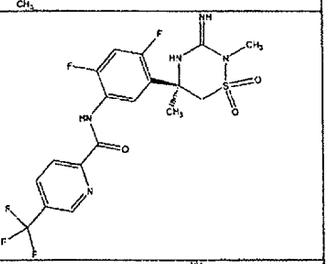
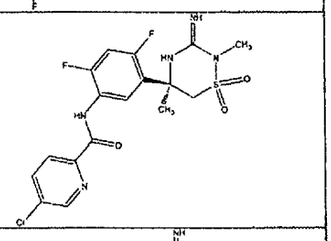
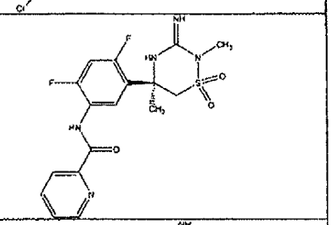
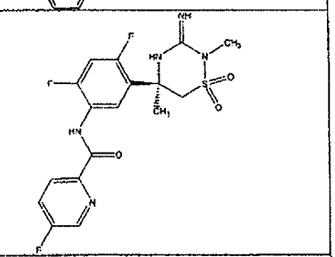
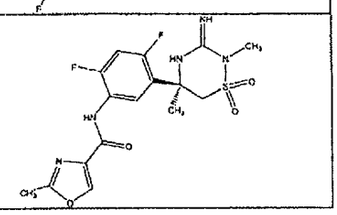
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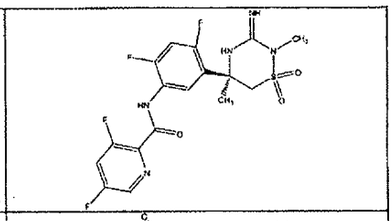
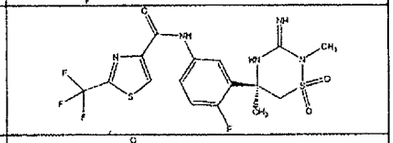
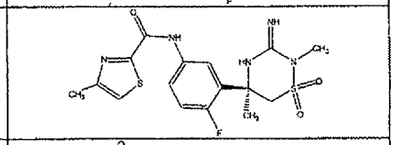
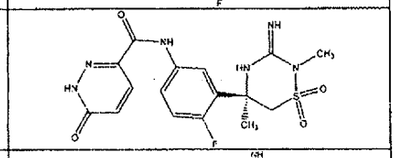
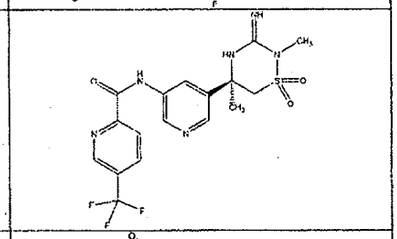
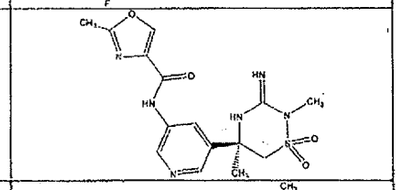
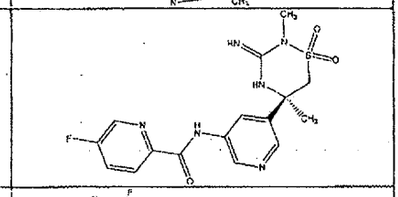
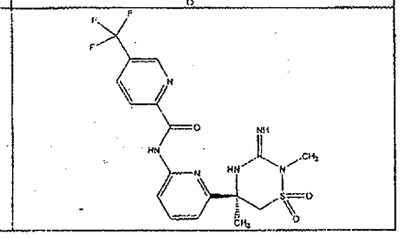
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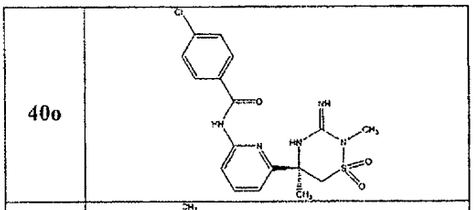
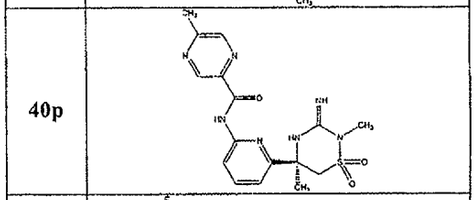
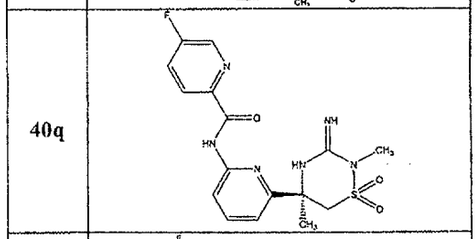
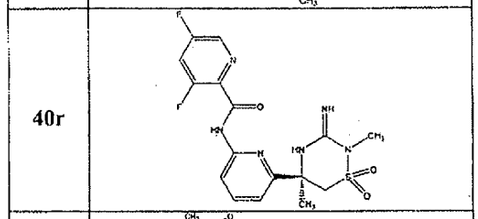
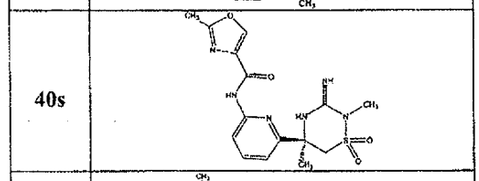
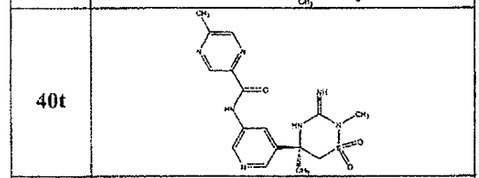
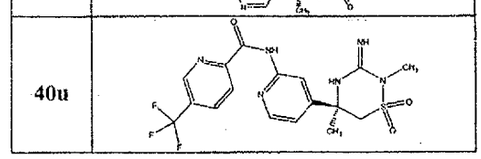
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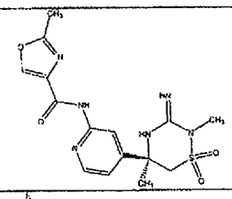
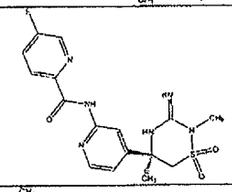
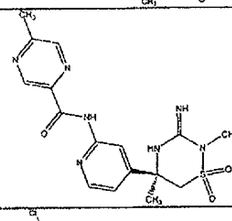
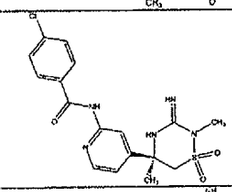
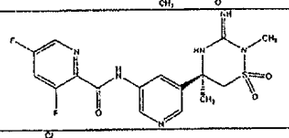
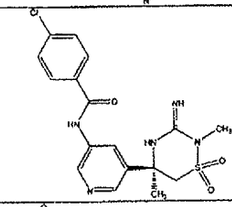
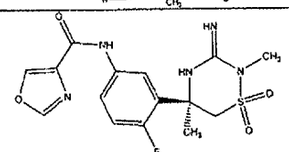
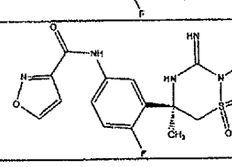
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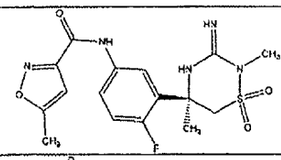
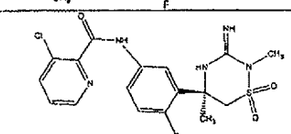
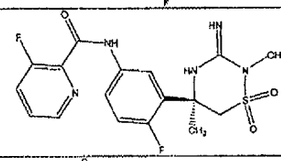
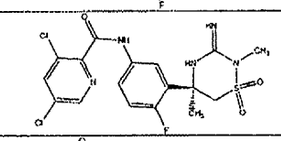
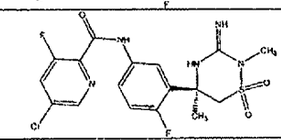
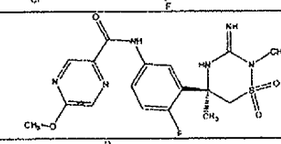
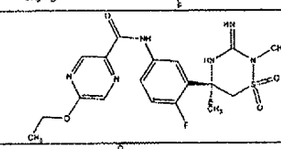
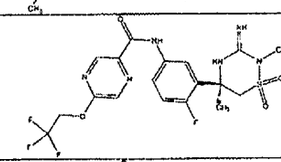
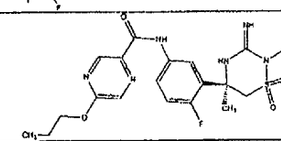
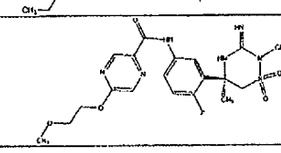
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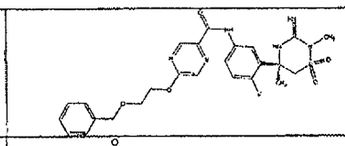
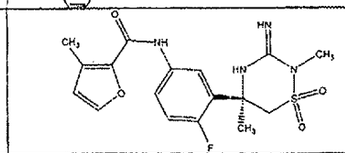
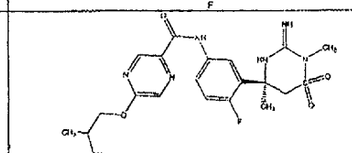
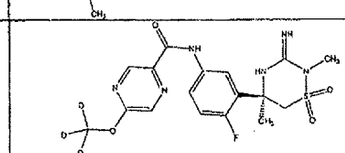
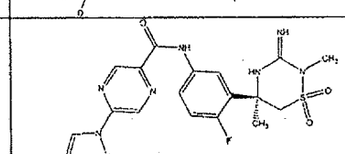
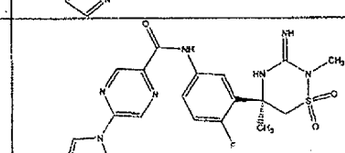
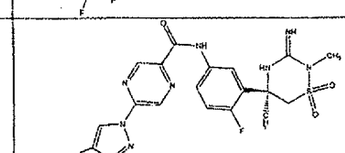
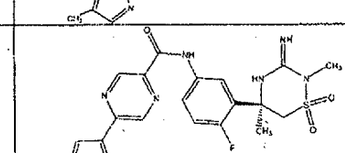
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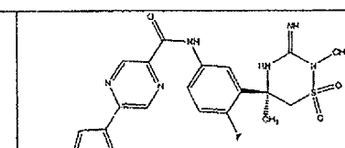
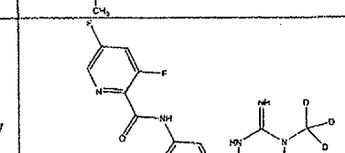
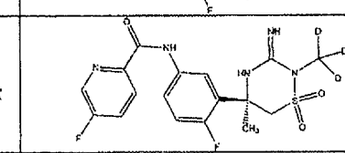
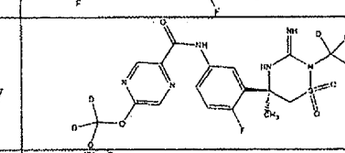
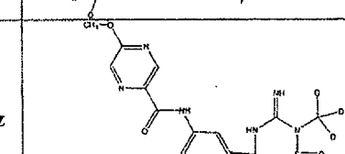
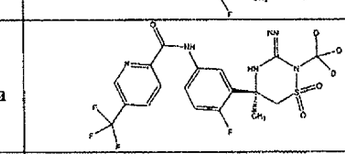
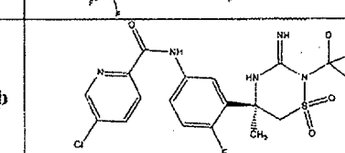
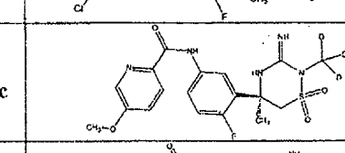
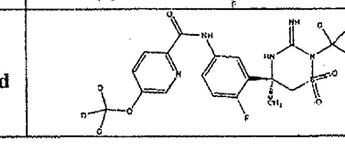
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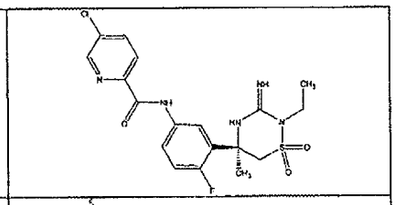
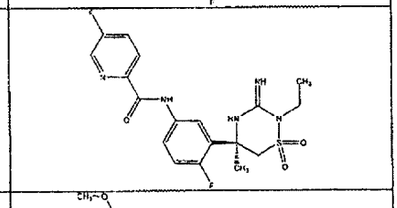
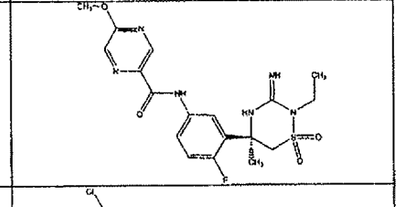
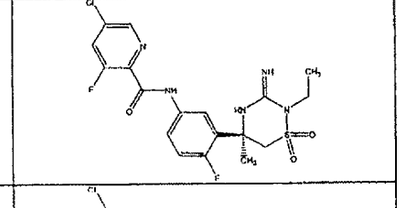
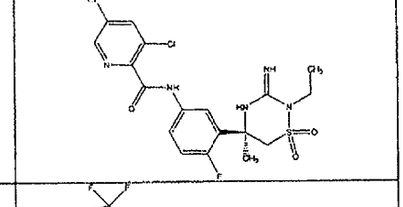
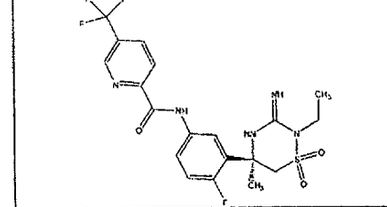
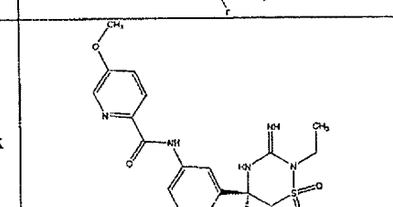
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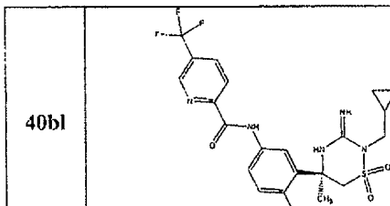
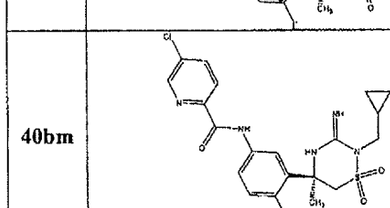
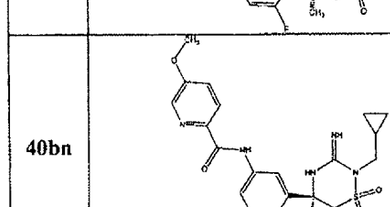
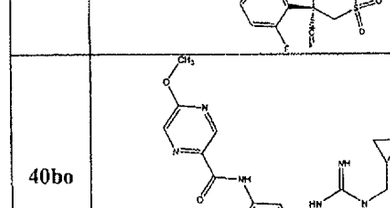
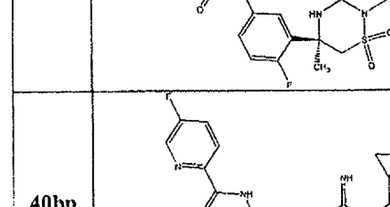
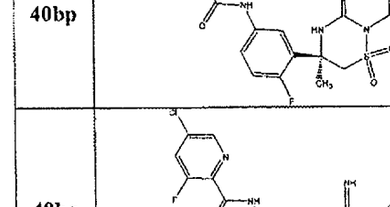
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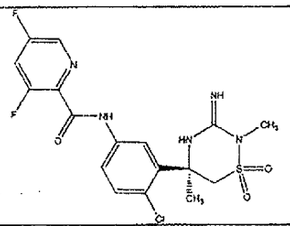
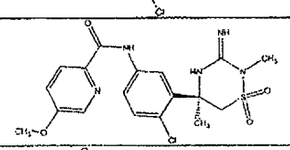
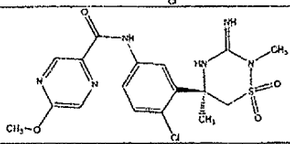
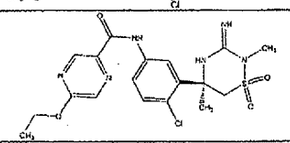
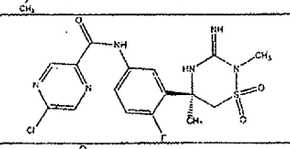
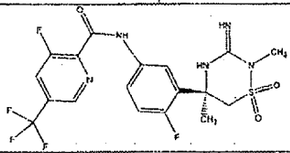
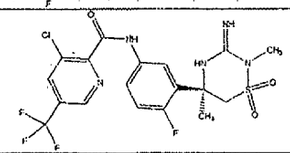
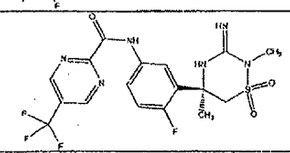
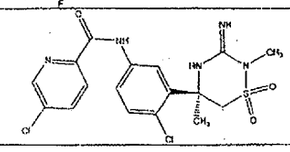
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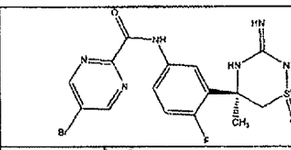
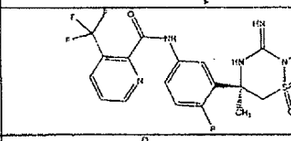
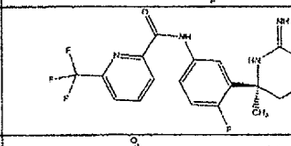
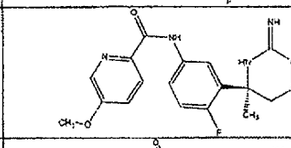
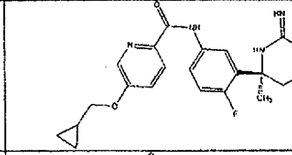
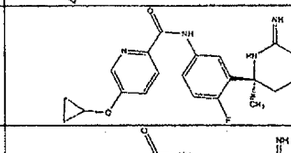
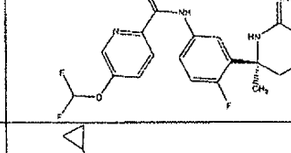
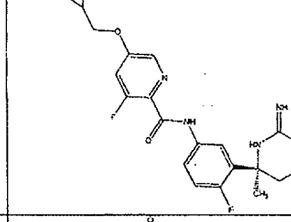
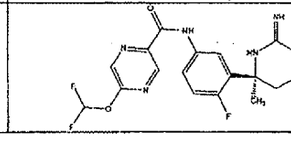
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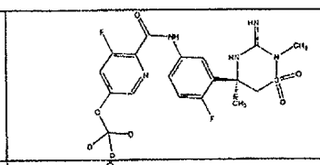
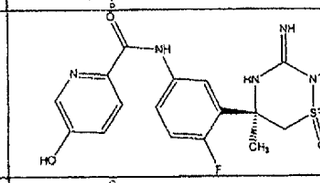
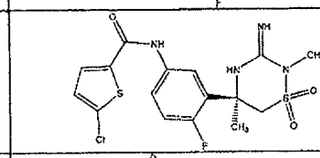
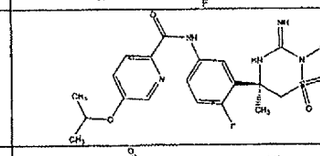
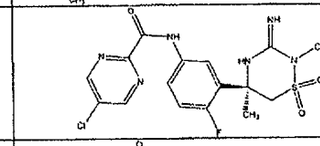
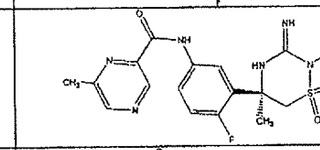
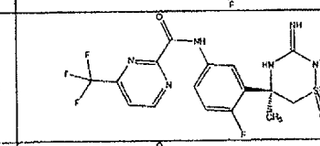
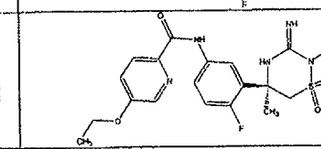
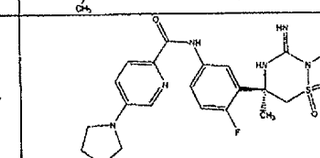
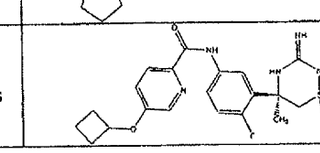
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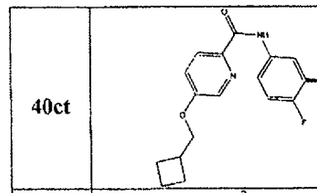
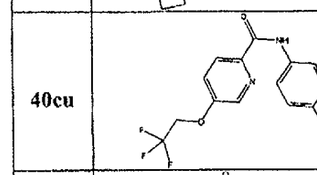
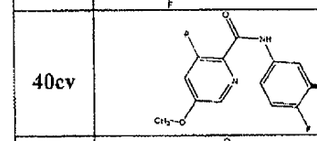
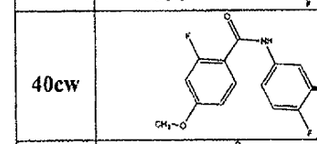
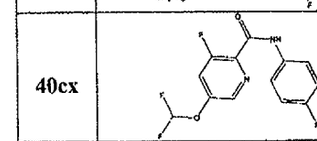
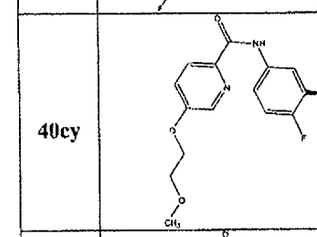
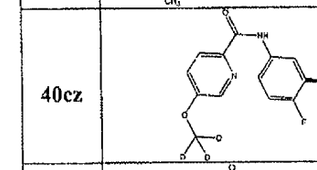
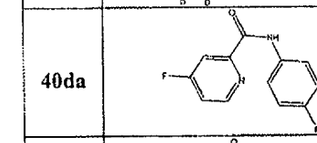
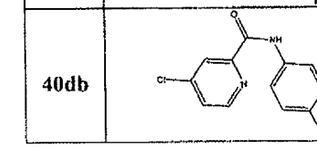
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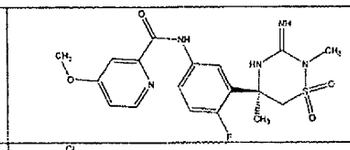
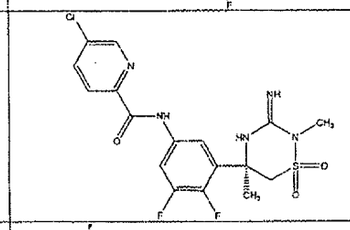
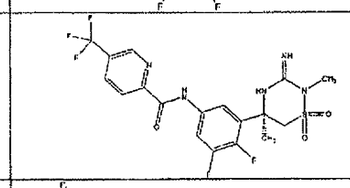
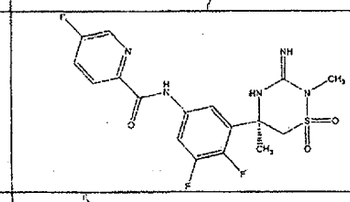
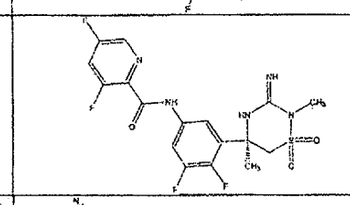
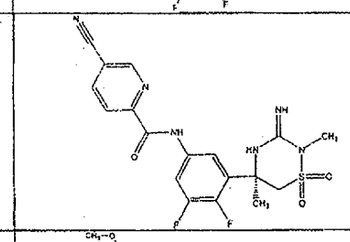
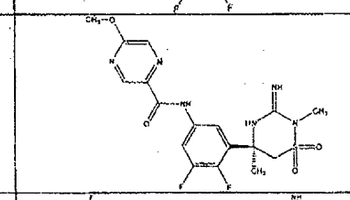
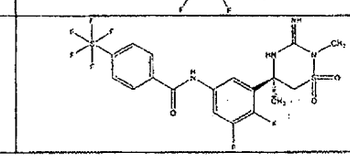
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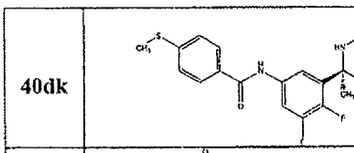
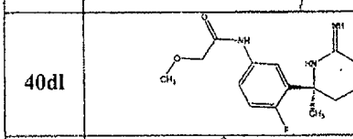
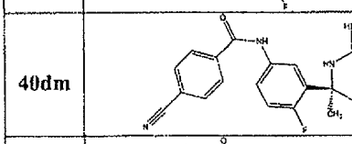
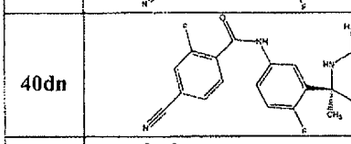
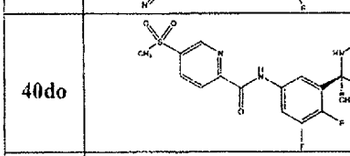
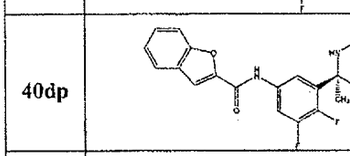
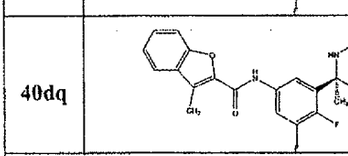
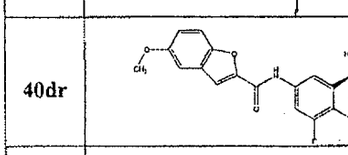
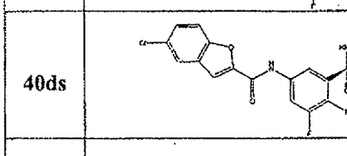
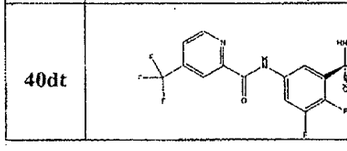
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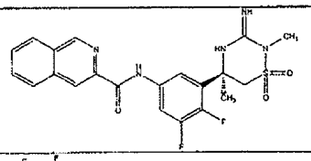
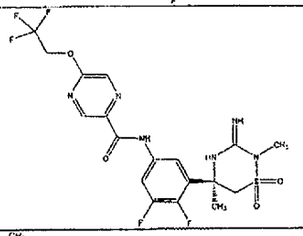
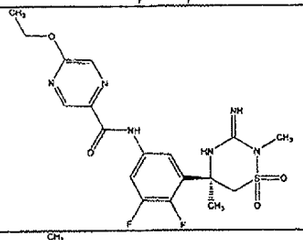
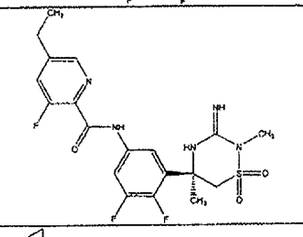
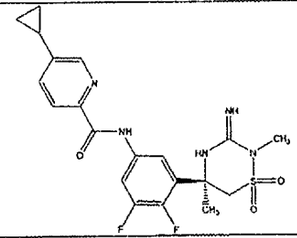
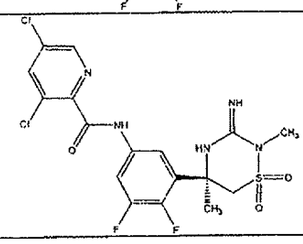
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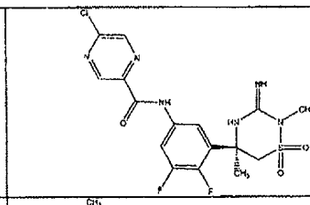
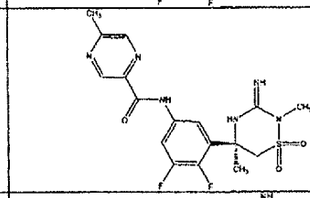
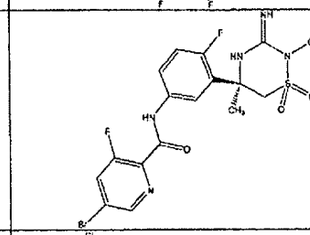
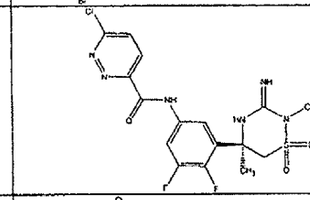
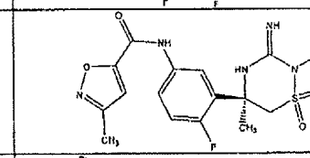
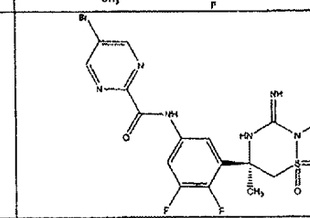
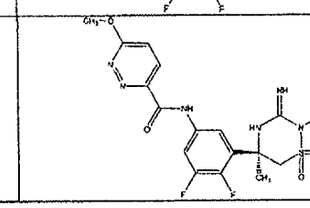
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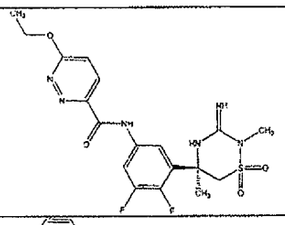
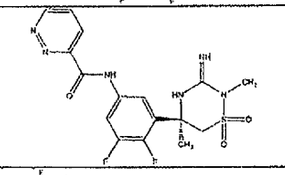
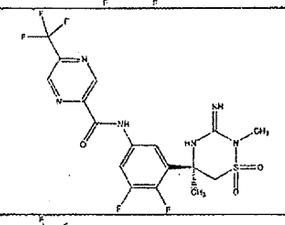
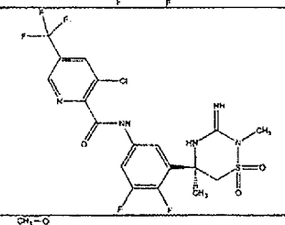
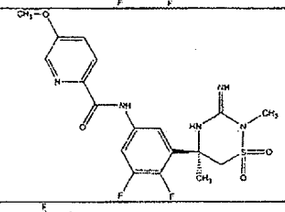
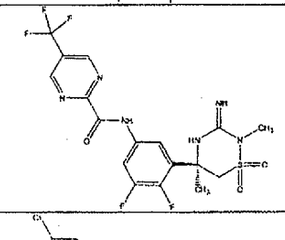
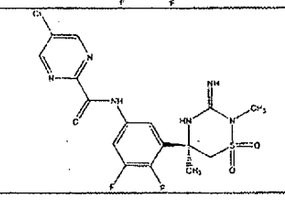
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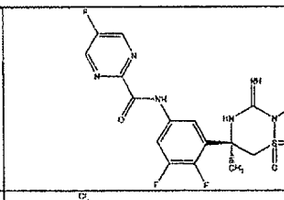
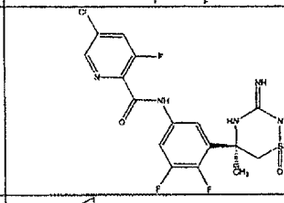
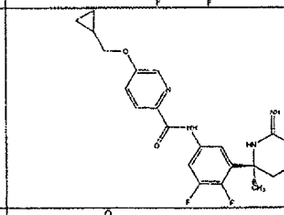
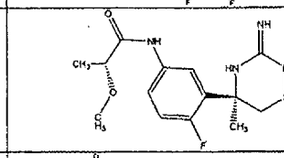
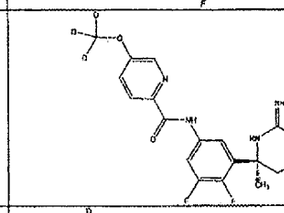
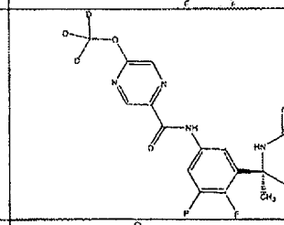
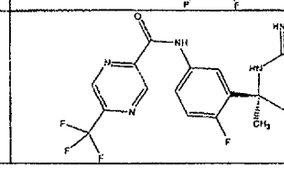
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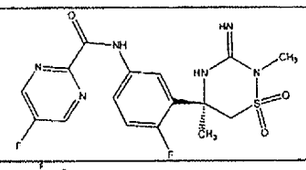
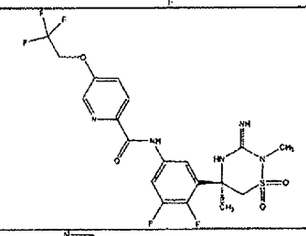
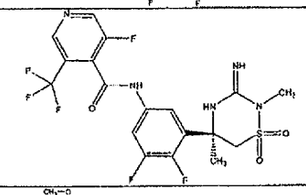
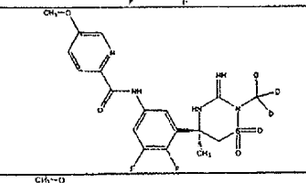
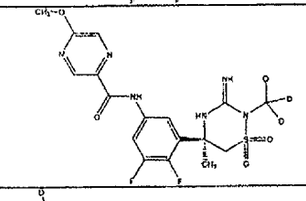
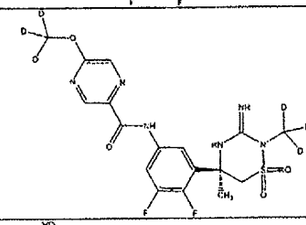
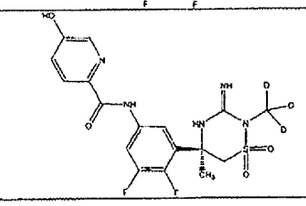
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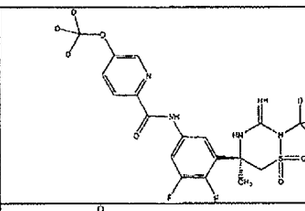
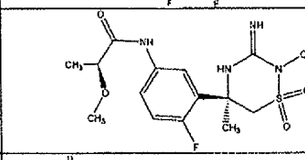
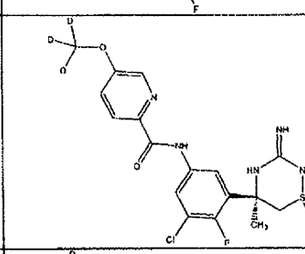
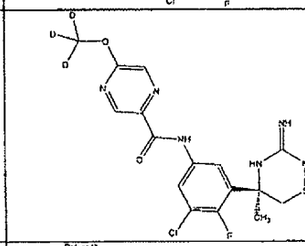
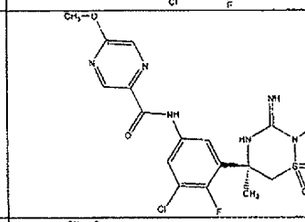
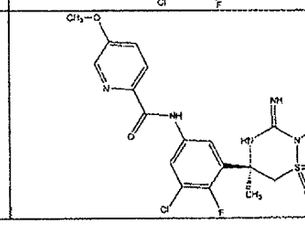
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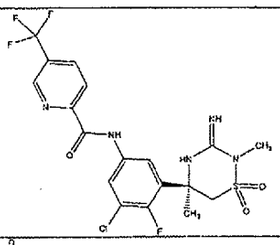
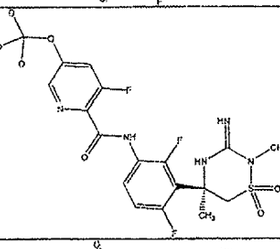
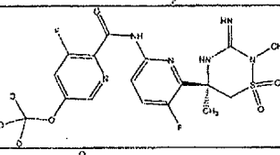
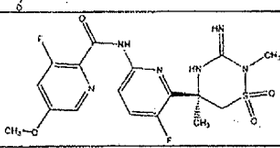
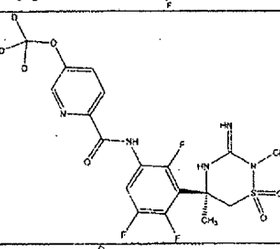
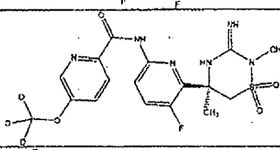
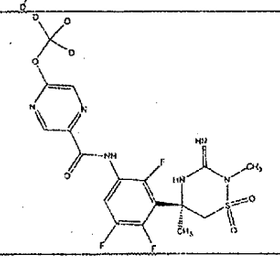
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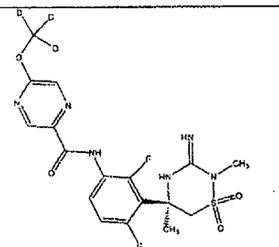
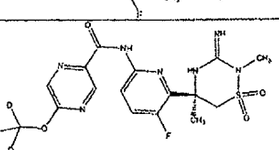
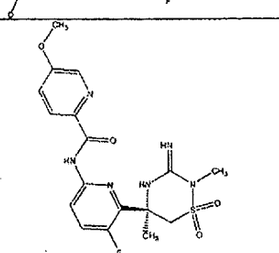
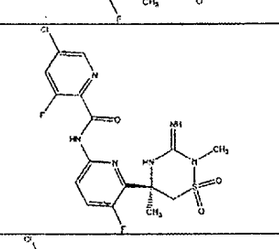
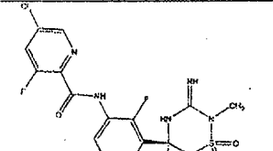
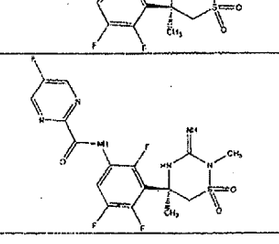
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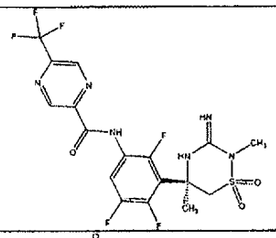
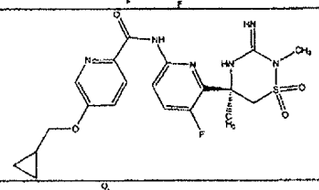
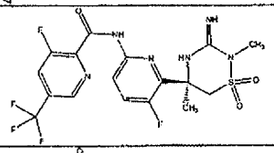
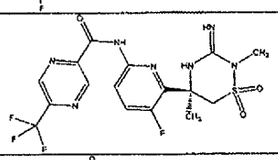
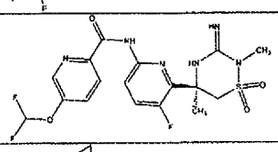
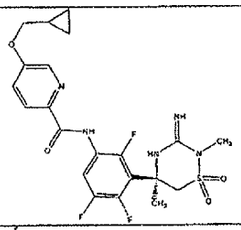
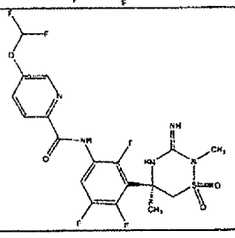
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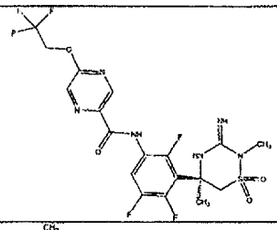
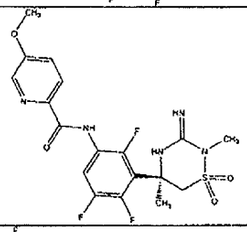
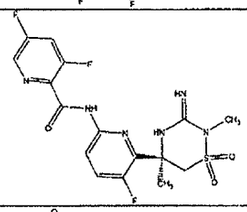
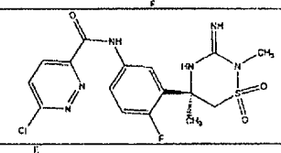
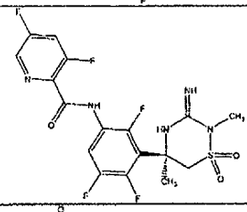
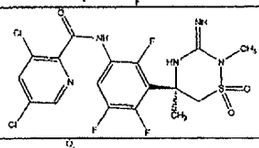
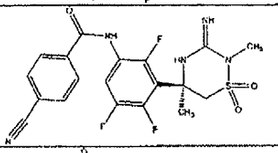
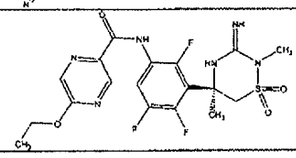
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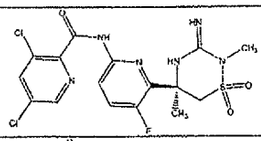
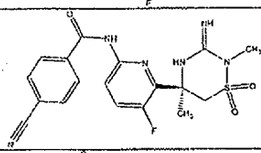
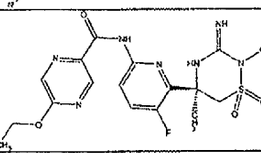
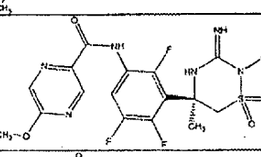
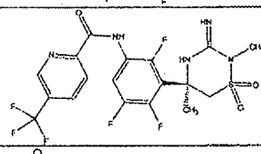
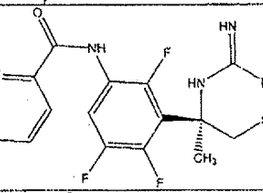
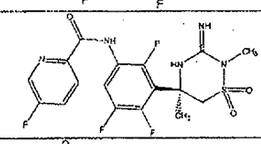
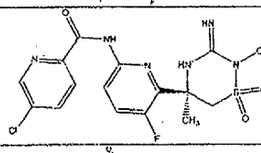
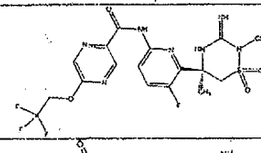
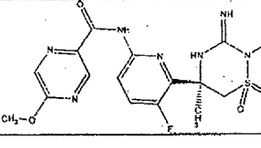
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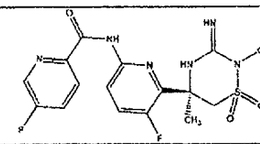
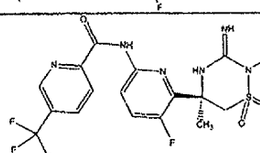
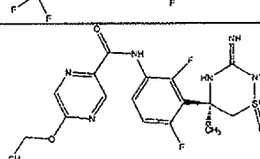
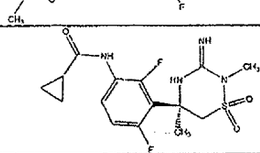
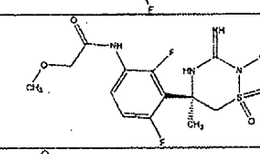
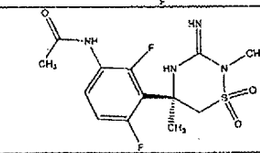
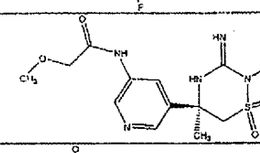
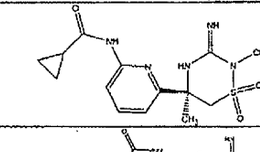
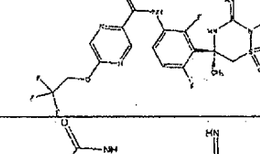
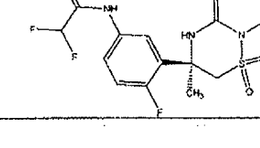
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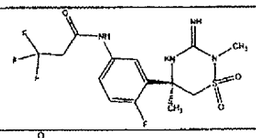
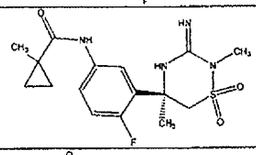
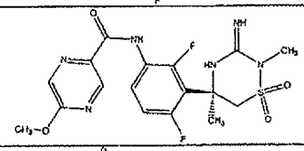
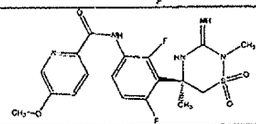
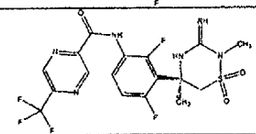
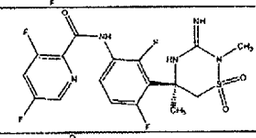
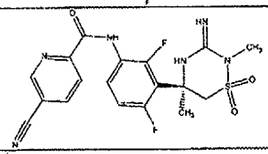
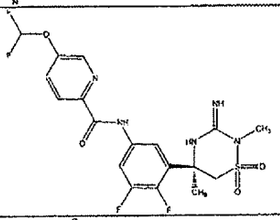
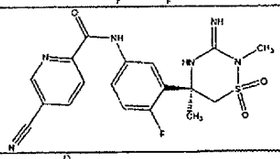
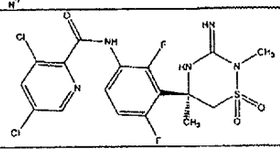
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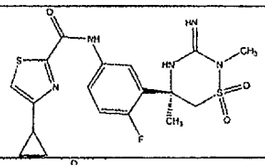
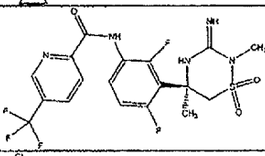
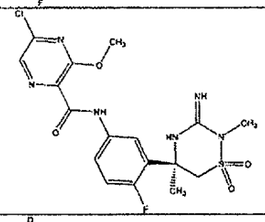
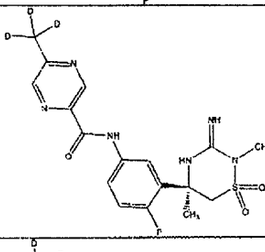
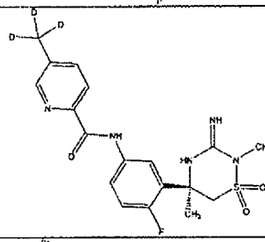
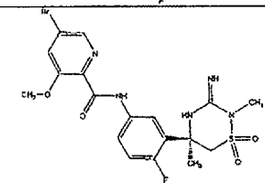
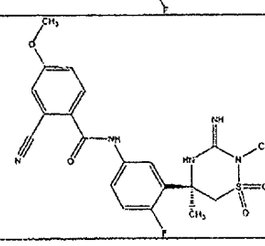
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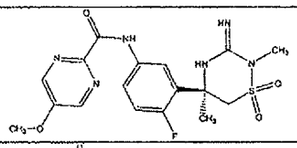
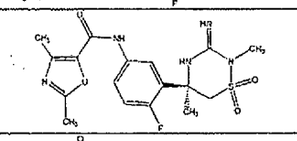
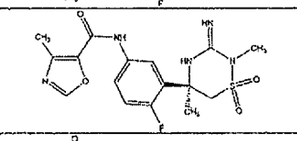
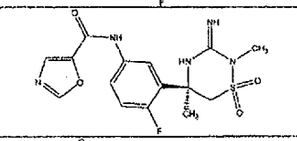
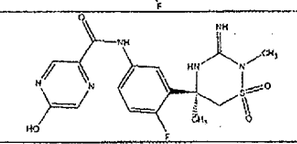
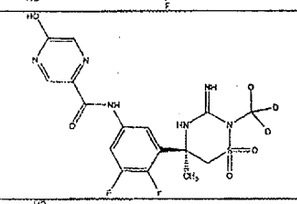
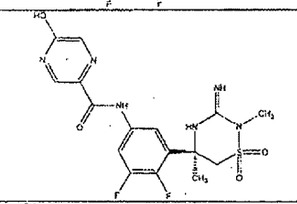
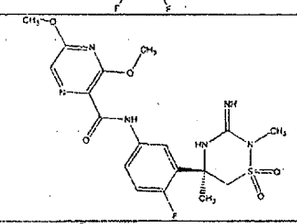
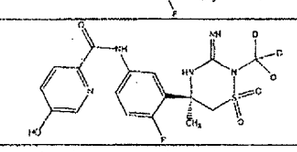
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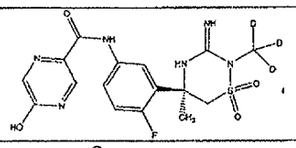
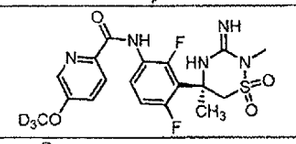
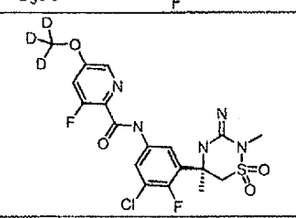
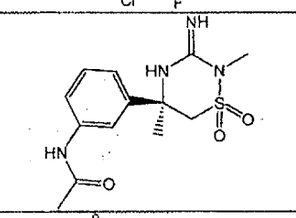
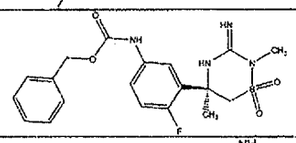
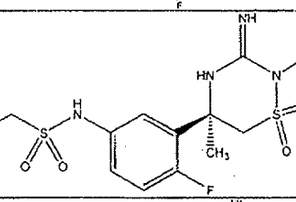
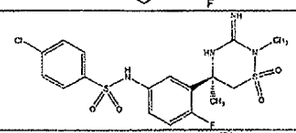
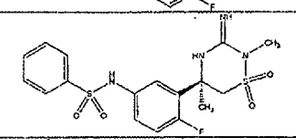
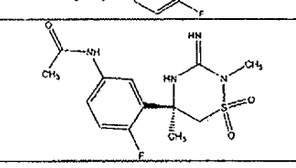
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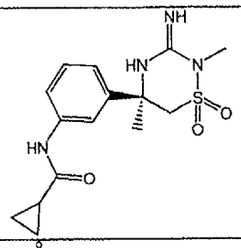
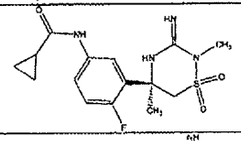
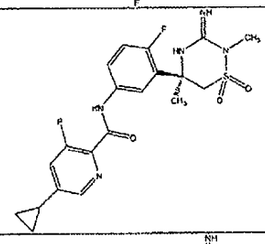
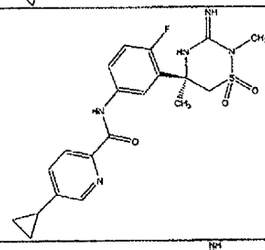
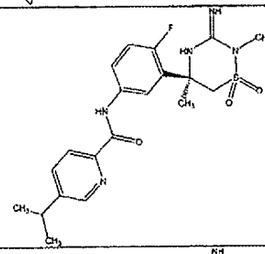
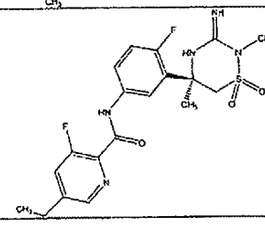
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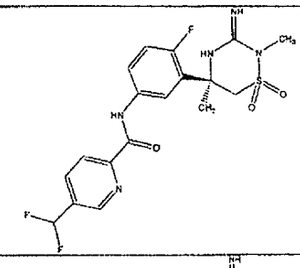
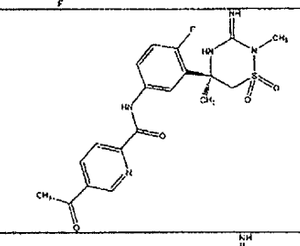
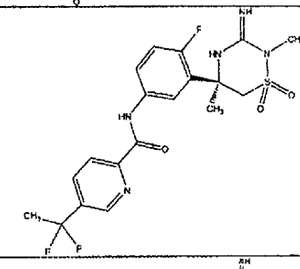
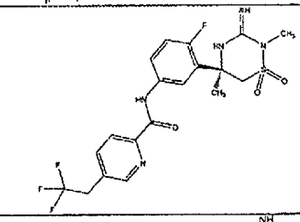
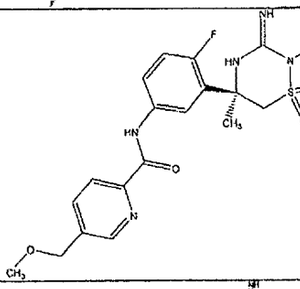
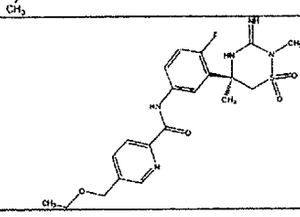
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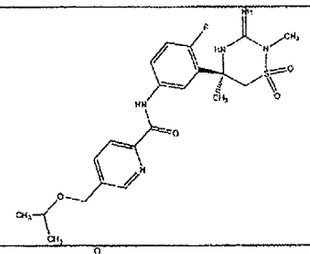
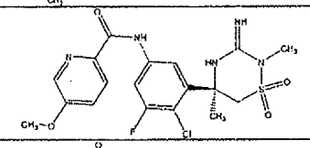
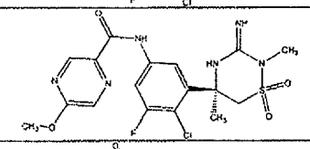
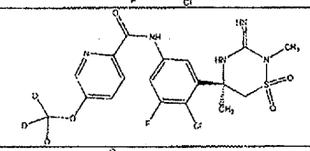
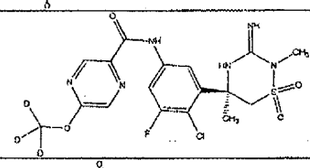
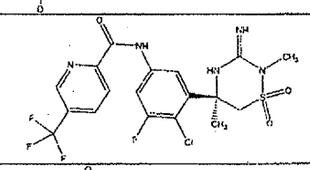
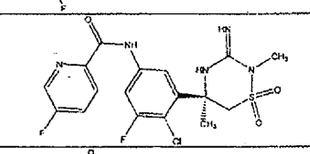
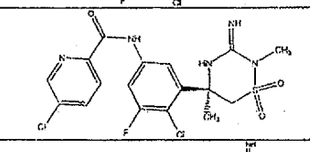
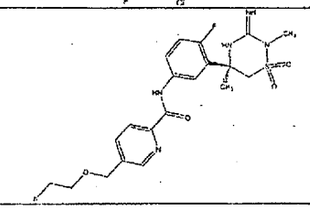
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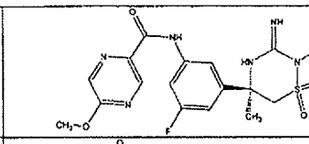
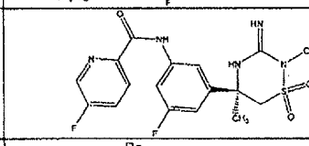
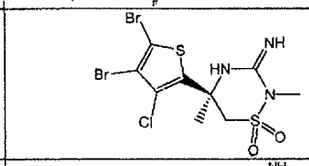
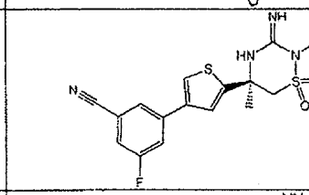
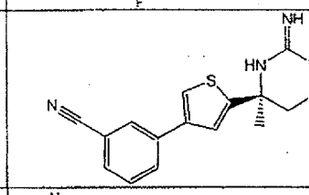
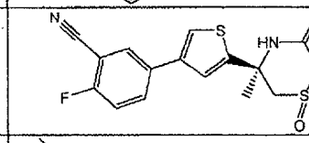
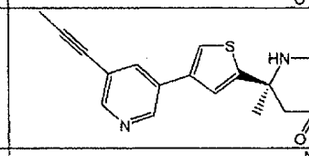
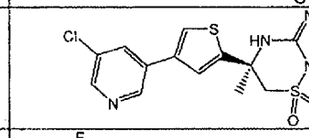
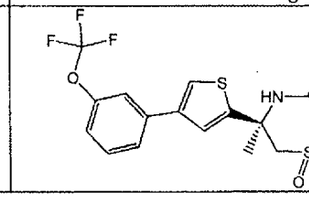
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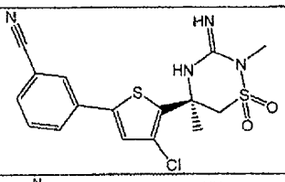
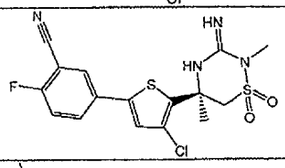
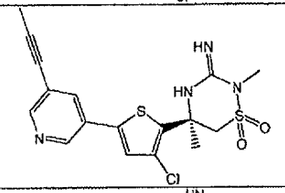
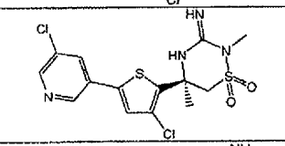
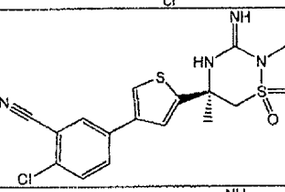
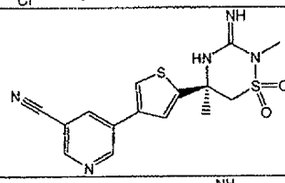
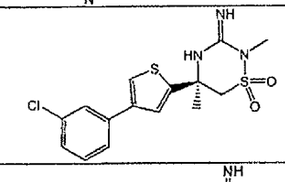
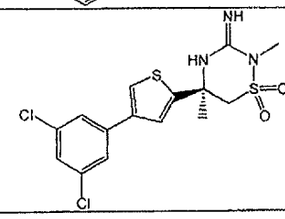
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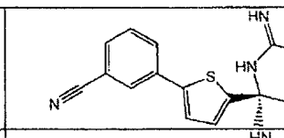
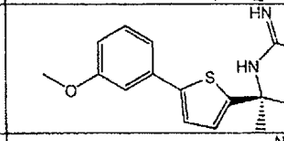
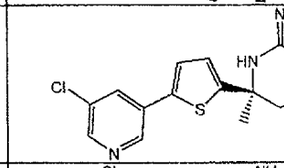
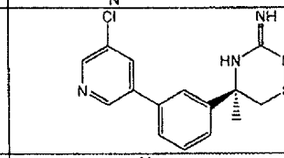
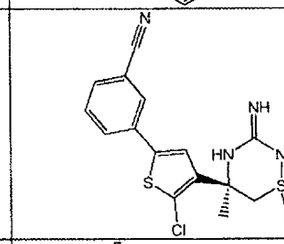
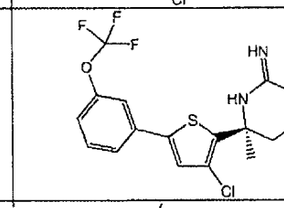
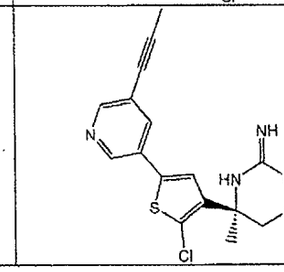
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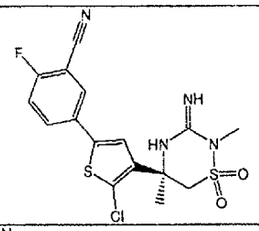
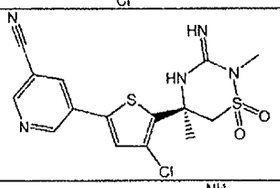
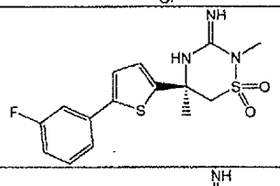
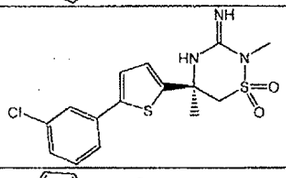
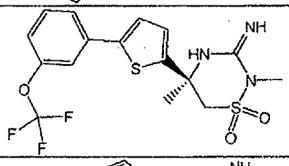
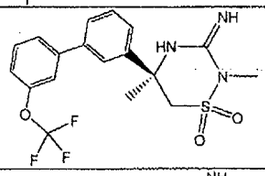
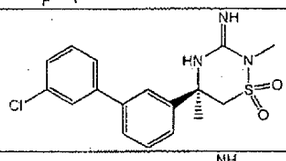
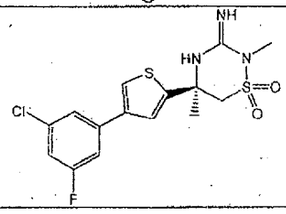
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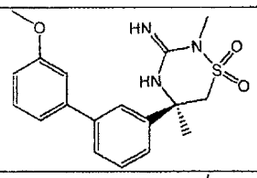
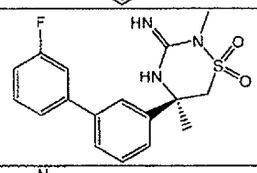
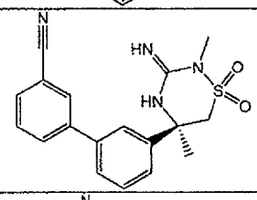
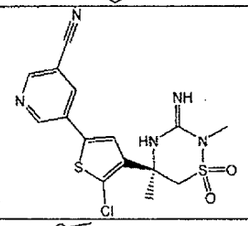
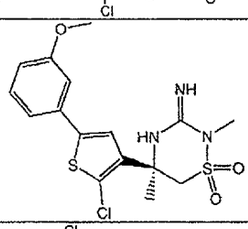
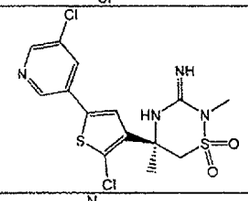
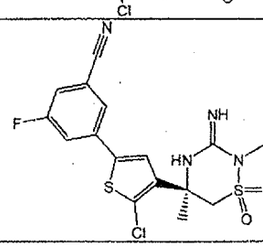
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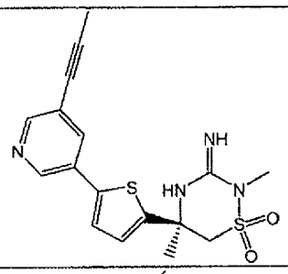
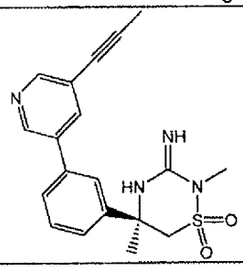
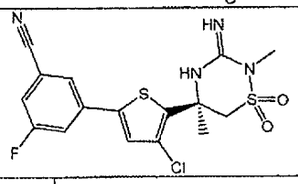
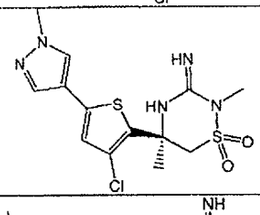
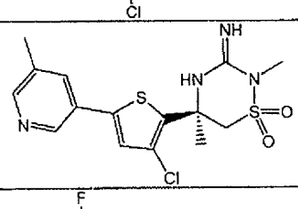
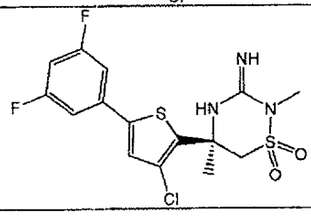
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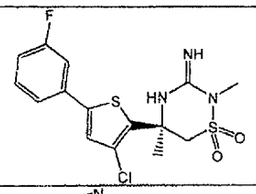
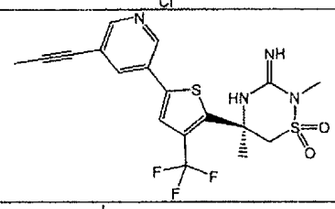
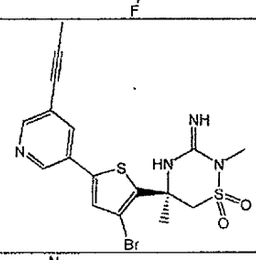
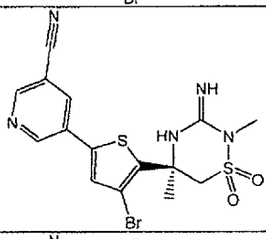
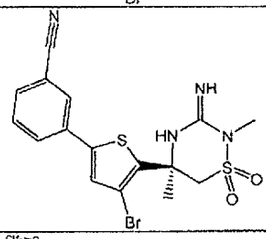
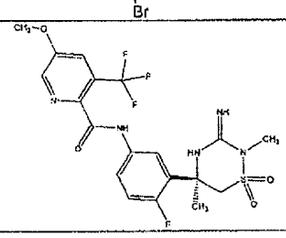
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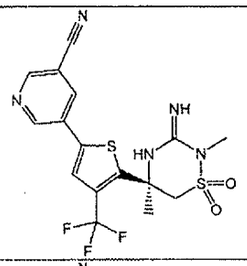
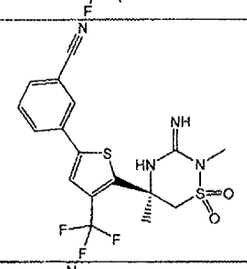
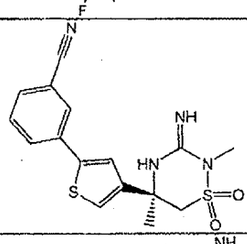
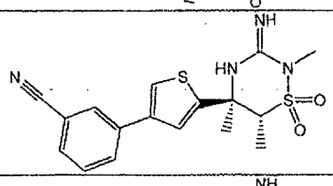
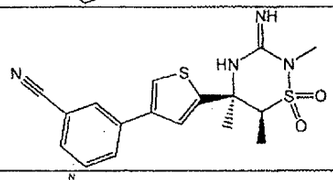
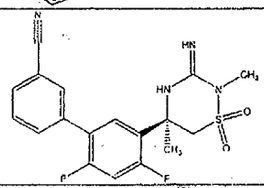
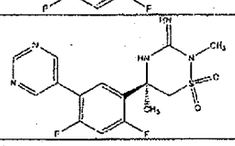
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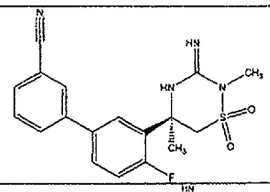
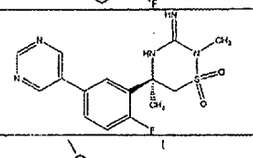
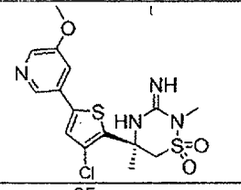
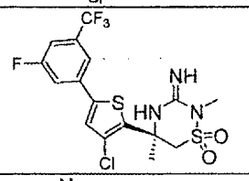
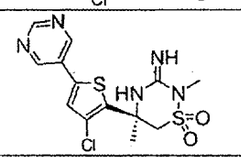
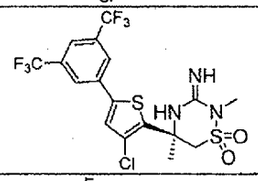
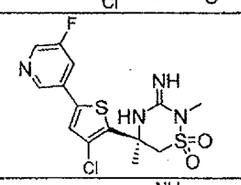
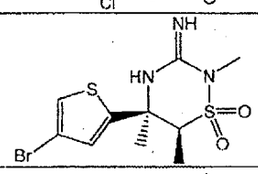
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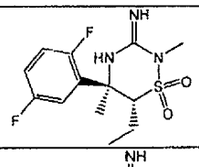
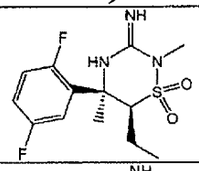
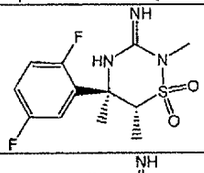
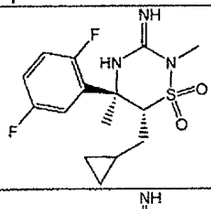
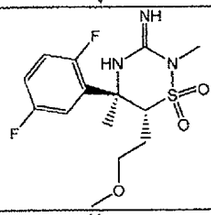
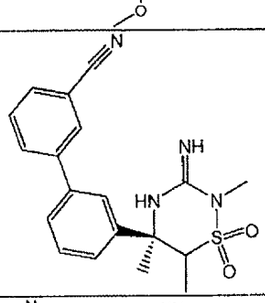
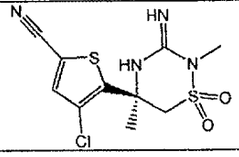
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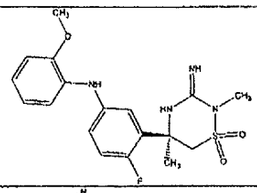
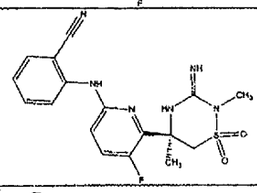
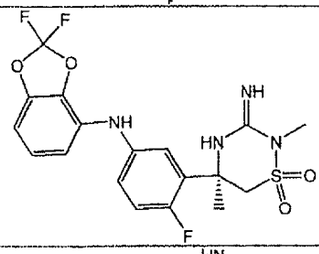
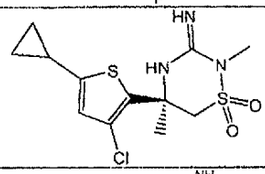
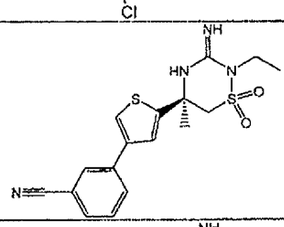
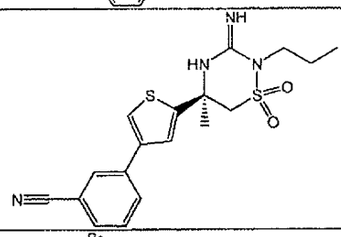
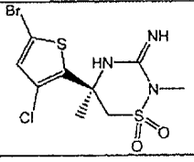
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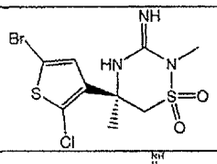
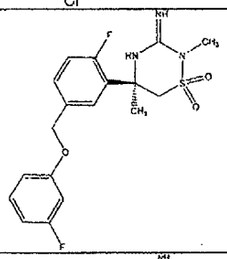
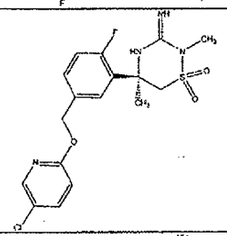
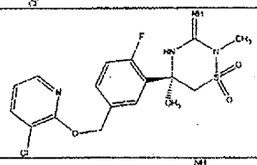
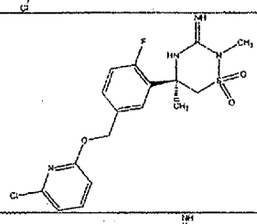
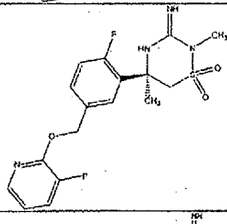
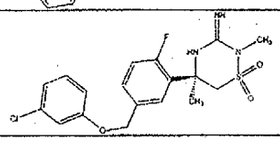
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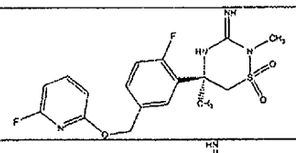
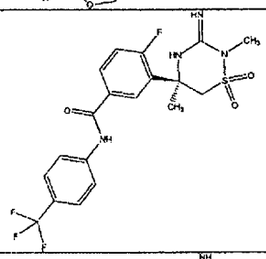
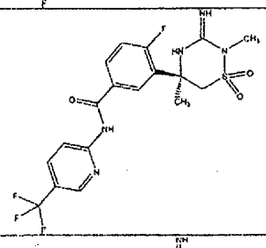
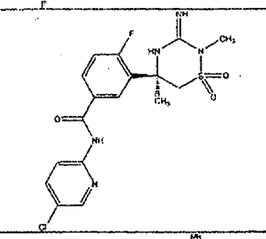
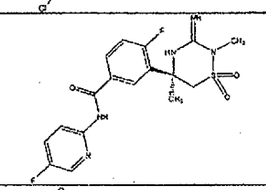
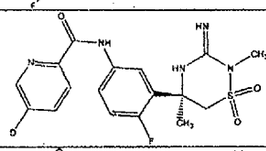
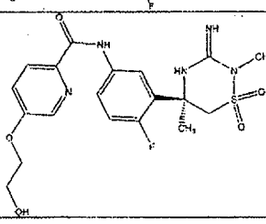
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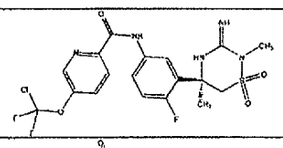
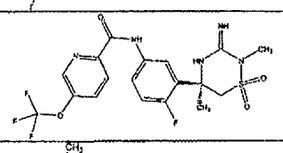
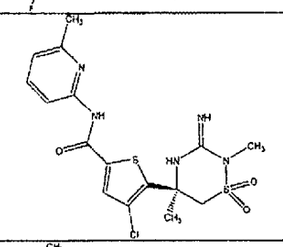
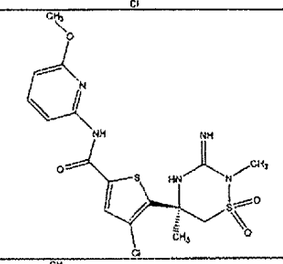
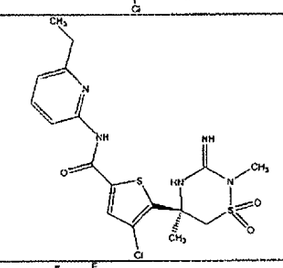
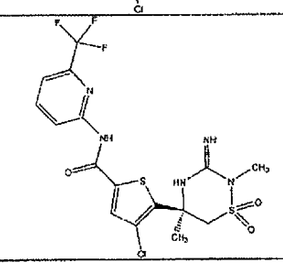
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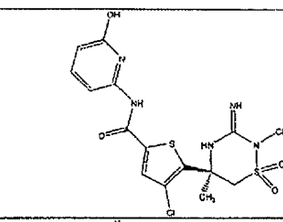
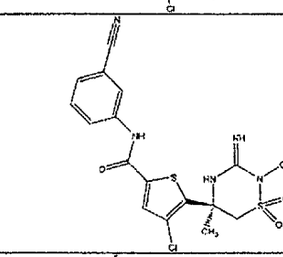
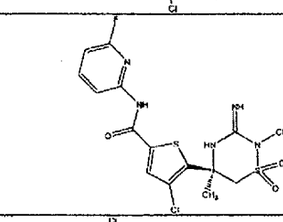
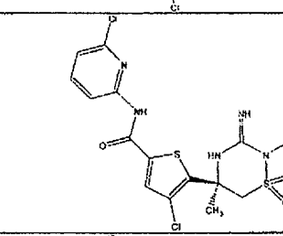
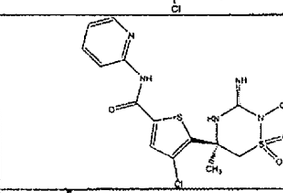
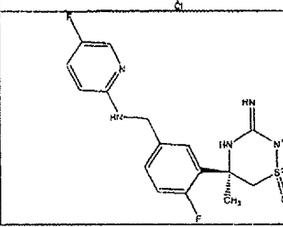
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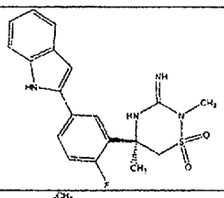
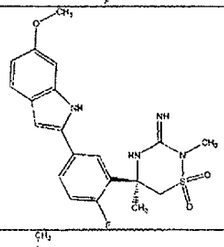
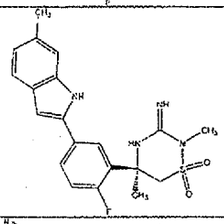
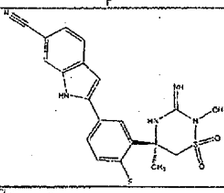
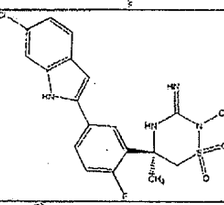
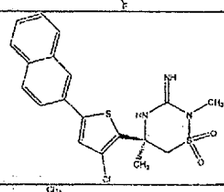
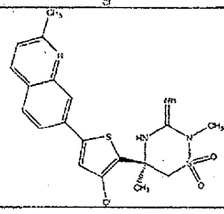
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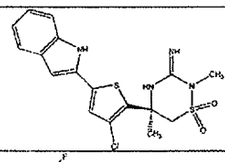
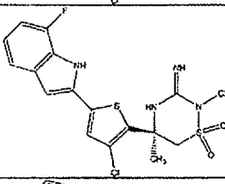
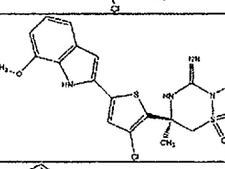
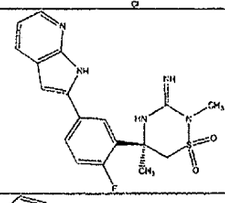
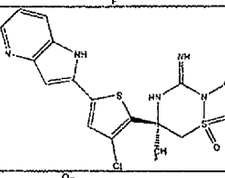
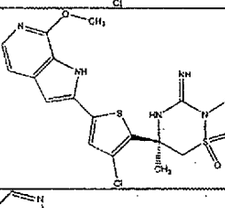
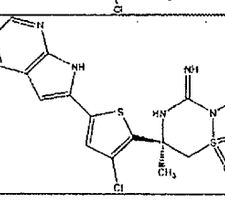
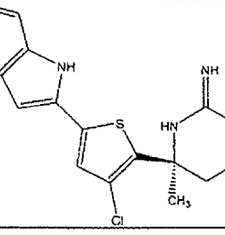
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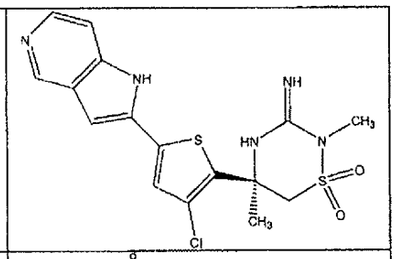
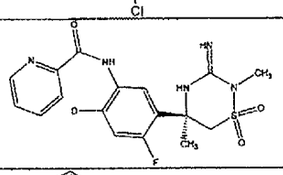
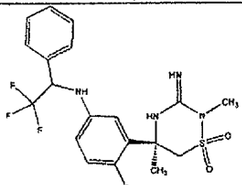
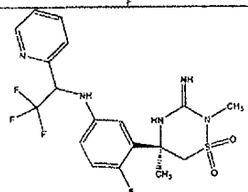
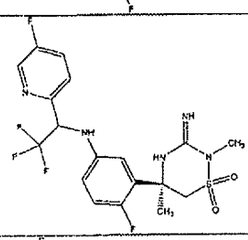
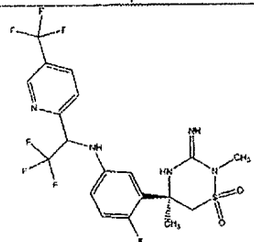
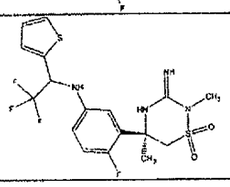
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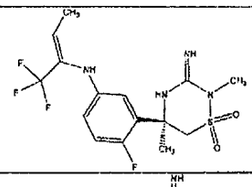
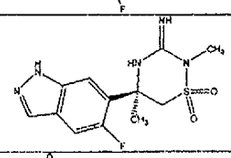
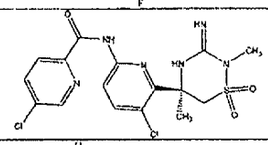
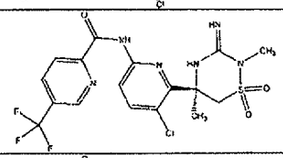
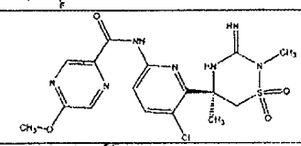
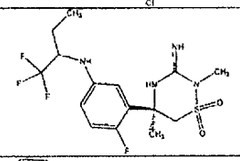
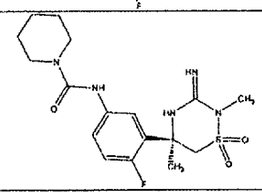
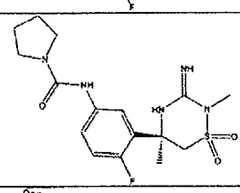
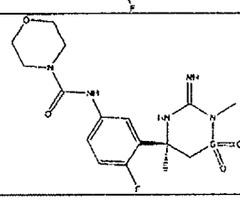
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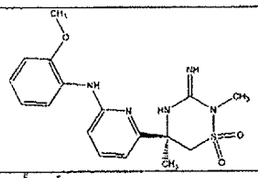
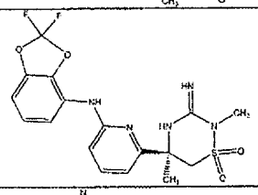
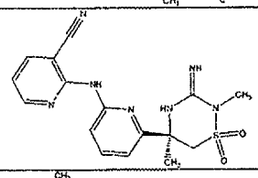
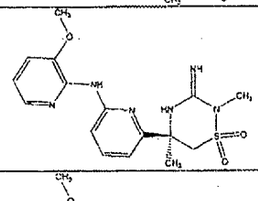
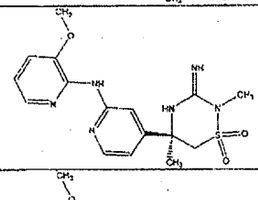
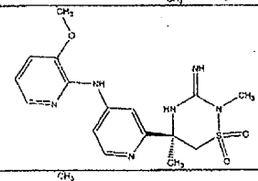
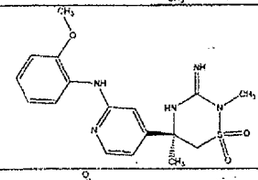
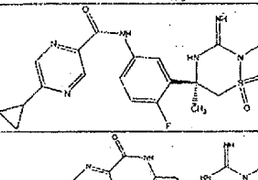
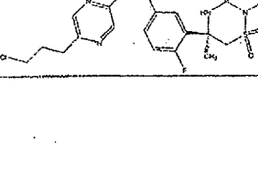
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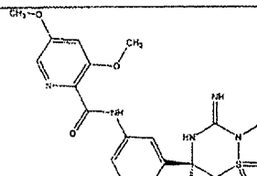
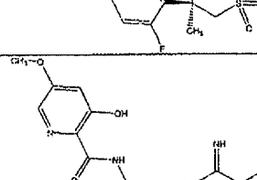
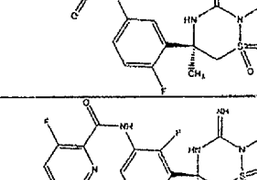
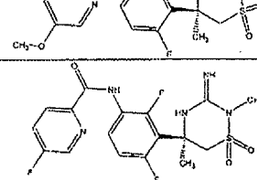
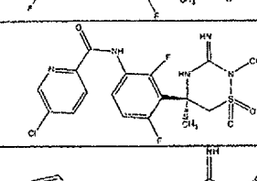
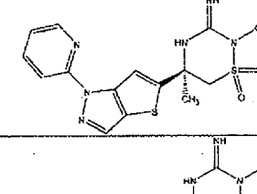
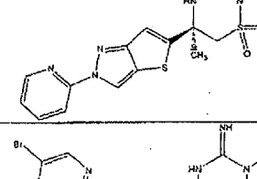
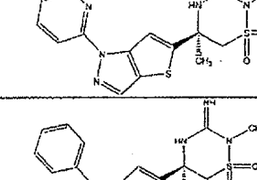
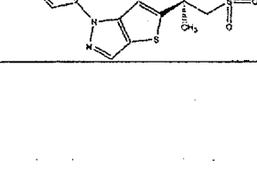
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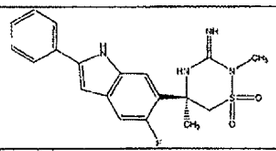
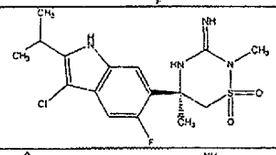
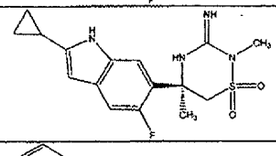
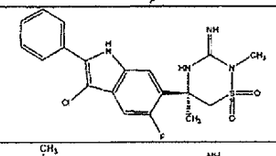
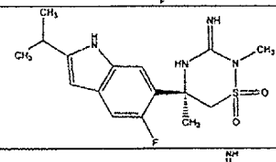
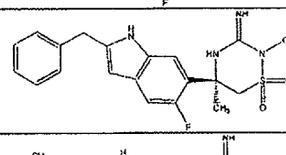
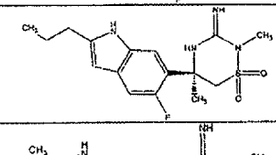
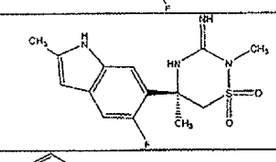
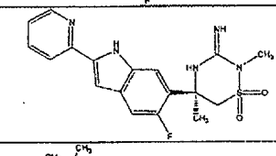
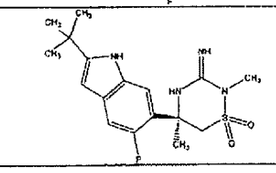
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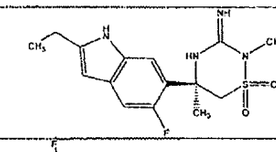
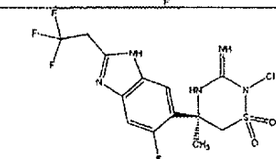
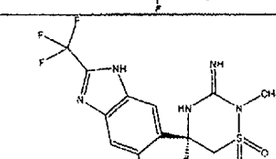
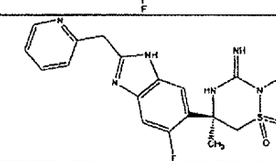
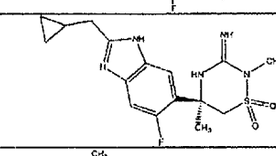
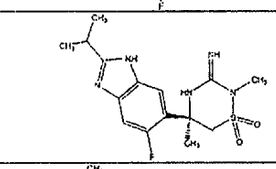
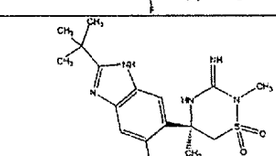
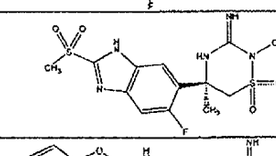
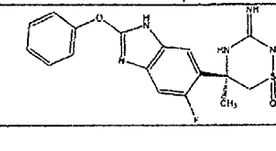
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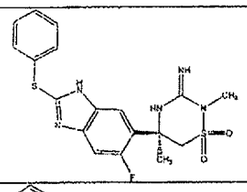
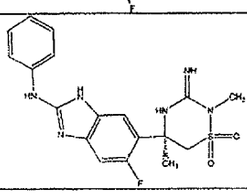
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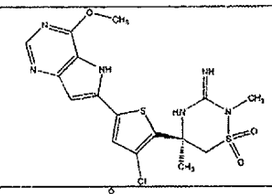
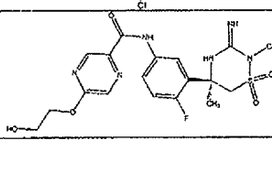
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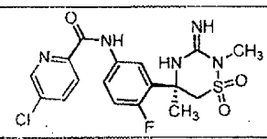
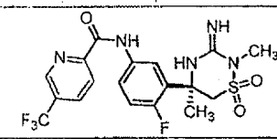
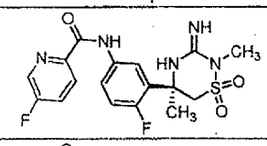
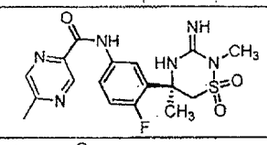
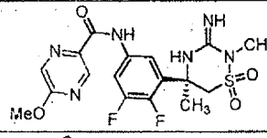
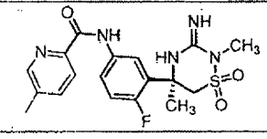
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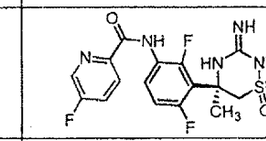
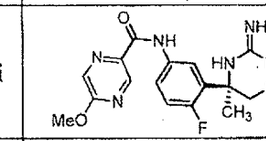
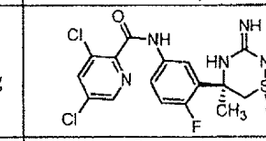
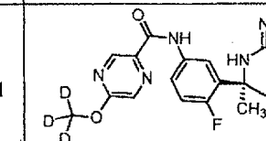
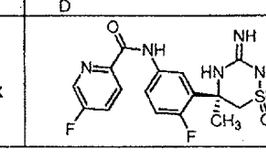
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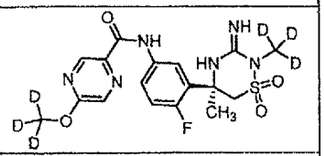
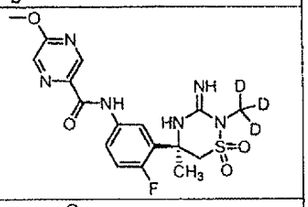
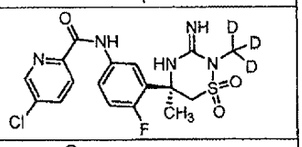
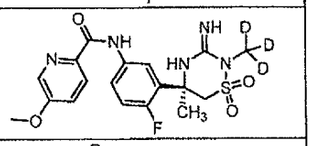
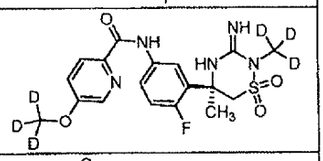
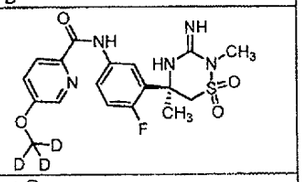
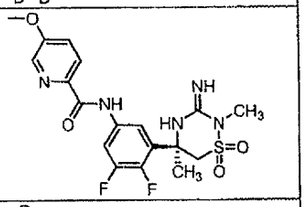
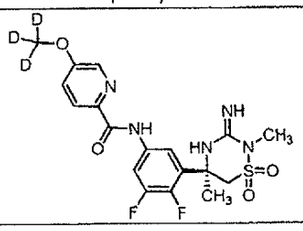
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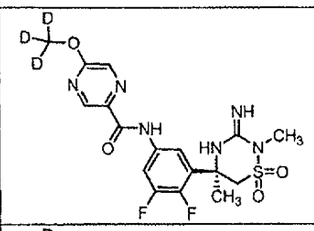
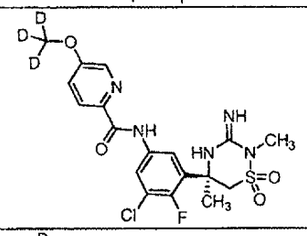
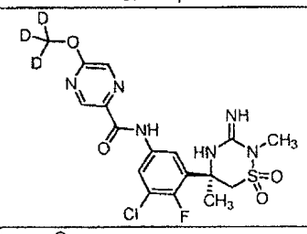
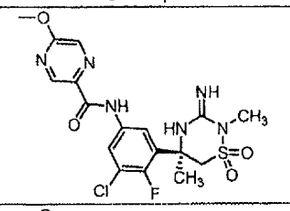
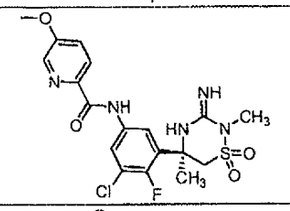
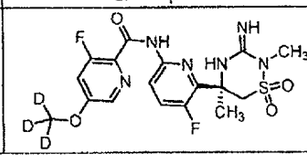
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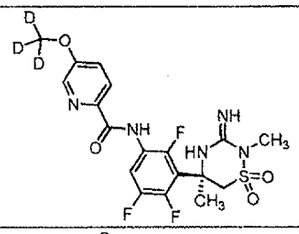
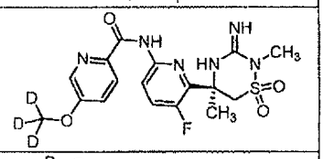
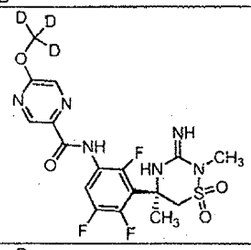
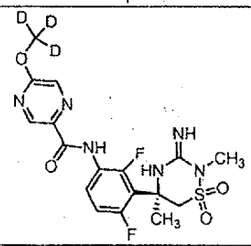
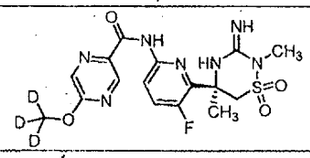
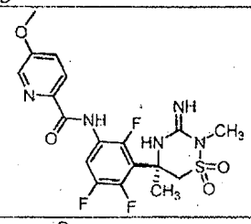
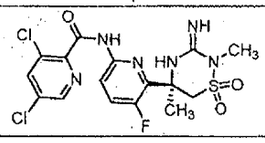
9. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of:

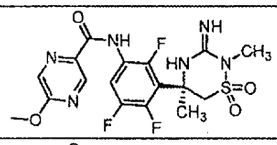
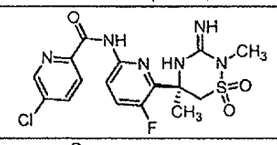
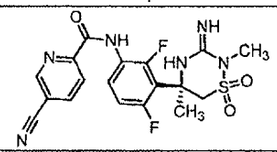
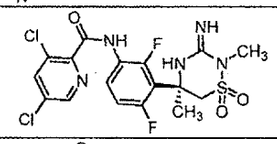
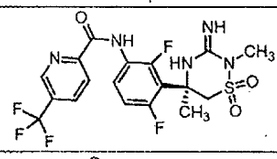
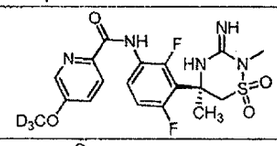
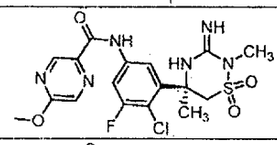
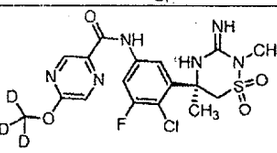
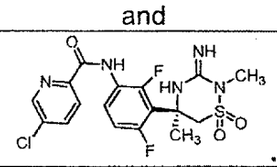
Ex. #	Structure
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40di	
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Ex. #	Structure
173	
40ai	
40ag	
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Ex. #	Structure
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40bc	
40bd	
40cz	
40el	
40es	

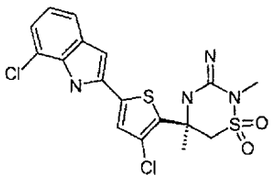
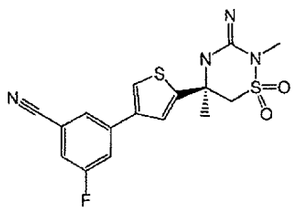
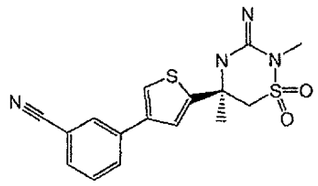
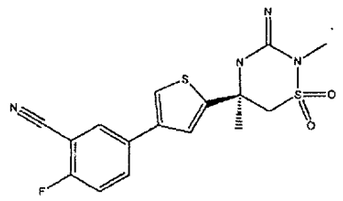
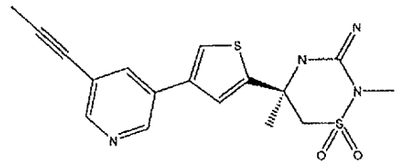
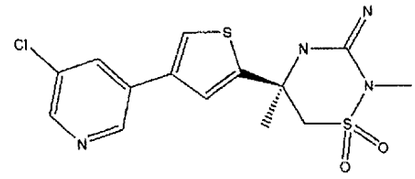
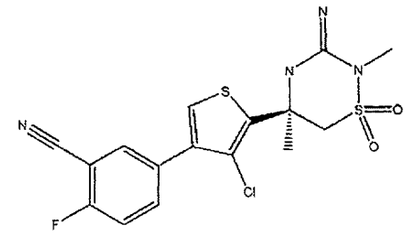
Ex. #	Structure
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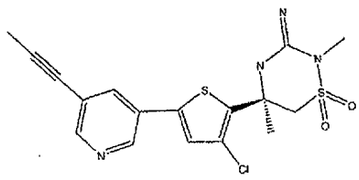
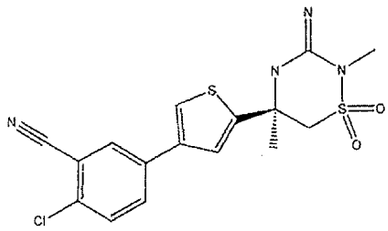
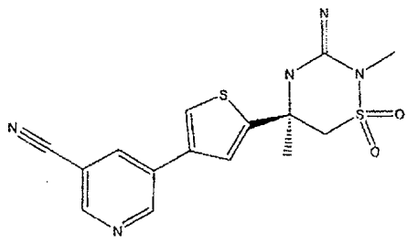
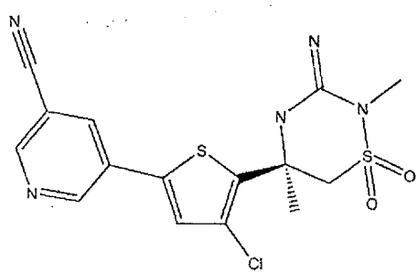
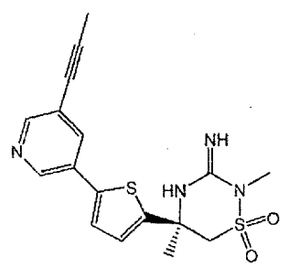
Ex. #	Structure
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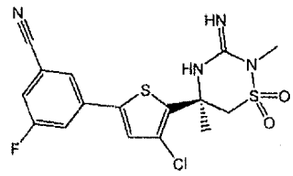
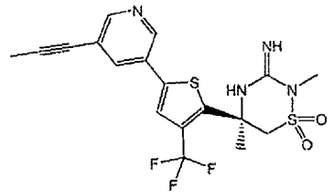
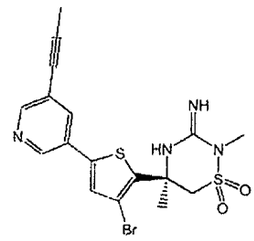
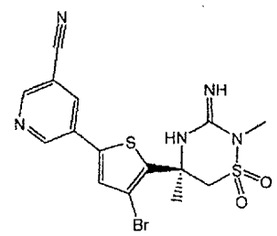
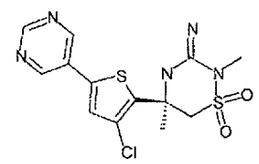
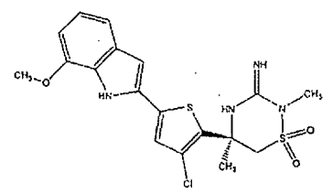
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40hp	
40hr	
40ii	
42n	
42p	
	and
174	

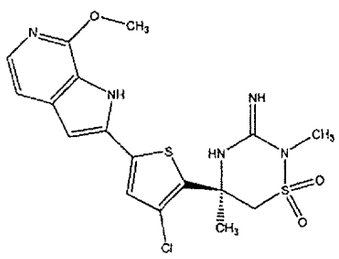
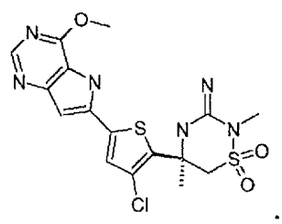
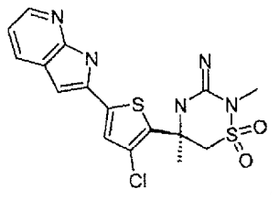
10. A compound, or a tautomer thereof,

10. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of

Ex.	Structure
141a	
44	
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48	
51	

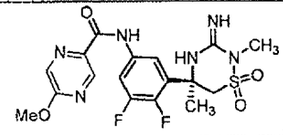
Ex.	Structure
52	
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55	
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80	

Ex.	Structure
82	
87	
88	
89	
95g	
141	

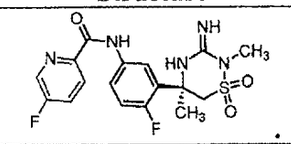
Ex.	Structure	Ex.	Structure
144		200	
145			

, and

11. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:

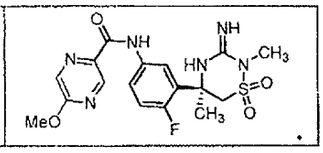
Ex #	Structure
40di	

12. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:

Ex #	Structure
25	

13. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:

Ex #	Structure

40ai	

14. A pharmaceutical composition comprising at least one compound of any one of claims 1-13, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, together with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or diluent.

16. A pharmaceutical composition of claim 15, wherein said at least one additional therapeutic agent is at least one agent selected from:

m_1 agonists; m_2 antagonists; cholinesterase inhibitors; galantamine; rivastigimine; N-methyl-D-aspartate receptor antagonists; combinations of cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists; gamma secretase modulators; gamma secretase inhibitors; non-steroidal anti-inflammatory agents; anti-inflammatory agents that can reduce neuroinflammation; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists; CB1 receptor antagonists; antibiotics; 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; Tau kinase inhibitors; Tau aggregation inhibitors; RAGE inhibitors; anti-Abeta vaccine; APP ligands; agents that upregulate insulin, cholesterol lowering agents; cholesterol absorption inhibitors; combinations of HMG-CoA reductase inhibitors and cholesterol absorption inhibitors; fibrates; combinations of fibrates and cholesterol lowering agents and/or cholesterol absorption inhibitors; nicotinic receptor agonists; niacin; combinations of niacin and cholesterol absorption inhibitors and/or cholesterol lowering agents; LXR agonists; LRP mimics; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; 5-HT4

agonists; 5-HT6 receptor antagonists; mGluR1 receptor modulators or antagonists; mGluR5 receptor modulators or antagonists; mGluR2/3 antagonists; Prostaglandin EP2 receptor antagonists; PAI-1 inhibitors; agents that can induce Abeta efflux; Metal-protein attenuating compound; GPR3 modulators; and antihistamines.

17. A method of treating, preventing, and/or delaying the onset of an amyloid β pathology ("Aβ pathology") and/or one or more symptoms of said pathology comprising administering at least one compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, to a patient in need thereof in an amount effective to treat said pathology.

18. A method of claim 17, wherein said Aβ pathology is selected from Alzheimer's disease, Down's syndrome, Parkinson's disease, memory loss, memory loss associated with Alzheimer's disease, memory loss associated with Parkinson's disease, attention deficit symptoms, attention deficit symptoms associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, dementia, stroke, microgliosis and brain inflammation, pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment, olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes, diabetes-associated amyloidogenesis, hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI"), Creutzfeld-Jakob disease, and traumatic brain injury.

19. A method of claim 18, wherein said Aβ pathology is Alzheimer's disease.

126
127

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/51553

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/54 (2010.01)
USPC - 514/222.5
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)
USPC: 514/222.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 222.8, 223.2, 223.8, 224.2, 226.8, 227.2, 227.8, 228.2; 544/8, 10, 13 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Patentscope
1,2,4-thiadiazine, thiadiazin$, $thiadiazine, iminothiadiazine, aspartyl protease, beta-secretase, BACE$, inhibit$, modulat$, Alzheimer's, treat$, ameliorat$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/065277 A2 (ZHU et al.) 22 June 2006 (22.06.2006) pg 1, ln 14-19; pg 2, ln 16 to pg 3, ln 7; pg 3, ln 32 to pg 4, ln 20; pg 7, ln 11-23; pg 11, ln 10-12; pg 12, ln 6-19; pg 17, ln 11-12; ln 21-28; pg 19, ln 31-32; pg 24, ln 6-9 This document can be viewed by entering the doc number at the following url: http://ep.espacenet.com/numberSearch?locale=en_EP	1-19
Y	US 2008/0200445 A1 (ZHU et al.) 21 August 2008 (21.08.2008) para [0057], [0156], [0660]	1-19

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
15 November 2010 (15.11.2010)	03 DEC 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

127

COMPUESTOS DE DIÓXIDO DE IMINOTIADIAZINA COMO INHIBIDORES DE BACE, COMPOSICIONES, Y SU USO

SOLICITUDES RELACIONADAS

Esta solicitud reclama prioridad frente a la solicitud provisoria Estadounidense Nº de Acta 61/249.685, presentada el 08 de octubre del 2009, incorporada a la presente como referencia.

CAMPO DE LA INVENCIÓN

Esta invención proporciona ciertos compuestos de dióxido de iminotiadiazina y composiciones que comprenden estos compuestos. Se ha descubierto, sorprendentemente, que los compuestos de dióxido de iminotiadiazina novedosos de la invención exhiben propiedades las cuales se espera que los convierta en ventajosos como inhibidores de BACE y/o para el tratamiento y prevención de diversas patologías relacionadas con la producción de β–amiloides ("Aβ").

ANTECEDENTES

El péptido beta amiloide ("Aβ") es un componente primario de fibrillas y placas β amiloides, las cuales se considera que tienen un rol en una cantidad cada vez mayor de patologías. Los ejemplos de ese tipo de patologías incluyen, aunque sin limitarse a, la enfermedad de Alzheimer, síndrome de Down, enfermedad de Parkinson, pérdida de memoria (incluyendo pérdida de memoria asociada con la enfermedad de Alzheimer y la enfermedad de Parkinson), síntomas de déficit de atención (incluyendo síntomas de déficit atencional asociados con la enfermedad de Alzheimer ("EA"), enfermedad de Parkinson, y síndrome de Down), demencia (incluyendo demencia presenil, demencia senil, demencia asociada con la enfermedad de Alzheimer, enfermedad de Parkinson, y síndrome de Down), parálisis supranuclear progresiva, degeneración córtico–basal, neurodegeneración, deterioro olfativo (incluyendo deterioro olfativo asociado con la enfermedad de Alzheimer, enfermedad de Parkinson, y síndrome de Down), angiopatía β–amiloide (incluyendo angiopatía amiloide cerebral), hemorragia

cerebral hereditaria, deterioro cognitivo leve (MCI, correspondiente a "deterioro cognitivo leve"), glaucoma, amiloidosis, diabetes tipo II, hemodiálisis (microglobulinas β2 y complicaciones que surgen de las mismas), enfermedades neurodegenerativas tales como scrapie (o tembladera), encefalitis espongiforme bovina, enfermedad de Creutzfeld–Jakob, lesión cerebral traumática y enfermedades similares.

Los péptidos Aβ son péptidos cortos los cuales son hechos de la descomposición proteolítica de la proteína de transmembrana llamada proteína precursora amiloide ("APP", del inglés "amyloid precursor protein"). Los péptidos Aβ son hechos de la disociación de APP por actividad de β–secretasa cerca de la posición cercana al término N de Aβ, y por la actividad de gamma–secretasa en una posición cercana al término C de Aβ. (APP es también disociada por la actividad de α–secretasa, dando como resultado el fragmento secretado, no amiloidogénico conocido como APPα soluble.) La Enzima de Disociación de APP de sitio Beta "BACE–1", según el inglés "Beta site APP Cleaving Enzyme") es considerada la aspartil–proteasa primaria responsable de la producción de Aβ por actividad de β–secretasa. La inhibición de BACE–1 ha demostrado inhibir la producción de Aβ.

Se estima que la EA afecta a más de 20 millones de personas en el mundo entero y se cree que es la causa más común de demencia. La EA es una enfermedad caracterizada por la degeneración y pérdida de neuronas y también por la formación de placas seniles y enmarañamientos neurofibrilares. En la actualidad, el tratamiento de la enfermedad de Alzheimer es encuentra limitado al tratamiento de sus síntomas más que de las causas subyacentes. Los agentes mejoradores de los síntomas aprobados para este propósito incluyen, por ejemplo, antagonistas del receptor de N–metil–D–aspartato tal como memantina (Namenda®, Forrest Pharmaceuticals, Inc.), inhibidores de colinesterasa tales como donepezil (Aricept®, Pfizer), rivastigmina (Exelon®, Novartis), galantamina (Razadyne Reminyl®), y tacrina (Cognex®).

En la EA, los péptidos Aβ, formados a través de la actividad de β–secretasa y *gamma*–secretasa, pueden formar estructuras terciarias que se agregan para

formar fibrillas amiloides. Los péptidos Aβ también han demostrado formar oligómeros de Aβ (algunas veces denominados "agregados de Aβ" o "Abeta oligómeros"). Aβ oligómeros son pequeñas estructuras multiméricas compuestas por 2 a 12 péptidos Aβ que son estructuralmente distintos de las fibrillas Aβ. Las fibrillas amiloides pueden depositarse fuera de las neuronas en formaciones densas conocidas como placas seniles, placas neuríticas, o placas difusas en regiones del cerebro importantes para la memoria y la cognición. Aβ oligómeros son citotóxicos cuando se inyectan en los cerebros de ratas o en cultivo celular. Esta formación y deposición de placas Aβ y/o formación de oligómeros Aβ, y la muerte neuronal y deterioro cognitivo resultantes, están entre las características distintivas de la fisiopatología de EA. Otras características distintivas de la fisiopatología de EA incluyen enmarañamientos neurofibrilares intracelulares compuestos por proteína tau anormalmente fosforilada, y neuroinflamación.

La evidencia sugiere que Aβ, fibrillas Aβ, agregados, oligómeros, y/o placas juegan un rol causal en la fisiopatología de la EA. (Ohno et al., Neurobiology of Disease, No. 26 (2007), 134–145). Las mutaciones en los genes para APP y presenilinas 1/2 (PS1/2) se sabe que causan EA familiar y un aumento en la producción de la forma de 42 aminoácidos de Aβ es considerado causante. Se ha demostrado que Aβ es neurotóxico en cultivo e in vivo. Por ejemplo, cuando se inyecta en los cerebros de primates envejecidos, Aβ fibrilar causa la muerte celular neuronal alrededor del sitio de inyección. Otra evidencia directa y circunstancial del rol de Aβ en la etiología de Alzheimer también ha sido publicada.

BACE–1 se ha convertido en un objetivo terapéutico aceptado para el tratamiento de la enfermedad de Alzheimer. Por ejemplo, McConlogue et al., J. Bio. Chem., Vol. 282, No. 36 (Sept. 2007), han demostrado que reducciones parciales de la actividad de la enzima BACE–1 y reducciones concomitantes de los niveles de Aβ conducen a una inhibición dramática de la patología del tipo EA accionada por Aβ, haciendo de β–secretasa un objetivo para la intervención terapéutica en EA. Ohno et al. Neurobiology of Disease, No. 26 (2007), 134–145, informan que la supresión genética de BACE–1 en ratones 5XFAD anula la generación de Aβ, bloquea la deposición de amiloide, evita la pérdida neuronal

encontrada en la corteza cerebral y subiculum (regiones del cerebro que manifiestan la amiloidosis más severa en ratones 5XFAD), y rescata déficits de memoria en ratones 5XFAD. El grupo también informa que Aβ es finalmente responsable de la muerte neuronal en EA y concluye que la inhibición de BACE–1 ha sido validada como un enfoque para el tratamiento de EA. Roberds et al., Human Mol. Genetics, 2001, Vol. 10, No. 12, 1317–1324, establecieron que la inhibición o pérdida de actividad de β–secretasa no produce defectos fenotípicos profundos induciendo al mismo tiempo una reducción concomitante en Aβ. Luo et al., Nature Neuroscience, Vol. 4, No. 3, Marzo 2001, informan que ratones deficientes en BACE–1 tienen fenotipo normal y generación de β–amiloides anulada.

BACE–1 también ha sido identificada o implicada como un objetivo terapéutico para una cantidad de otras patologías diversas en las cuales se ha identificado que Aβ o fragmentos de Aβ juegan un rol causante. Un ejemplo de ese tipo es en el tratamiento de síntomas tipo EA de pacientes con síndrome de Down. El gen que codifica APP es encontrado en el cromosoma 21, el cual es también el cromosoma encontrado como una copia extra en el síndrome de Down. Los pacientes con síndrome de Down tienden a adquirir EA en una edad temprana, casi todos con más de 40 años de edad muestran patología del tipo Alzheimer. Se cree que esto se debe a la copia extra del gen de APP encontrado en estos pacientes, lo cual conduce a la sobreexpresión de APP y, por lo tanto, a niveles aumentados de Aβ lo cual causa la prevalencia de EA observada en esta población. Por añadidura, los pacientes con síndrome de Down quienes tienen una duplicación de una pequeña región del cromosoma 21 que no incluye el gen de APP no desarrollan patología de EA. Por consiguiente, se cree que los inhibidores de BACE–1 podrían ser útiles para reducir la patología del tipo Alzheimer en pacientes con síndrome de Down.

Otro ejemplo es en el tratamiento del glaucoma (Guo et al., PNAS, Vol. 104, No. 33, 14 de Agosto, 2007). El glaucoma es una enfermedad de la retina del ojo y una causa principal de ceguera irreversible en el mundo entero. Guo et al. informan que Aβ se colocaliza con células ganglionares retinales (RGCs, del inglés

"apoptotic retinal ganglion cells") apoptóticas en glaucoma experimental e induce pérdida celular de RGC significativa in vivo en forma dependiente de la dosis y del tiempo. El grupo informa que ha demostrado que el direccionamiento hacia componentes diferentes de la ruta de formación y agregación de Aβ, incluyendo la inhibición de β–secretasa sola y junto con otros métodos, puede reducir en forma eficaz la apoptosis de RGC glaucomatosa in vivo. Por lo tanto, la reducción de la producción de Aβ mediante la inhibición de BACE–1 podría ser útil, sola o en combinación con otros métodos, para el tratamiento del glaucoma.

Otro ejemplo es en el tratamiento del deterioro olfativo. Getchell et al., Neurobiology of Aging, 24 (2003), 663–673, han observado que el epitelio olfativo, un neuroepitelio que cubre la región posterior–dorsal de la cavidad nasal, exhibe muchos de los mismos cambios patológicos encontrados en los cerebros de pacientes con EA, incluyendo depósitos de Aβ, la presencia de proteína tau hiperfosforilada, y neuritos distróficos entre otros. Otra evidencia relacionada con esto ha sido informada por Bacon AW, et al., Ann NY Acad Sci 2002; 855:723–31; Crino PB, Martin JA, Hill WD, et al., Ann Otol Rhinol Laryngol, 1995;104:655–61; Davies DC, et al., Neurobiol Aging, 1993;14:353–7; Devanand DP, et al., Am J Psychiatr, 2000;157:1399–405; y Doty RL, et al., Brain Res Bull, 1987;18:597–600. Es razonable sugerir que encarar dichos cambios mediante reducción de Aβ por inhibición de BACE–1 podría ayudar a restaurar la sensibilidad olfativa en pacientes con EA.

Para los compuestos que son inhibidores de BACE–2, otro ejemplo es en el tratamiento de la diabetes tipo II, incluyendo diabetes asociada con amiloidogénesis. BACE–2 es expresada en el páncreas. Se ha reportado inmunorreactividad de BACE–2 en gránulos secretorios de células beta, co–almacenados con insulina e IAPP, pero que carecen de otros tipos celulares endocrinos y exocrinos. Stoffel et al., WO2010/063718, describen el uso de inhibidores de BACE–2 en el tratamiento de enfermedades metabólicas tales como la diabetes tipo II. La presencia de BACE–2 en gránulos secretorios de células beta sugiere que puede jugar un rol en la amiloidogénesis asociada con diabetes. (Finzi, G. Franzi, et al., Ultrastruct Pathol. 2008 Nov–Dic; 32(6):246–51.)

Otras patologías diversas caracterizadas por la formación y deposición de Aβ o sus fragmentos, y/o por la presencia de fibrillas amiloides, oligómeros, y/o placas, incluyen enfermedades neurodegenerativas tales como el scrapie, encefalitis espongiforme bovina, lesión cerebral traumática ("TBI", siglas correspondientes a "lesión cerebral traumática"), enfermedad de Creutzfeld–Jakob y enfermedades similares, diabetes tipo II (la cual se caracteriza por la acumulación localizada de fibrillas amiloides citotóxicas en las células productoras de insulina del páncreas), y angiopatía amiloide. Con respecto a esto, puede hacerse referencia a la literatura de patentes. Por ejemplo, Kong et al., US2008/0015180, describen métodos y composiciones para tratar la amiloidosis con agentes que inhiben la formación de péptidos Aβ. Como otro ejemplo, Loane, et al. informan el direccionamiento de secretasas de proteína precursora de amiloide como objetivos terapéuticos para la lesión cerebral traumática. (Loane et al., "Amyloid precursor protein secretases as therapeutic targets for lesión cerebral traumática", Nature Medicine, Advance Online Publication, publicado en Internet el 15 de marzo, 2009.) Aun otras patologías diversas caracterizadas por la formación y deposición inapropiadas de Aβ o sus fragmentos, y/o por la presencia de fibrillas amiloides, y/o para las cuales se espera que el o los inhibidores de BACE–1 sea o sean de valor terapéutico son descritas más adelante en la presente invención.

El potencial terapéutico para inhibir la deposición de Aβ ha motivado a muchos grupos a caracterizar BACE–1 y a identificar inhibidores de BACE–1 y de otros inhibidores de enzima secretasa. Los ejemplos de la bibliografía técnica de patentes están creciendo e incluyen WO2006009653, WO2007005404, WO2007005366, WO2007038271, WO2007016012, US2005/0282826, US2007072925, WO2007149033, WO2007145568, WO2007145569, WO2007145570,WO2007145571, WO2007114771, US20070299087, WO2005/016876, WO2005/014540, WO2005/058311, WO2006/065277, WO2006/014762, WO2006/014944, WO2006/138195, WO2006/138264, WO2006/138192, WO2006/138217, WO2007/050721, WO2007/053506, WO2007/146225, WO2006/138230, WO2006/138265, WO2006/138266,

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WO2007/053506, WO2007/146225, WO2008/073365, WO2008/073370, WO2008/103351, US2009/041201, US2009/041202, y WO2010/047372.

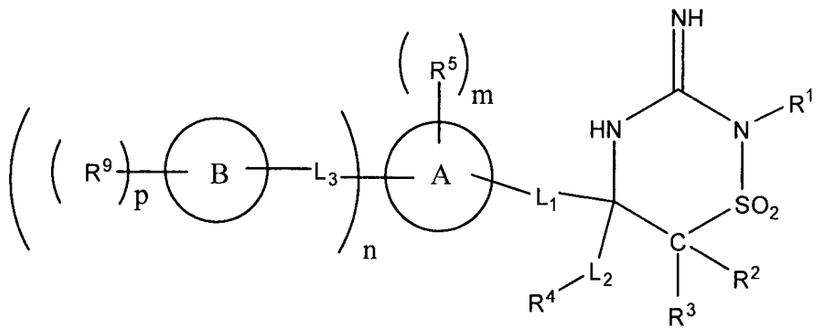
SÍNTESIS DE LA INVENCIÓN

La presente invención proporciona ciertos compuestos de dióxido de iminotiadiazina los cuales son colectiva o individualmente denominados en esta invención "compuesto(s) de la invención", según lo descrito en la presente invención. Se ha descubierto, sorprendentemente, que los compuestos de dióxido de iminotiadiazina novedosos de la invención exhiben propiedades que se espera que los convierta en ventajosos como inhibidores de BACE y/o para el tratamiento y prevención de las diversas patologías descritas en esta invención.

En cada una de las diversas realizaciones de los compuestos de la invención descritos en la presente invención, cada variable incluyendo aquellas de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), y sus diversas realizaciones, cada variable se selecciona independientemente de las otras a menos que se indique lo contrario.

En cada una de las diversas realizaciones de los compuestos de la invención descritos en este documento, incluyendo aquellos de Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), y sus diversas realizaciones y los compuestos de los ejemplos, dichas fórmulas y ejemplos tienen el propósito de abarcar todas las formas de los compuestos tales como, por ejemplo, cualquier solvato, hidrato, estereoisómero y tautómero de dichos compuestos y de cualquiera de sus sales farmacéuticamente aceptables.

En una realización, los compuestos de la invención tienen la Fórmula estructural (I):



(I)

e incluyen tautómeros, solvatos, prodrogas y ésteres de los mismos, y las sales farmacéuticamente aceptables de dichos compuestos, tautómeros, solvatos, prodrogas, y ésteres,

donde:

$-L_1-$ representa un enlace o un resto divalente seleccionado del grupo formado por –alquil–, –haloalquil–, –heteroalquil–, –alquenil–, y –alquinil–;

$-L_2-$ representa un enlace o un resto divalente seleccionado del grupo formado por –alquil–, –haloalquil–, –heteroalquil–, –alquenil–, y –alquinil–;

cada $-L_3-$ representa un enlace o un resto divalente seleccionado independientemente del grupo formado por –alquil–, –haloalquil–, –heteroalquil–, –alquenil–, –alquinil–, $-N(R^7)-$, –NHC(O)–, –C(O)NH–, $-NHS(O)_2-$, $-S(O)_2NH-$, –O–alquil–, –alquil–O–, $-N(R^7)$–alquil–, –alquil–$N(R^7)-$, –haloalquil–NH–, y –NH–haloalquil–;

m, n, y p son cada uno números enteros seleccionados independientemente, donde:

m es 0 o más;

n es 0 o más; y

p es 0 o más,

donde el valor máximo de la suma de m y n es el número máximo de átomos de hidrógeno sustituibles disponibles en el anillo A, y donde el valor máximo de p es el número máximo de átomos de hidrógeno sustituibles disponibles en el anillo B;

131
132

R^1 se selecciona del grupo formado por: H, alquilo, haloalquilo, heteroalquilo, heterohaloalquilo, cicloalquilo, cicloalquilalquil–, heterocicloalquilo, heterocicloalquilalquil–, arilo, arilalquil–, heteroarilo, y heteroarilalquil–,

donde cada uno de dicho alquilo, haloalquilo, heteroalquilo, heterohaloalquilo, cicloalquilo, cicloalquilalquil–, heterocicloalquilo, heterocicloalquilalquil–, arilo, arilalquil–, heteroarilo, y heteroarilalquil– de R^1 es no sustituido o sustituido con uno o más grupos R^{10} independientemente seleccionados;

R^2 se selecciona del grupo formado por H, halo, alquilo, haloalquilo, y heteroalquilo,

donde cada uno de dicho alquilo y dicho haloalquilo de R^2 está no sustituido o está sustituido con uno o más grupos R^{10} independientemente seleccionados;

R^3 se selecciona del grupo formado por H, halo, alquilo, haloalquilo, y heteroalquilo,

donde cada uno de dicho alquilo y dicho haloalquilo de R^2 está no sustituido o está sustituido con uno o más grupos R^{10} independientemente seleccionados;

R^4 se selecciona del grupo formado por alquilo, arilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, y heterocicloalquenilo,

donde cada uno de dicho alquilo, arilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, y heterocicloalquenilo de R^4 está no sustituido o está sustituido con uno o más grupos R^{10} seleccionados independientemente;

el anillo A se selecciona del grupo formado por arilo monocíclico, heteroarilo monocíclico, cicloalquilo monocíclico, cicloalquenilo monocíclico, heterocicloalquilo monocíclico, heterocicloalquenilo monocíclico, y un grupo multicíclico;

cada anillo B (cuando está presente) se selecciona independientemente del grupo formado por arilo monocíclico, heteroarilo monocíclico, cicloalquilo monocíclico, cicloalquenilo monocíclico, heterocicloalquilo monocíclico, heterocicloalquenilo monocíclico, y un grupo multicíclico;

cada R^5 (cuando está presente) se selecciona independientemente del grupo formado por halo, –CN, $–SF_5$, $–OSF_5$, $–NO_2$, $–Si(R^6)_3$, $–P(O)(OR^7)_2$, $–P(O)(OR^7)(R^7)$, $–N(R^8)_2$, $–NR^8C(O)R^7$, $–NR^8S(O)_2R^7$, $–NR^8C(O)N(R^8)_2$, $–NR^8C(O)OR^7$, $–C(O)R^7$, $–C(O)_2R^7$, $–C(O)N(R^8)_2$, $–S(O)R^7$, $–S(O)_2R^7$, $–S(O)_2N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo,

donde cada uno de dicho alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de R^5 (cuando está presente) está opcional e independientemente sin sustituir o adicionalmente sustituido con uno o más grupos seleccionados independientemente seleccionados del grupo formado por alquilo inferior, alquenilo inferior, alquinilo inferior, heteroalquilo inferior, halo, –CN, $–SF_5$, $–OSF_5$, $–NO_2$, $–N(R^8)_2$, $–OR^7$, $–C(O)N(R^8)_2$, y cicloalquilo;

cada R^6 (cuando está presente) se selecciona independientemente del grupo formado por alquilo, arilo, arilalquil–, haloalquilo, cicloalquilo, cicloalquilalquil–, heteroarilo, y heteroarilalquil–;

cada R^7 (cuando está presente) se selecciona independientemente del grupo formado por H, alquilo, alquenilo, heteroalquilo, haloalquilo, arilo, arilalquil–, heteroarilo, heteroarilalquil–, cicloalquilo, cicloalquilalquil–, heterocicloalquilo, y heterocicloalquilalquil–;

cada R^8 (cuando está presente) se selecciona independientemente del grupo formado por H, alquilo, alquenilo, heteroalquilo, haloalquilo, haloalquenilo, arilo, arilalquil–, heteroarilo, heteroarilalquil–, cicloalquilo, cicloalquilalquil–, heterocicloalquilo, y heterocicloalquilalquil–;

cada R^9 (cuando está presente) se selecciona independientemente del grupo formado por: halógeno, –CN, $–SF_5$, $–OSF_5$, $–NO_2$, $–Si(R^6)_3$, $–P(O)(OR^7)_2$, $–P(O)(OR^7)(R^7)$, $–N(R^8)_2$, $–NR^8C(O)R^7$, $–NR^8S(O)_2R^7$, $–NR^8C(O)N(R^8)_2$, $–NR^8C(O)OR^7$, $–C(O)R^7$, $–C(O)_2R^7$, $–C(O)N(R^8)_2$, $–S(O)R^7$, $–S(O)_2R^7$, $–S(O)_2N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo, haloalquilo, heteroalquilo, alquenilo, alquinilo, arilo, arilalquil–, cicloalquilo, heteroarilo, heteroarilalquil–, y heterocicloalquilo;

cada R^{10} (cuando está presente) se selecciona independientemente del grupo formado por halo, –CN, $–NO_2$, $–Si(R^6)_3$, $–P(O)(OR^7)_2$, $–P(O)(OR^7)(R^7)$, $–N(R^8)_2$, $–NR^8C(O)R^7$, $–NR^8S(O)_2R^7$, $–NR^8C(O)N(R^8)_2$, $–NR^8C(O)OR^7$, $–C(O)R^7$, $–C(O)_2R^7$, $–C(O)N(R^8)_2$, $–S(O)R^7$, $–S(O)_2R^7$, $–S(O)_2N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, y cicloalquilo,

donde cada uno de dichos alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, y cicloalquilo de R^{10} (cuando está presente) está opcional e independientemente sin sustituir o adicionalmente sustituido con uno o más grupos seleccionados independientemente seleccionados del grupo formado por alquilo inferior, alquenilo inferior, alquinilo inferior, heteroalquilo inferior, halo, –CN, $–NO_2$, $–N(R^8)_2$, $–OR^7$, y $–C(O)N(R^8)_2$.

En otras realizaciones, la invención proporciona composiciones, incluyendo composiciones farmacéuticas, que comprenden uno o más compuestos de la invención (por ej., un compuesto de la invención), o un tautómero del mismo, o una sal o solvato aceptable farmacéuticamente de dicho(s) compuesto(s) y/o dicho(s) tautómero(s), opcionalmente junto con uno o más agentes terapéuticos adicionales, opcionalmente en un portador o diluyente aceptable (por ej., farmacéuticamente aceptable).

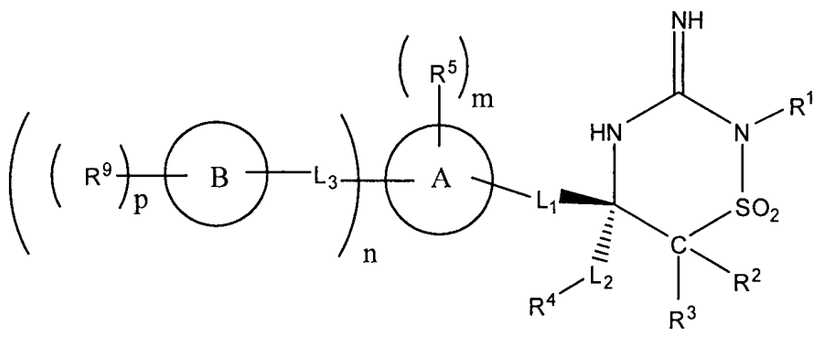
En otras realizaciones, la invención proporciona diversos métodos para tratar, prevenir, mejorar y/o retrasar el inicio de una patología de amiloide β (patología de Aβ) y/o un síntoma o síntomas de la misma, que comprenden administrar una composición que comprende una cantidad eficaz de uno o más compuestos de la invención, o un tautómero de los mismos, o una sal o solvato farmacéuticamente aceptable de dicho(s) compuesto(s) y/o dicho(s) tautómero(s), a un paciente que lo necesita. Dichos métodos comprenden en forma opcional y adicional administrar una cantidad eficaz de uno o más agentes terapéuticos adicionales adecuados para tratar al paciente que se está tratando.

Estas y otras realizaciones de la invención, las cuales son descritas en forma detallada a continuación o serán fácilmente evidentes para los expertos en la técnica, son incluidas dentro del alcance de la invención.

DESCRIPCIÓN DETALLADA:

En una realización, los compuestos de la invención tienen la Fórmula estructural (I) según lo descrito más arriba.

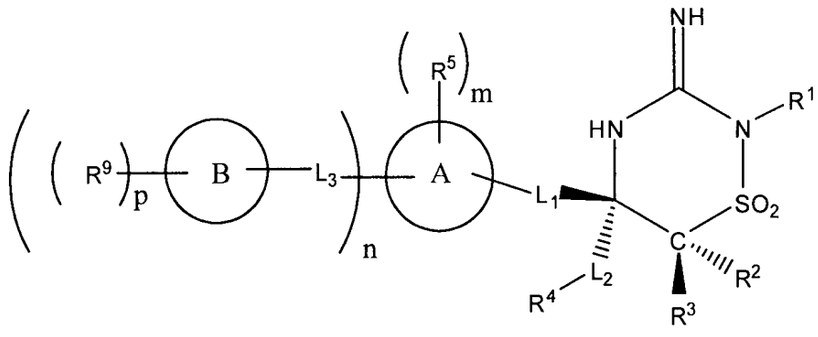
En una realización, los compuestos de la invención tienen la Fórmula estructural (IA):



(IA)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, el anillo A, el anillo B, m, n, y p son cada uno según lo definido en la Fórmula (I).

En una realización, los compuestos de la invención tienen la Fórmula estructural (IA–1):

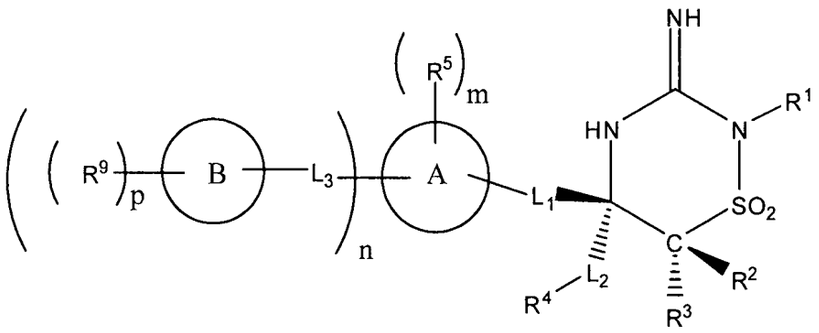


(IA–1)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, el anillo A, el anillo B, m, n, y p son cada uno según lo definido en la Fórmula (I).

153
154

En una realización, los compuestos de la invención tienen la Fórmula estructural (IA–2):



(IA–2)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, el anillo A, el anillo B, m, n, y p son cada uno según lo definido en la Fórmula (I).

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^1 se selecciona del grupo formado por H, alquilo inferior, y ciclopropilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^1 se selecciona del grupo formado por H y metilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^1 es H.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^1 es metilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^2 es H.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2):

R^1 se selecciona del grupo formado por H, alquilo inferior, y ciclopropilo; y

R^2 es H.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^3 es H y R^2 es H.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^3 se selecciona del grupo formado por H, alquilo, haloalquilo, y heteroalquilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^3 se selecciona del grupo formado por H, alquilo inferior, haloalquilo inferior, y éter alquilo inferior.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^3 se selecciona del grupo formado por H, alquilo, haloalquilo, y heteroalquilo; y R^2 es H.

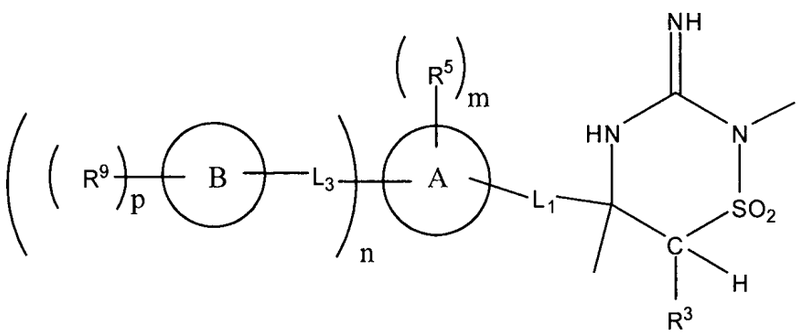
En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^3 se selecciona del grupo formado por H, alquilo inferior, haloalquilo inferior, y éter alquilo inferior; y R^2 es H.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), $–L_2–$ es un enlace y R^4 es alquilo inferior.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), $–L_2–$ es un enlace y R^4 es metilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), y (IA–2), R^1 es alquilo inferior, R^2 es H, $–L_2–$ es un enlace, y R^4 es alquilo.

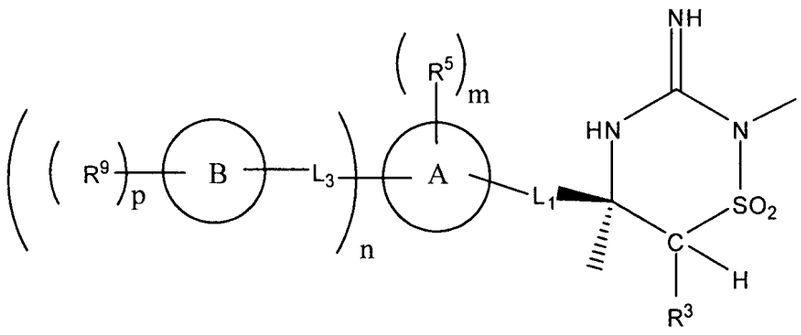
En una realización, los compuestos de la invención tienen la Fórmula estructural (II):



(II)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^3, L_1, L_2, el anillo A, el anillo B, R^5, R^9, m, n, y p son cada uno según lo definido en la Fórmula (I).

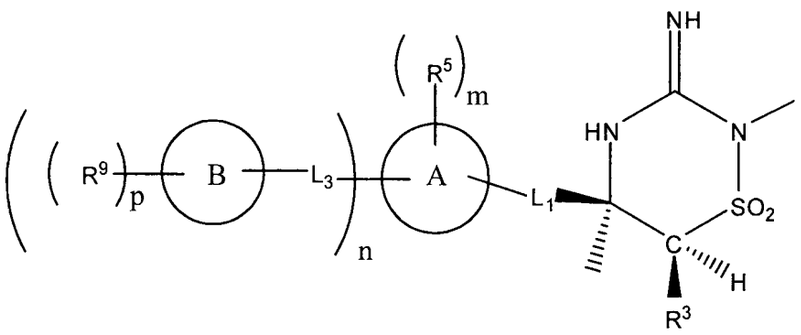
En una realización, los compuestos de la invención tienen la Fórmula estructural (IIA):



(IIA)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^3, L_1, L_3, el anillo A, el anillo B, R^5, R^9, m, n, y p son cada uno según lo definido en la Fórmula (I).

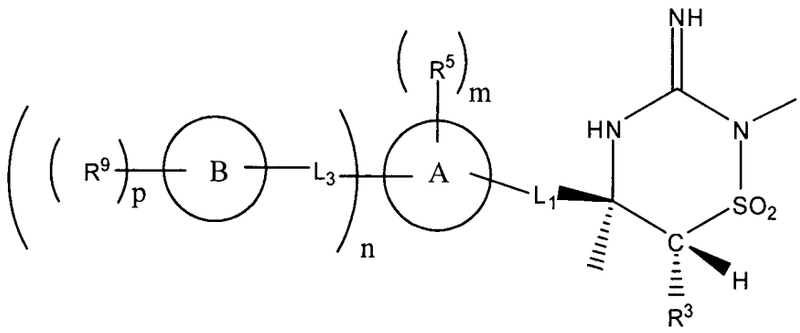
En una realización, los compuestos de la invención tienen la Fórmula estructural (IIA–1):



(IIA–1)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^3, L_1, L_3, el anillo A, el anillo B, R^5, R^9, m, n, y p son cada uno según lo definido en la Fórmula (I).

En una realización, los compuestos de la invención tienen la Fórmula estructural (IIA–2):



(IIA–2)

e incluyen a sus tautómeros y prodrogas, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, tautómeros y prodrogas, donde R^3, L_1, L_3, el anillo A, el anillo B, R^5, R^9, m, n, y p son cada uno según lo definido en la Fórmula (I).

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2), R^3 se selecciona del grupo formado por H, alquilo, haloalquilo, y heteroalquilo.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (IIA–2), R^3 se selecciona del grupo formado por H, alquilo inferior, haloalquilo inferior, y éter de alquilo inferior.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2), R^3 es H.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$–L_1–$ representa un enlace o un resto divalente seleccionado del grupo formado por –alquil–, –haloalquil–, –heteroalquil–, y –alquenil–.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$–L_1–$ representa un resto divalente seleccionado del grupo formado por –alquil–, –haloalquil–, –heteroalquil–, y –alquenil–.

$–L_1–$ representa un resto divalente seleccionado del grupo formado por –alquil–, y –haloalquil–.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$–L_1–$ representa un enlace o un resto divalente de alquilo inferior.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

135

$-L_1-$ representa un enlace, $-CH_2-$, o $-CH_2CH_2-$.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$-L_1-$ representa un enlace.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$-L_1-$ representa un resto alquilo inferior divalente.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$-L_1-$ representa $-CH_2-$.

En una realización, en cada una de las Fórmulas (II), (IIA), (IIA–1), y (II–A2):

$-L_1-$ representa $-CH_2CH_2-$.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 0 y m es 1 o más.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1 o más, p es 0 o más, y m es 0.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 0 o más.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 0, 1, 2, o 3.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 0, 1, o 2.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 0 o 1.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 1.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 2.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 1, p es 0 o más, y m es 3.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2): $-L_1-$ representa un enlace o $-CH_2-$.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, imidazolilo, pirazolilo, quinazolinilo, benzofuranilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, benzotienilo, naftilo, quinolilo, isoquinolilo, indazolilo, indolilo, y tienopirazolilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

el anillo A se selecciona del grupo formado por fenilo, piridilo, tienilo, tiazolilo, naftilo, isoquinolinilo, benzotienilo, bencimidazolilo, indazolilo, indolilo, y tienopirazolilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

cada $–L_3–$ representa independientemente un enlace o un resto divalente seleccionado del grupo formado por –NHC(O), –C(O)NH–, $–NHS(O)_2–$, $–S(O)_2NH–$, $–O–CH_2–$, $–CH_2–O–$, $–NHCH_2–$, $–CH_2NH–$, y $–CH(CF_3)NH–$.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

cada $–L_3–$ representa independientemente un enlace o un resto divalente seleccionado del grupo formado por –NHC(O)– y –C(O)NH–.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 y $–L_3–$ representa un enlace o un resto divalente seleccionado del grupo formado por –NHC(O)– y –C(O)NH–.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 y $–L_3–$ representa un enlace.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 y $–L_3–$ es un resto divalente seleccionado del grupo formado por –NHC(O)– y –C(O)NH–.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 y $–L_3–$ es –C(O)NH–.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 y $–L_3–$ es –NHC(O)–.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 o más;

p es 0 o más; y

cada anillo B se selecciona independientemente del grupo formado por fenilo, piridilo, pirimidinilo, oxazolilo, isoxazolilo, pirazinilo, tienilo, pirazolilo, furanilo, tiazolilo, piridazinilo, isotiazolilo, isoxazolilo, isotiazolilo, indolilo, pirrolopiridinilo, y pirrolopirimidinilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 1 o más;

p es 0 o más; y

cada anillo B se selecciona independientemente del grupo formado por fenilo, piridilo, pirimidinilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, indolilo, pirrolopiridilo, y pirrolopirimidinilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

m es 1 o más y cada grupo R^5 se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–OSF_5$, $–N(R^8)_2$, $–NR^8C(O)R^7$, $–NR^8S(O)_2R^7$, $–NR^8C(O)N(R^8)_2$, $–NR^8C(O)OR^7$, $–C(O)R^7$, $–C(O)_2R^7$, $–C(O)N(R^8)_2$, $–S(O)R^7$, $–S(O)_2R^7$, $–S(O)_2N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, cicloalquilo, heteroarilo, y heterocicloalquilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

m es 1 o más y cada grupo R^5 se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y cicloalquilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

m es 1 o más y cada grupo R^5 se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y ciclopropilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

m es 0 o más, n es 1 o más, p es 1 o más, y cada grupo R^9 se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–OSF_5$, $–N(R^8)_2$, $–NR^8C(O)R^7$, $–NR^8S(O)_2R^7$, $–NR^8C(O)N(R^8)_2$, $–NR^8C(O)OR^7$, $–C(O)R^7$, $–C(O)_2R^7$, $–C(O)N(R^8)_2$, $–S(O)R^7$, $–S(O)_2R^7$, $–S(O)_2N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, arilo, arilalquil–, cicloalquilo, heteroarilo, heteroarilalquil–, y heterocicloalquilo.

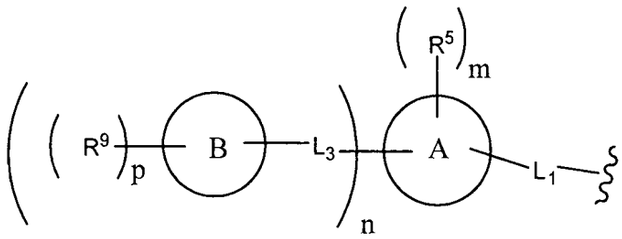
En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

m es 0 o más, n es 1 o más, p es 1 o más, y cada grupo R^9 se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, fenilo, bencilo, y cicloalquilo.

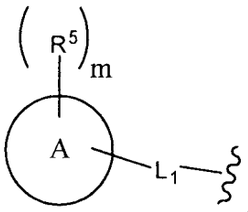
En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

m es 0 o más, n es 1 o más, p es 1 o más, y cada grupo R^9 se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, fenilo, bencilo, y ciclopropilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2), n es 0 y el resto:



, tiene la forma



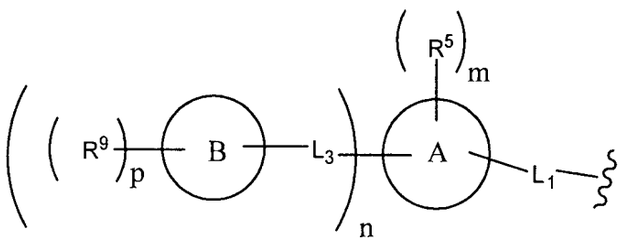
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En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

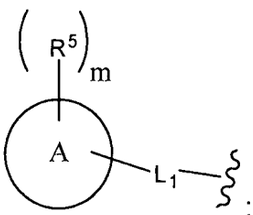
n es 0;

m es 1 o más;

el resto:



, tiene la forma



;

$–L_1–$ representa un enlace, $–CH_2–$, o $–CH_2CH_2–$;

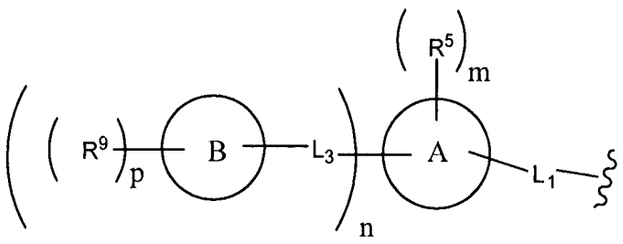
el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, benzotienilo, bencimidazolilo, indazolilo, indolilo, y tienopirazolilo; y

cada grupo R^5 se selecciona independientemente del grupo formado por halógeno, $–CN$, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y cicloalquilo.

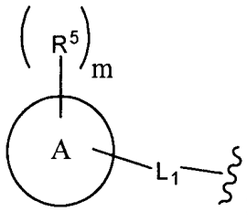
En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

n es 0;

el resto:



, tiene la forma



;

$–L_1–$ representa un enlace, $–CH_2–$, o $–CH_2CH_2–$;

el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, benzotienilo, bencimidazolilo, indazolilo, indolilo, y tienopirazolilo;

m es 0 o más; y

cada grupo R^5 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, $–CN$, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y ciclopropilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, benzotienilo, bencimidazolilo, indazolilo, indolilo, y tienopirazolilo;

m es 0 o más;

cada grupo R^5 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, $–CN$, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y cicloalquilo;

n es 1;

$–L_3–$ representa un enlace o un resto divalente seleccionado del grupo formado por $–NHC(O)–$ y $–C(O)NH–$;

el anillo B se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, isoxazolilo, isotiazolilo, indolilo, pirrolopiridilo, y pirrolopirimidinilo;

p es 0 o más; y

cada grupo R^9 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, fenilo, bencilo, y cicloalquilo.

En una realización, en cada una de las Fórmulas (I), (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2):

$–L_1–$ representa un enlace;

el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, imidazolilo, pirazolilo, quinazolinilo, benzofuranilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, benzotienilo, naftilo, quinolilo, isoquinolilo, indazolilo, indolilo, y tienopirazolilo.

m es 0 o más;

cada grupo R^5 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y ciclopropilo;

n es 1;

$–L_3–$ representa un enlace o un resto divalente seleccionado del grupo formado por $–NHC(O)$, $–C(O)NH–$, $–NHS(O)_2–$, $–S(O)_2NH–$, $–O–CH_2–$, $–CH_2–O–$, $–NHCH_2–$, $–CH_2NH–$, y $–CH(CF_3)NH–$;

el anillo B se selecciona del grupo formado por fenilo, piridilo, pirimidinilo, oxazolilo, isoxazolilo, pirazinilo, tienilo, pirazolilo, furanilo, tiazolilo, piridazinilo, isotiazolilo, isoxazolilo, isotiazolilo, indolilo, pirrolopiridinilo, y pirrolopirimidinilo;

p es 0 o más; y

cada grupo R^9 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, –CN, $–SF_5$, $–OSF_5$, $–N(R^8)_2$, $–NR^8C(O)R^7$, $–NR^8S(O)_2R^7$, $–NR^8C(O)N(R^8)_2$, $–NR^8C(O)OR^7$, $–C(O)R^7$, $–C(O)_2R^7$, $–C(O)N(R^8)_2$, $–S(O)R^7$, $–S(O)_2R^7$, $–S(O)_2N(R^8)_2$, $–OR^7$, $–SR^7$, alquilo inferior, haloalquilo inferior,

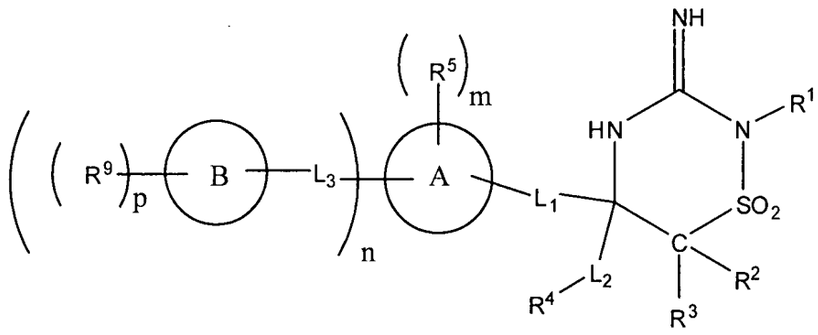
heteroalquilo inferior, alquinilo inferior, arilo, arilalquil–, cicloalquilo, heteroarilo, heteroarilalquil–, y heterocicloalquilo. En una realización de ese tipo, m y p son cada uno independientemente 0, 1, 2, o 3 hasta el número máximo de átomos de hidrógeno sustituibles.

En una realización de ese tipo, cada R^5 (cuando está presente) se selecciona independientemente del grupo formado por halo.

En una realización de ese tipo, cada R^9 (cuando está presente) se selecciona independientemente del grupo formado por alquilo, alquenilo, alquinilo, haloalquilo, heteroalquilo, heteroalquilo halo–sustituido, halo, –O–alquilo, –O–alquil–OH, –O–deuteroalquilo, –O–heteroalquilo, –O–heteroalquil–arilo, –O–haloalquilo, heteroarilo, heteroarilo sustituido con alquilo, cicloalquilo, –O–alquil–cicloalquilo, –O–cicloalquilo, OH, heterocicloalquilo, heteroarilo sustituido con halo, CN, $–S(F)_5$, –S–alquilo, y $–S(O)_2$alquilo.

En otra realización, la presente invención abarca a los deuterados de los compuestos de la invención, o sus tautómeros, o una sal farmacéuticamente aceptable de dicho compuesto o tautómero deuterado de la invención. Los ejemplos específicos, no limitativos, de los compuestos deuterados de la invención son según lo descrito y ejemplificado en esta invención e incluyen, compuestos deuterados de Fórmulas (I^d), (II^d), y (III^d). Los expertos en la técnica apreciarán fácilmente que, además de los ejemplos no limitativos mostrados, otros átomos de hidrógeno disponibles pueden ser deuterados en forma similar según lo descrito en esta invención más adelante. Dichos compuestos deuterados son también considerados como estando entre los compuestos de la invención. El compuesto resultante es denominado en esta invención un compuesto "deuterado" de la invención o, alternativamente, como "deuterato(s)" de los compuestos de la invención. Los compuestos de la invención pueden ser deuterados en forma conocida por los expertos en la técnica, por ej., según lo descrito en la presente invención.

Por consiguiente, en una realización no limitativa, los compuestos deuterados de la invención tienen la Fórmula estructural (I^d):



(I^d)

donde:

uno o más átomos de hidrógeno presentes en R^1, R^2, R^3, R^4, R^5 (cuando están presentes) y/o R^9 (cuando está presente), o uno o más de cualquiera de los átomos de hidrógeno disponibles presentes en el anillo A o en el anillo B (cuando está presente) se reemplaza por deuterio; y

cada una de las variables restantes es según lo definido en la Fórmula (I), o según lo descrito en cualquiera de las realizaciones descritas en esta invención, por ej., aquellos de las Fórmulas (IA), (IA–1), (IA–2), (II), (IIA), (IIA–1), y (IIA–2) y sus diversas realizaciones, también se encuentran dentro del alcance de los compuestos de Fórmula (I^d).

Por ejemplo, en una realización no limitativa, en la Fórmula (I^d), R^1 es $–CD_3$ y cada uno de R^2, R^3, R^4, R^5, R^9, $–L_1–$, $–L_2–$, $–L_3–$, el anillo A, el anillo B, m, n, y p son según lo definido en la Fórmula (I) o como en cualquiera de (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), o (II–A2), o en las diversas realizaciones descritas en la presente invención.

Como otro ejemplo, en otra realización no limitativa, en la Fórmula (I^d), R^2 es D y cada uno de R^1, R^3, R^4, R^5, R^9, $–L_1–$, $–L_2–$, $–L_3–$, el anillo A, el anillo B, m, n, y p son según lo definido en la Fórmula (I) o como en cualquiera de (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), o (II–A2), o en las diversas realizaciones descritas en la presente invención.

Como otro ejemplo, en otra realización no limitativa, en la Fórmula (I^d), R^3 es D y cada uno de R^1, R^2, R^4, R^5, R^9, $–L_1–$, $–L_2–$, $–L_3–$, el anillo A, el anillo B, m, n, y p son según lo definido en la Fórmula (I) o como en cualquiera de (IA), (IA–1),

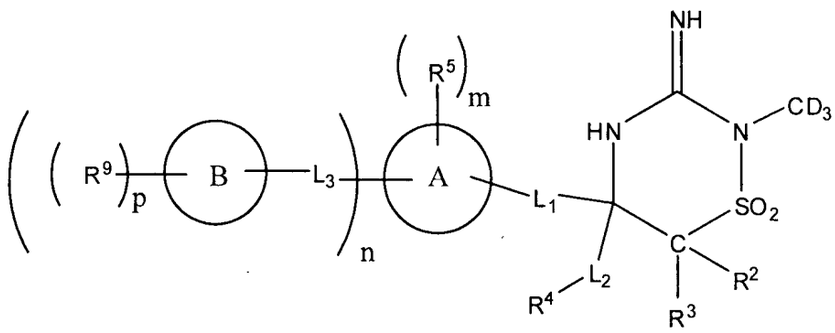
(IA–2), (II), (II–A), (II–A1), o (II–A2), o en las diversas realizaciones descritas en la presente invención.

Como otro ejemplo, en otra realización no limitativa, en la Fórmula (I^d), R^4 es alquilo inferior parcial o totalmente deuterado y cada uno de R^1, R^2, R^3, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, el anillo A, el anillo B, m, n, y p son según lo definido en la Fórmula (I) o como en cualquiera de (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), o (II–A2), o en las diversas realizaciones descritas en la presente invención.

Como otro ejemplo, en otra realización no limitativa, en la Fórmula (I^d), R^5 es D y cada uno de R^1, R^2, R^3, R^4, R^9, $-L_1-$, $-L_2-$, $-L_3-$, el anillo A, el anillo B, m, n, y p son según lo definido en la Fórmula (I) o como en cualquiera de (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), o (II–A2), o en las diversas realizaciones descritas en la presente invención.

Como otro ejemplo, en otra realización no limitativa, en la Fórmula (I^d), R^9 es D y cada uno de R^1, R^2, R^3, R^4, R^5, $-L_1-$, $-L_2-$, $-L_3-$, el anillo A, el anillo B, m, n, y p son según lo definido en la Fórmula (I) o como en cualquiera de (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), o (II–A2), o en las diversas realizaciones descritas en la presente invención.

A modo de ilustración adicional, en otra realización no limitativa, los compuestos deuterados de la invención tienen la Fórmula estructural (II^d):



(II^d)

donde:

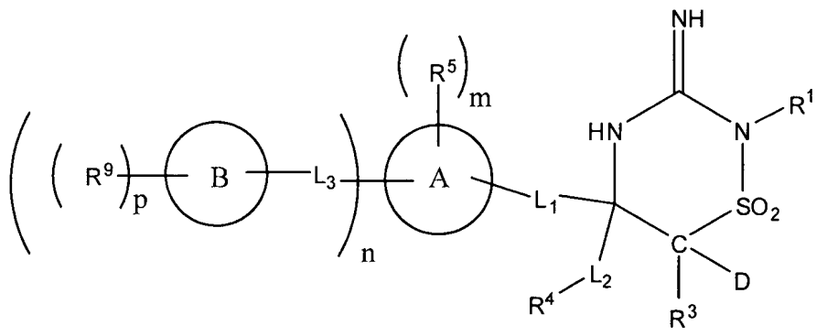
el resto $-CD_3$ representa una forma deuterada del resto $-CH_3$; y

cada una de las variables restantes es según lo definido en la Fórmula (I), o según lo descrito en cualquiera de las realizaciones descritas en esta invención, por ej., aquellas de fórmulas (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), y (II–A2), y sus

140
141

diversas realizaciones, también se encuentran dentro del alcance de los compuestos de fórmula (II^d).

A modo de ilustración adicional, en otra realización no limitativa, los compuestos deuterados de la invención tienen la Fórmula estructural (III^d):



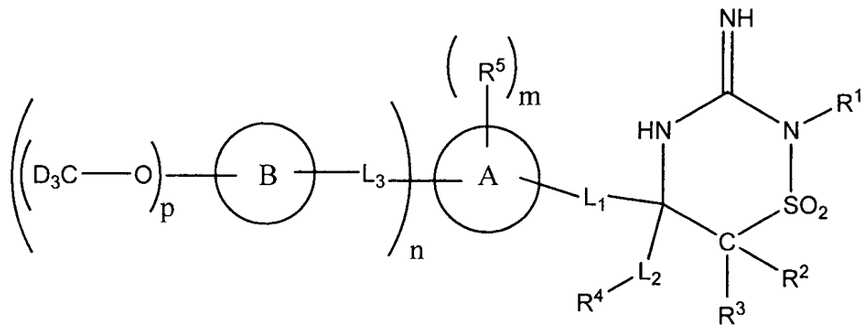
(III^d)

donde:

el resto –D representa una forma deuterada de hidrógeno; y

cada una de las variables restantes es según lo definido en la Fórmula (I), o según lo descrito en cualquiera de las realizaciones descritas en esta invención, por ej., aquellas de fórmulas (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), y (II–A2), y sus diversas realizaciones, también se encuentran dentro del alcance de los compuestos de fórmula (III^d). En una realización, en la Fórmula (III^d), R^3 es D.

A modo de ilustración adicional, en otra realización no limitativa, los compuestos deuterados de la invención tienen la Fórmula estructural (IV^d):



(IV^d)

donde:

el resto –D representa una forma deuterada de hidrógeno; y

cada una de las variables restantes es según lo definido en la Fórmula (I), o según lo descrito en cualquiera de las realizaciones descritas en esta invención, por ej., aquellas de fórmulas (IA), (IA–1), (IA–2), (II), (II–A), (II–A1), y (II–A2), y sus

diversas realizaciones, también se encuentran dentro del alcance de los compuestos de fórmula (IV^d).

En otra realización, la presente invención abarca un estereoisómero o mezcla racémica de un compuesto de la invención, o un tautómero del mismo, o una sal farmacéuticamente aceptable de dicho compuesto o dicho tautómero. Se apreciará que, si bien la presente invención abarca a todos los estereoisómeros y mezclas racémicas de los compuestos de la invención, la estereoconfiguración mostrada en las fórmulas estructurales y en los ejemplos son también contemplados como estando dentro del alcance de la invención.

En otra realización, 1 a 3 átomos de carbono de los compuestos de la invención pueden ser reemplazados con de 1 a 3 átomos de silicio siempre y cuando todos los requerimientos de valencia sean satisfechos.

En otra realización, los compuestos de la invención son cada uno de los compuestos de las tablas que aparecen más adelante y tienen una estructura mostrada para el ejemplo correspondiente en los ejemplos preparativos que aparecen más adelante.

La presente invención incluye a los tautómeros y estereoisómros de cada uno de los compuestos de ejemplo de la invención, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, dichos estereoisómeros, y/o dichos tautómeros. Dichos tautómeros y estereoisómeros de cada uno de los compuestos de ejemplo, y las sales y solvatos farmacéuticamente aceptables de dichos compuestos, dichos estereoisómeros, y/o dichos tautómeros, cada uno representa realizaciones adicionales de la invención.

En otra realización, la invención proporciona una composición que comprende por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o sal o solvato de dicho compuesto, dicho estereoisómero, o dicho tautómero, y un portador o diluyente adecuado.

En otra realización, la invención proporciona una composición farmacéutica que comprende por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de

dicho compuesto, dicho estereoisómero, o dicho tautómero, y un portador o diluyente farmacéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende por lo menos un solvato de un compuesto de la invención, o su tautómero o isómero, o una sal o solvato farmacéuticamente aceptable de dicho compuesto o dicho tautómero, y un portador o diluyente farmacéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende por lo menos una sal farmacéuticamente aceptable de un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, y un portador o diluyente farmacéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende por lo menos un tautómero de un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, y un portador o diluyente farmacéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, junto con por lo menos un agente terapéutico adicional, y un portador o diluyente farmacéuticamente aceptable.

Los ejemplos no limitativos de agentes terapéuticos adicionales para utilizar en combinación con los compuestos de la invención incluyen drogas seleccionadas del grupo formado por: (a) drogas útiles para el tratamiento de la enfermedad de Alzheimer y/o drogas útiles para tratar uno o más síntomas de la enfermedad de Alzheimer, (b) drogas útiles para inhibir la síntesis de Aβ, y (c) drogas útiles para tratar enfermedades neurodegenerativas.

Los ejemplos no limitativos adicionales de agentes terapéuticos adicionales para utilizar en combinación con los compuestos de la invención incluyen drogas útiles para el tratamiento, prevención, retraso del inicio, mejora de cualquier patología asociada con Aβ y/o un síntoma de los mismos. Los ejemplos no limitativos de patologías asociadas con Aβ incluyen: enfermedad de Alzheimer, síndrome de Down, enfermedad de Parkinson, pérdida de memoria, pérdida de memoria asociada con la enfermedad de Alzheimer, pérdida de memoria asociada con la enfermedad de Parkinson, síntomas de déficit atencional, síntomas de déficit atencional asociados con la enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, demencia, accidente cerebrovascular, microgliosis e inflamación cerebral, demencia pre–senil, demencia senil, demencia asociada con la enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, parálisis supranuclear progresiva, degeneración córtico-basal, neurodegeneración, deterioro olfativo, deterioro olfativo asociado con la enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, angiopatía β–amiloide, angiopatía amiloide cerebral, hemorragia cerebral hereditaria, deterioro cognitivo leve ("MCI"), glaucoma, amiloidosis, diabetes tipo II, complicaciones de hemodiálisis (de microglobulinas β_2 y complicaciones que surgen de las mismas en pacientes con hemodiálisis), scrapie, encefalitis espongiforme bovina, lesión cerebral traumática ("TBI", según siglas en inglés), y enfermedad Creutzfeld–Jakob, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o su tautómero o isómero, o una sal o solvato farmacéuticamente aceptable de dicho compuesto o dicho tautómero, en una cantidad eficaz para inhibir dicha patología o patologías.

En realizaciones de la invención que comprenden por lo menos un agente terapéutico adicional, los ejemplos no limitativos adicionales de agentes terapéuticos adicionales para utilizar en combinación con compuestos de la invención incluyen: los antagonistas muscarínicos (por ej., agonistas m_1 (tales como acetilcolina, oxotremorina, carbacol, o McNa343), o antagonistas m_2 (tales como atropina, diciclovérina, tolterodina, oxibutinina, ipratropio, metoctramina, triptamina, o galamina)); inhibidores de colinesterasa (por ej., inhibidores de acetil–

y/o butirilclolinesterasa tales como donepezil (Aricept®), galantamina (Razadyne®), y rivastigmina (Exelon®); antagonistas del receptor de N–metil–D–aspartato (por ej., Namenda® (memantina HCl, disponible de Forrest Pharmaceuticals, Inc.); combinaciones de inhibidores de colinesterasa y antagonistas del receptor de N–metil–D–aspartato; moduladores de gamma secretasa; inhibidores de gamma secretasa; agentes antiinflamatorios no esteroideos; agentes antiinflamatorios que pueden reducir la neuroinflamación; anticuerpos anti–amiloides (tales como bapineuzemab, Wyeth/Elan); vitamina E; agonistas del receptor de acetilcolina nicotínico; agonistas inversos del receptor CB1 o antagonistas del receptor CB1; antibióticos; secretagogos de la hormona del crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de la agregación de amiloides; inhibidores de glucógeno sintasa quinasa beta; promotores de actividad de alfa secretasa; inhibidores de PDE–10; inhibidores de tau quinasa (por ej., inhibidores de GSK3beta, inhibidores de cdk5, o inhibidores de ERK); inhibidores de la agregación de tau (por ej., Rember®); inhibidores de RAGE (por ej., TTP 488 (PF–4494700)); vacuna anti–Abeta; ligandos de APP; agentes que regulan ascendentemente insulina, agentes reductores de colesterol tales como inhibidores de HMG–CoA reductasa (por ejemplo, estatinas tales como Atorvastatina, Fluvastatina, Lovastatina, Mevastatina, Pitavastatina, Pravastatina, Rosuvastatina, Simvastatina) y/o inhibidores de la absorción de colesterol (tales como Ezetimibe), o combinaciones de inhibidores de HMG–CoA reductasa e inhibidores de la absorción de colesterol (tales como, por ejemplo, Vytorin®); fibratos (tales como, por ejemplo, clofibrato, Clofibride, Etofibrato, y Clofibrato de Aluminio); combinaciones de fibratos y agentes reductores de colesterol y/o inhibidores de la absorción de colesterol; agonistas del receptor nicotínico; niacina; combinaciones de inhibidores de la absorción de colesterol y niacina y/o agentes reductores de colesterol (por ej., Simcor® (niacina/simvastatina, disponibles de Abbott Laboratories, Inc.); agonistas de LXR; mímicos de LRP; antagonistas del receptor de H3; inhibidores de histona desacetilasa; inhibidores de hsp90; agonistas de 5–HT4 (por ej., PRX–03140 (Epix Pharmaceuticals));

antagonistas del receptor de 5–HT6; moduladores o antagonistas del receptor de mGluR1; moduladores o antagonistas del receptor mGluR5; antagonistas de mGluR2/3; antagonistas del receptor de prostaglandina EP2; inhibidores de PAI–1; agentes que pueden inducir el eflujo de Abeta tales como gelsolina; compuesto atenuador de proteína metálica (por ej., PBT2); y moduladores de GPR3; y antihistaminas tales como Dimebolin (por ej., Dimebon®, Pfizer).

En otra realización, la invención proporciona una composición farmacéutica que comprende una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención, y una cantidad eficaz de uno o más inhibidores de colinesterasa (por ej., inhibidores de acetil– y/o butirilclolinesterasa), y un portador farmacéuticamente aceptable.

En otra realización, la invención proporciona una composición farmacéutica que comprende una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención, y una cantidad eficaz de uno o más agonistas o antagonistas muscarínicos (por ej., agonistas m_1 o antagonistas m_2), y un portador farmacéuticamente aceptable.

En una realización, la invención proporciona combinaciones que comprenden una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención, en combinación con una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos seleccionados del grupo formado por inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metil]–1 H –inden–1–ona, es decir, clorhidrato de donepezil, disponible como la marca Aricept ® de clorhidrato de donepezilo), inhibidores del receptor de N–metil–D–aspartato (tales como, por ejemplo, Namenda® (memantina HCl)); anticuerpos anti–amiloides (tales como bapineuzumab, Wyeth/Elan), inhibidores de gamma secretasa, moduladores de gamma secretasa, e inhibidores de beta secretasa que no son los compuestos de la invención.

En una realización, la invención proporciona combinaciones que comprenden una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención, en combinación con una cantidad eficaz (es decir,

terapéuticamente eficaz) de uno o más compuestos seleccionados del grupo formado por inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metil]–1 H –inden–1–ona, es decir, clorhidrato de donepezilo, disponible como la marca Aricept ® de clorhidrato de donepezilo), inhibidores del receptor de N–metil–D–aspartato (tales como, por ejemplo, Namenda® (memantina HCl)).

En una realización, la invención proporciona combinaciones que comprenden una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención, en combinación con una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más inhibidores de gamma secretasa.

En una realización, la invención proporciona combinaciones que comprenden una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención, en combinación con una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más moduladores de gamma secretasa.

En una realización, la invención proporciona combinaciones que comprenden una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en combinación con una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más inhibidores de gamma secretasa y adicionalmente en combinación con uno o más moduladores de gamma secretasa.

En otra realización, la invención proporciona un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en forma pura, en forma aislada, y/o en forma aislada y pura.

Las prodrogas de los compuestos de la invención, o sus tautómeros o estereoisómeros, o las sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos estereoisómeros, y/o dichos tautómeros, son también contemplados como estando incluidos dentro del alcance de la invención, y son descritos en forma más completa más adelante.

Los deuteratos de los compuestos de la invención, o los tautómeros o estereoisómeros de dichos deuterados, o las sales o solvatos farmacéuticamente aceptables de dichos deuteratos, dichos estereoisómeros, y/o dichos tautómeros, se contempla también que están incluidos dentro del alcance de la invención, y son descritos en forma más completa en lo que antecede.

En otra realización, la invención proporciona un método para preparar una composición farmacéutica que comprende el paso de mezclar por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, y un portador o diluyente farmacéuticamente aceptable.

En otra realización, la invención proporciona un método para inhibir β–secretasa que comprende exponer una población de células que expresan β–secretasa a por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir β–secretasa.

En otra realización, la invención proporciona un método para inhibir β–secretasa en un paciente que lo necesita que comprende administrar por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad terapéuticamente eficaz para inhibir β–secretasa en dicho paciente.

En otra realización, la invención proporciona un método para inhibir BACE–1 que comprende exponer una población de células que expresan BACE–1 a por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto o dicho tautómero, en una cantidad eficaz para inhibir BACE–1 en dichas células. En una realización de ese tipo, dicha población de células es *in vivo.* En otra realización de ese tipo, dicha población de células es *ex vivo.* En otra realización de ese tipo, dicha población de células es *in vitro.*

En otra realización, la invención proporciona un método para inhibir BACE–2 que comprende exponer una población de células que expresan BACE–2 a por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto o dicho tautómero, en una cantidad eficaz para inhibir BACE–2 en dichas células. En una realización de ese tipo, dicha población de células es *in vivo*. En otra realización de ese tipo, dicha población de células es *ex vivo*. En otra realización de ese tipo, dicha población de células es *in vitro*.

En otra realización, la invención proporciona un método para inhibir BACE–1 en un paciente que lo necesita que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad terapéuticamente eficaz para inhibir BACE–1 en dicho paciente.

En otra realización, la invención proporciona un método para inhibir BACE–2 en un paciente que lo necesita que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad terapéuticamente eficaz para inhibir BACE–2 en dicho paciente.

En otra realización, la invención proporciona un método para inhibir la formación de Aβ de APP en un paciente que lo necesita, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha formación de Aβ.

En otra realización, la invención proporciona un método para inhibir la formación de placa de Aβ en un paciente que lo necesita, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente

aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha formación de placas Aβ.

En otra realización, la invención proporciona un método para inhibir la formación de fibrillas Aβ en un paciente que lo necesita, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha formación de fibrillas Aβ.

En otra realización, la invención proporciona un método para inhibir la formación de oligómeros de Aβ en un paciente que lo necesita, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha formación de fibrillas de Aβ.

En otra realización, la invención proporciona un método para inhibir la formación de fibrillas de Aβ y oligómeros de Aβ en un paciente que lo necesita, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha formación de fibrillas de Aβ.

En otra realización, la invención proporciona un método para inhibir la formación de placas seniles y/o enmarañamientos neurofibrilares en un paciente que lo necesita, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha formación de fibrillas de Aβ.

En otra realización, la invención proporciona un método para tratar, prevenir y/o retardar el comienzo de una patología de amiloides β ("patología de Aβ") y/o uno o más síntomas de dicha patología que comprende administrar por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una

sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, a un paciente que lo necesita en una cantidad eficaz para tratar dicha patología.

En otra realización, la invención proporciona un método para tratar, prevenir y/o retardar el inicio de una o más patologías asociadas con Aβ y/o uno o más síntomas de una o más patologías asociadas con Aβ. Los ejemplos no limitativos de patologías asociadas con Aβ incluyen: enfermedad de Alzheimer, síndrome de Down, enfermedad de Parkinson, pérdida de memoria, pérdida de memoria asociada con la enfermedad de Alzheimer, pérdida de memoria asociada con enfermedad de Parkinson, síntomas de déficit atencional, síntomas de déficit atencional asociado con la enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, demencia, accidente cerebrovascular, microgliosis e inflamación cerebral, demencia pre–senil, demencia senil, demencia asociada con enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, parálisis supranuclear progresiva, degeneración córtico-basal, neurodegeneración, deterioro olfativo, deterioro olfativo asociado con enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, angiopatía β–amiloide, angiopatía amiloide cerebral, hemorragia cerebral hereditaria, deterioro cognitivo leve ("MCI"), glaucoma, amiloidosis, diabetes tipo II, amiloidogénesis asociada con diabetes, complicaciones de hemodiálisis (de microglobulinas β_2 y complicaciones que surgen de las mismas en pacientes con hemodiálisis), scrapie, encefalitis espongiforme bovina, lesión cerebral traumática ("TBI") y enfermedad de Creutzfeld–Jakob, que comprende administrar a dicho paciente por lo menos un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en una cantidad eficaz para inhibir dicha patología o patologías.

En una realización, la invención proporciona un método para tratar una o más enfermedades neurodegenerativas, que comprende administrar una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato

farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), solos u opcionalmente en combinación con uno o más agentes terapéuticos adicionales útiles para tratar una o más enfermedades neurodegenerativas, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para inhibir la deposición de proteína amiloide (por ej., proteína beta amiloide) en, sobre o alrededor de tejido neurológico (por ej., el cerebro), que comprende administrar una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), solo u opcionalmente en combinación con uno o más agentes terapéuticos adicionales útiles para tratar una o más enfermedades neurodegenerativas, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la enfermedad de Alzheimer, que comprende administrar una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes terapéuticos adicionales útiles para tratar la enfermedad de Alzheimer, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar el síndrome de Down, que comprende administrar una cantidad eficaz (es decir, terapéuticamente eficaz) de uno o más compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con una cantidad eficaz (por ej., terapéuticamente eficaz) de uno o más agentes activos adicionales útiles para tratar el síndrome de Down, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar el deterioro cognitivo leve, que comprende administrar una cantidad eficaz de uno o

más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar el deterioro cognitivo leve, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar glaucoma, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar glaucoma, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la angiopatía amiloide cerebral, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar la angiopatía amiloide cerebral, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar el accidente cerebrovascular, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero) , por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar el accidente cerebrovascular, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la demencia, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho

estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar la demencia, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la microgliosis, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar la microgliosis, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la inflamación cerebral, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar la inflamación cerebral, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la lesión cerebral traumática, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles para tratar la lesión cerebral traumática, a un paciente que necesita de dicho tratamiento.

En una realización, la invención proporciona un método para tratar la pérdida de la función olfativa, que comprende administrar una cantidad eficaz de uno o más (por ej., uno) compuestos de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero), por si solo u opcionalmente en combinación con uno o más agentes activos adicionales útiles

148 147

para tratar la pérdida de la función olfativa, a un paciente que necesita de dicho tratamiento.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más inhibidores de colinesterasa (tales como, por ejemplo, clorhidrato de (±)–2,3–dihidro–5,6–dimetoxi–2–[[1–(fenilmetil)–4–piperidinil]metil]–1 H –inden–1–ona, es decir, clorhidrato de donepezilo, disponible como la marca Aricept® de clorhidrato de donepezilo).

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dicho uno o más agentes terapéuticos adicionales se seleccionan del grupo formado por inhibidores de anticuerpos de Aβ, inhibidores de gamma secretasa, moduladores de gamma secretasa, e inhibidores de beta secretasa que no son un compuesto de la invención.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dicho uno o más agente terapéutico adicional es Exelon (rivastigmina).

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre Cognex (tacrina).

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre inhibidor de tau quinasa (por ej., inhibidor de GSK3beta, inhibidor de cdk5, inhibidor de ERK).

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre una vacuna anti–Aβ.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre un ligando de APP.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan

entre uno o más agentes que regulan ascendentemente la enzima degradadora de insulina y/o neprilisina.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más agentes reductores de colesterol. Los ejemplos no limitativos de dichos agentes reductores de colesterol incluyen: estatinas tales como Atorvastatina, Fluvastatina, Lovastatina, Mevastatina, Pitavastatina, Pravastatina, Rosuvastatina, Simvastatina, e inhibidores de la absorción de colesterol tales como Ezetimibe y fitonutrientes.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más fibratos. Los ejemplos no limitativos de dichos fibratos incluyen clofibrato, Clofibrida, Etofibrato, y Clofibrato de Aluminio.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más agonistas de LXR.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más mímicos de LRP.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más antagonistas del receptor de 5–HT6.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más agonistas de receptor nicotínico.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más antagonistas del receptor de H3.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más inhibidores de histona desacetilasa.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más inhibidores de hsp90.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más agonistas de receptores muscarínicos m1.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más antagonistas de receptor de 5–HT6, mGluR1, y moduladores o agonistas alostéricos positivos de mGluR5.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más antagonistas de mGluR2/3.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más agentes antiinflamatorios que pueden reducir la neuroinflamación.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más antagonistas del receptor EP2 de prostaglandina.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más inhibidores de PAI–1.

En una realización, en cada uno de los métodos antes mencionados de tratamiento, dichos uno o más agentes terapéuticos adicionales se seleccionan entre uno o más agentes que pueden inducir el flujo hacia afuera de Aß. Un ejemplo no limitativo de un agente que puede inducir el flujo hacia dentro de Aß es gelsolina.

En una realización, la invención proporciona un kit que comprende, en contenedores separados, en un paquete único, composiciones farmacéuticas para utilizar en combinación, donde un contenedor comprende una cantidad eficaz de

un compuesto de la invención (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero) en un portador farmacéuticamente aceptable, y, opcionalmente, otro contenedor (es decir, un segundo contenedor) comprende una cantidad eficaz de otro ingrediente farmacéuticamente activo (según lo descrito más adelante), las cantidades combinadas del compuesto de la invención y el otro ingrediente farmacéuticamente activo son eficaces para: (a) tratar la enfermedad de Alzheimer, o (b) inhibir la deposición de proteína amiloide (por ej., proteína amiloide beta) en, sobre o alrededor de tejido neurológico (por ej., el cerebro), o (c) tratar enfermedades neurodegenerativas, o (d) inhibir BACE.

En sus diversas realizaciones, la invención proporciona cualquiera de los métodos descritos anteriormente y más adelante donde el o los compuestos de la invención es un compuesto o compuestos seleccionados del grupo formado por los compuestos ejemplares de la invención descritos más adelante.

En sus diversas realizaciones, la invención proporciona cualquiera de las composiciones farmacéuticas descritas anteriormente y más adelante donde el o los compuestos de la invención es un compuesto o compuestos seleccionados del grupo formado por los compuestos ejemplares de la invención descritos más adelante.

Otras realizaciones de esta invención se refieren a cualquiera de las realizaciones descritas anteriormente o más adelante que se refieren a los compuestos de la invención, o al uso de los compuestos de la invención (por ej., las realizaciones se refieren a métodos de tratamiento, composiciones farmacéuticas y kits).

En otra realización, la invención proporciona el uso de un compuesto de la invención, o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero, en la manufactura de un medicamento para utilizar en el tratamiento, el retardo del comienzo, y/o la prevención de una o más patologías de Aβ y/o en el tratamiento, el retraso del inicio, y/o la prevención de uno o más síntomas de una o más patologías de Aβ.

149

DEFINICIONES

Los términos empleados en esta invención tienen su significado común y el significado de dichos términos es independiente en cada una de sus apariciones. No obstante y excepto donde se indique lo contrario, las siguientes definiciones son aplicables a lo largo de la memoria descriptiva y las reivindicaciones. Las denominaciones químicas, nombres comunes y estructuras químicas pueden ser empleados de manera indistinta para describir esa misma estructura. Estas definiciones son aplicables, sin importar si un término es empleado por sí mismo o en combinación con otros términos, a menos que se indique lo contrario. Por ende, la definición de "alquilo" es aplicable a "alquilo" así como también la porción "alquilo" de "hidroxialquilo", "haloalquilo", arilalquil–, alquilaril–, "alcoxi" etc.

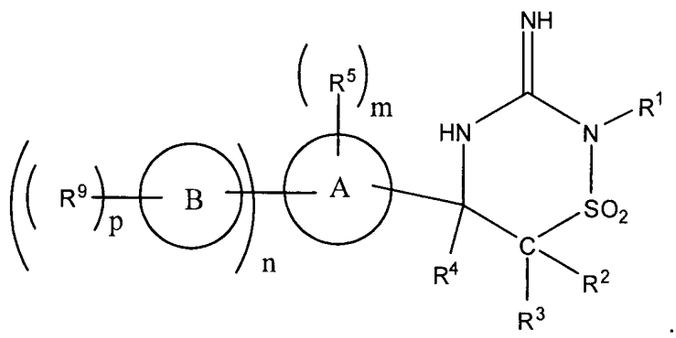
Se entenderá que, en las diversas realizaciones de la invención descrita en esta invención, cualquier variable no específicamente definida en el contexto de la realización es según lo definido en la Fórmula (I). Cualquier carbono así como también heteroátomo con valencias insatisfechas en el texto, esquemas, ejemplos y Tablas en esta invención se presume que tiene la cantidad suficiente de átomo(s) de hidrógeno para satisfacer las valencias.

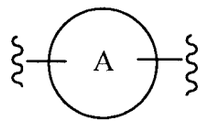
Según lo descrito en la presente invención, los "compuestos ejemplares de la invención" (o "compuestos ejemplares" o "ejemplos") incluyen, en forma conjunta e individual, cada uno de los compuestos expuestos con números de ejemplos en los ejemplos preparativos.

Según lo descrito en la presente invención, las variables tales como R^1, R^2, R^3, y R^4 pueden estar sin sustituir o sustituidas con uno o más grupos R^5. Se entenderá que el límite superior de la cantidad de sustituyentes (a los que se hace referencia en la frase "uno o más sustituyentes") es la cantidad de átomos de hidrógeno disponibles en el resto relevante (R^1, R^2, R^3, o R^4) que están disponibles para reemplazo por un sustituyente que dará como resultado un resto químicamente estable.

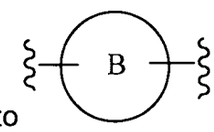
Según lo descrito en la presente invención, una o más de las variables $–L_1–$, $–L_2–$, y $–L_3–$ de las fórmulas generales representan, opcional e independientemente, un enlace. Se entenderá que donde esa variable representa

un enlace, los restos que se muestran conectados por esa variable están directamente unidos por enlace covalente. Por lo tanto, a modo de ilustración no limitativa, un compuesto de fórmula (I) donde $-L_1-$, $-L_2-$ y $-L_3-$ cada uno representa un enlace puede ser mostrado como:





El resto , que puede ser opcionalmente sustituido según lo descrito en la presente invención, representa un anillo denominado en esta invención "anillo A."



El resto , el cual puede ser opcionalmente sustituido según lo descrito en la presente invención, representa un anillo denominado en esta invención "anillo B."

"Por lo menos uno" significa uno o más de uno, por ejemplo, 1, 2, o 3, o en otro ejemplo, 1 o 2, o en otro ejemplo 1.

En las diversas Fórmulas de los compuestos de la invención, por ej., en la Fórmula (I), m, n, y p son cada uno números enteros independientemente seleccionados, donde:

m es 0 o más;

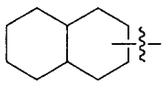
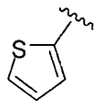
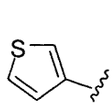
n es 0 o más; y

p es 0 o más,

donde el valor máximo de la suma de m y n es el número máximo de átomos de hidrógeno sustituibles disponibles en el anillo A, y donde el valor máximo de p es el número máximo de átomos de hidrógeno sustituibles disponibles en el anillo B. Excepto por las formas de sales, el "número máximo de

151 150

átomos de hidrógeno sustituibles disponibles" se refiere al número máximo que dará como resultado una molécula neutra.

A modo de ilustración no limitativa, cuando el anillo A es un grupo  , el valor máximo de la suma de m y n es 17. Cuando el anillo A es un grupo  o  , el valor máximo de la suma de m y n es 3.

En los compuestos de la invención, por ej., en la Fórmula (I), cada uno del anillo A y el anillo B (cuando está presente) se selecciona del grupo formado por un grupo arilo monocíclico, un grupo heteroarilo monocíclico, un grupo cicloalquilo monocíclico, un grupo cicloalquenilo monocíclico, un grupo heterocicloalquilo monocíclico, un grupo heterocicloalquenilo monocíclico, y un grupo multicíclico, cada uno de dichos grupos puede estar sin sustituir u opcionalmente sustituido adicionalmente según lo mostrado en la Fórmula (I).

Como se emplea en esta invención, el término "arilo monocíclico" se refiere a fenilo.

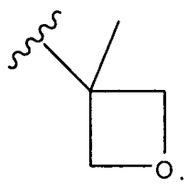
Como se emplea en esta invención, el término "heteroarilo monocíclico" se refiere a un grupo heteroarilo monocíclico de 4 a 7 miembros que comprende entre 1 y 4 heteroátomos del anillo, siendo dichos heteroátomos del anillo seleccionados independientemente del grupo formado por N, O, y S, y los óxidos de los mismos. El punto de unión al resto principal es a cualquier carbono del anillo o heteroátomo de anillo disponible. Los ejemplos no limitativos de restos heteroarilo monocíclicos incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, piridona, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, tiadiazolilo (por ej., 1,2,4–tiadiazolilo), pirazinilo, piridazinilo, imidazolilo, y triazinilo (por ej., 1,2,4–triazinilo), y los óxidos de los mismos.

Como se emplea en esta invención, el término "cicloalquilo monocíclico" se refiere a un grupo cicloalquilo monocíclico de 3 a 7 miembros. Los ejemplos no

limitativos de grupos cicloalquilo monocíclicos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y cicloheptilo.

Como se emplea en esta invención, el término "cicloalquenilo monocíclico" se refiere a un grupo cicloalquilo de 3 a 7 miembros no aromático el cual contiene uno o más enlaces dobles carbono- carbono. Los ejemplos no limitativos incluyen ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, y cicloheptenilo.

Como se emplea en esta invención, el término "heterocicloalquilo monocíclico" se refiere a un grupo heterocicloalquilo monocíclico de 4 a 7 miembros que comprende entre 1 y 4 heteroátomos de anillo, estando dichos heteroátomos de anillo seleccionados independientemente del grupo formado por N, N–óxido, O, S, S–óxido, S(O), y $S(O)_2$. El punto de unión al resto principal es a cualquier carbono del anillo o heteroátomo del anillo disponible. Los ejemplos no limitativos de grupos heterocicloalquilo monocíclico incluyen piperidilo, oxetanilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4–dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, *beta* lactama, *gamma* lactama, *delta* lactama, *beta* lactona, *gamma* lactona, *delta lactona,* y pirrolidinona, y sus óxidos.

Los ejemplos no limitativos de oxetanilo sustituido con alquilo inferior incluyen el resto:  .

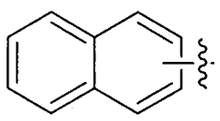
Como se emplea en esta invención, el término "heterocicloalquenilo monocíclico" se refiere a un grupo heterocicloalquenilo monocíclico de 4 a 7 miembros que comprende entre 1 y 4 heteroátomos de anillo, estando dichos heteroátomos de anillo seleccionados independientemente del grupo formado por N, N–óxido, O, S, S–óxido, S(O), y $S(O)_2$. El punto de unión al resto principal es a cualquier carbono del anillo o heteroátomo del anillo disponible. Los ejemplos no limitativos de grupos heterocicloalquenilo monocíclico incluyen 1,2,3,4–tetrahidropiridinilo, 1,2–dihidropiridinilo, 1,4–dihidropiridinilo, 1,2,3,6–tetrahidropiridinilo, 1,4,5,6–tetrahidropirimidinilo, 2–pirrolinilo, 3–pirrolinilo, 2–imidazolinilo, 2–pirazolinilo, dihidroimidazolilo, dihidrooxazolilo, dihidrooxadiazolilo,

dihidrotiazolilo, 3,4–dihidro–2H–piranilo, dihidrofuranilo, fluordihidrofuranilo, dihidrotiofenilo, y dihidrotiopiranilo, y óxidos de los mismos.

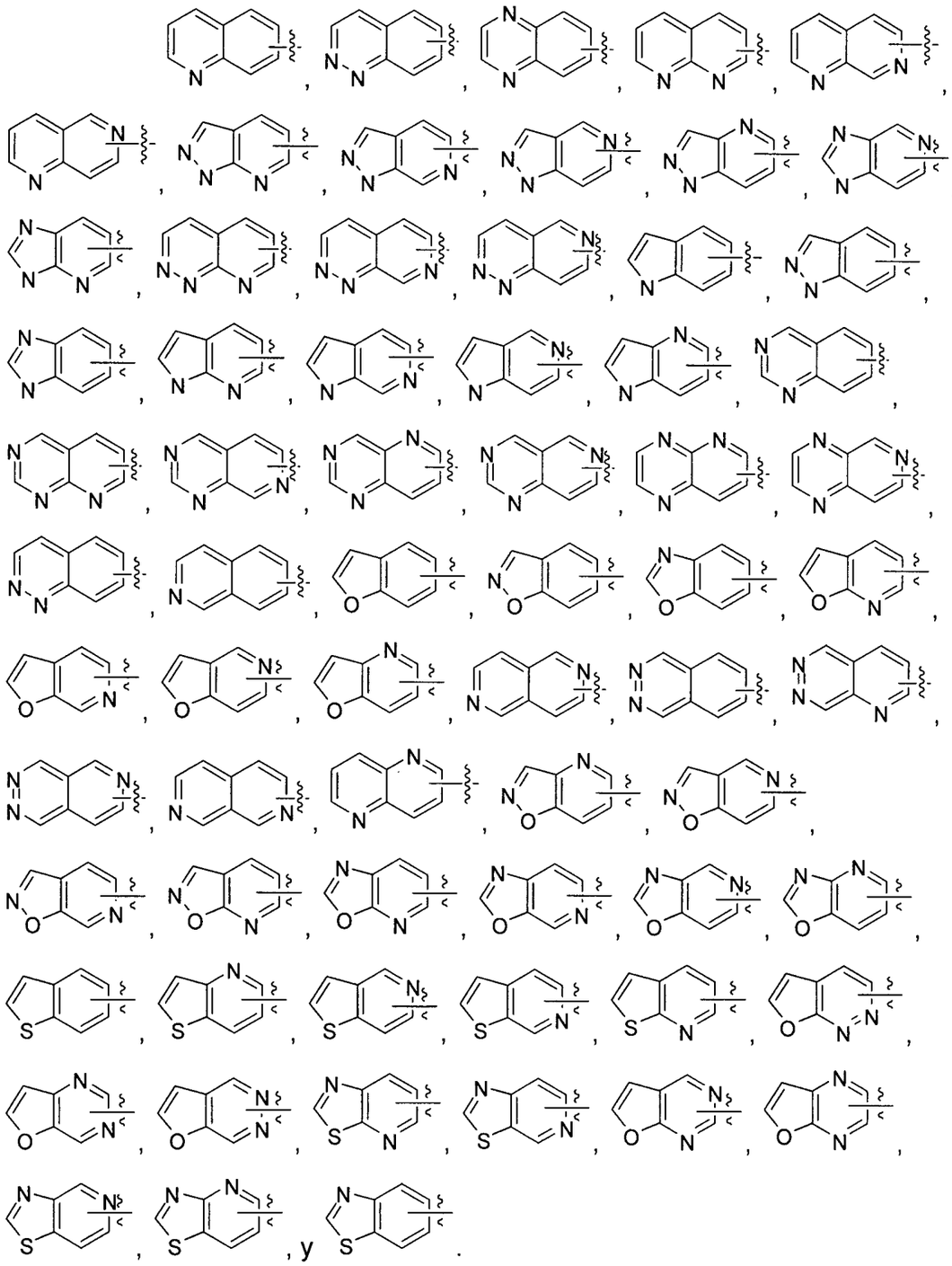
Como se emplea en esta invención, el término "grupo multicíclico" se refiere a un sistema de anillos fusionados que comprende dos (bicíclico), tres (tricíclico) o más anillos fusionados donde cada anillo del sistema de anillos fusionados se selecciona independientemente del grupo formado por fenilo, heteroarilo monocíclico, cicloalquilo monocíclico, cicloalquenilo monocíclico, heterocicloalquilo monocíclico, y heterocicloalquenilo monocíclico. El punto de unión al resto principal es a cualquier carbono del anillo disponible o (si está presente) heteroátomo del anillo en cualquiera de los anillos fusionados.

Se entenderá que cada uno de los siguientes grupos multicíclicos ilustrados puede estar sin sustituir o sustituido, según lo descrito en la presente invención. Solamente el punto de unión al resto principal es mostrado mediante la línea ondulada.

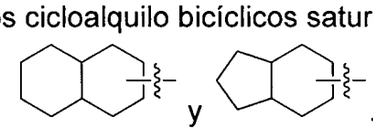
El término grupos multicíclicos incluye grupos aromáticos bicíclicos. Los ejemplos no limitativos de grupos multicíclicos los cuales son grupos aromáticos bicíclicos incluyen:



El término grupos multicíclicos incluye grupos heteroaromáticos bicíclicos que comprenden entre 1 y 3 o más heteroátomos del anillo, estando cada uno de dichos heteroátomos del anillo seleccionados independientemente del grupo formado por N, O, y S, S(O), $S(O)_2$, y óxidos de N, O, y S, y sus óxidos. Los ejemplos no limitativos de grupos multicíclicos los cuales son grupos heteroaromáticos bicíclicos que comprenden entre 1 y 3 heteroátomos del anillo, estando cada heteroátomo del anillo seleccionado independientemente entre N, O, y S incluyen a los siguientes, y sus óxidos:

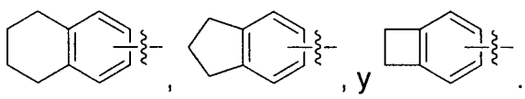


El término grupos multicíclicos incluye grupos cicloalquilo bicíclicos saturados.. Los ejemplos no limitativos de grupos multicíclicos los cuales son grupos cicloalquilo bicíclicos saturados incluyen a los siguientes:

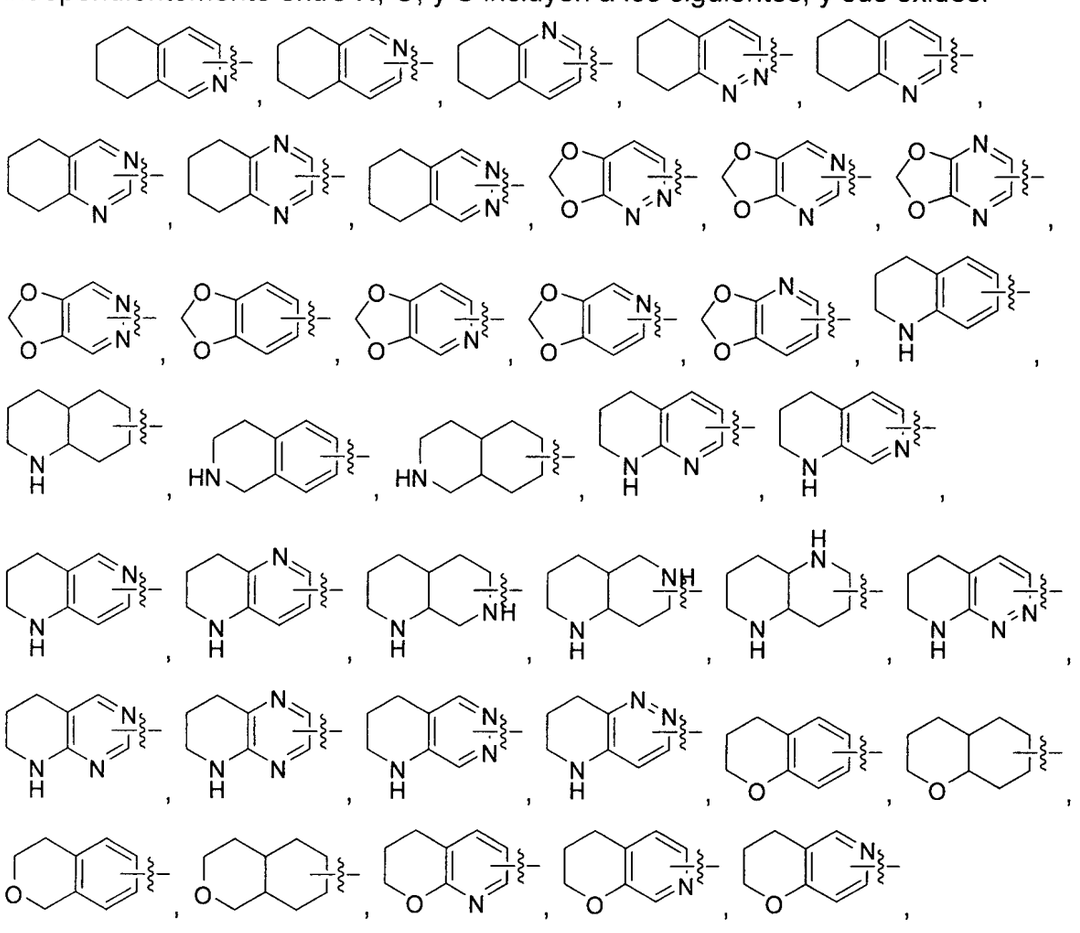


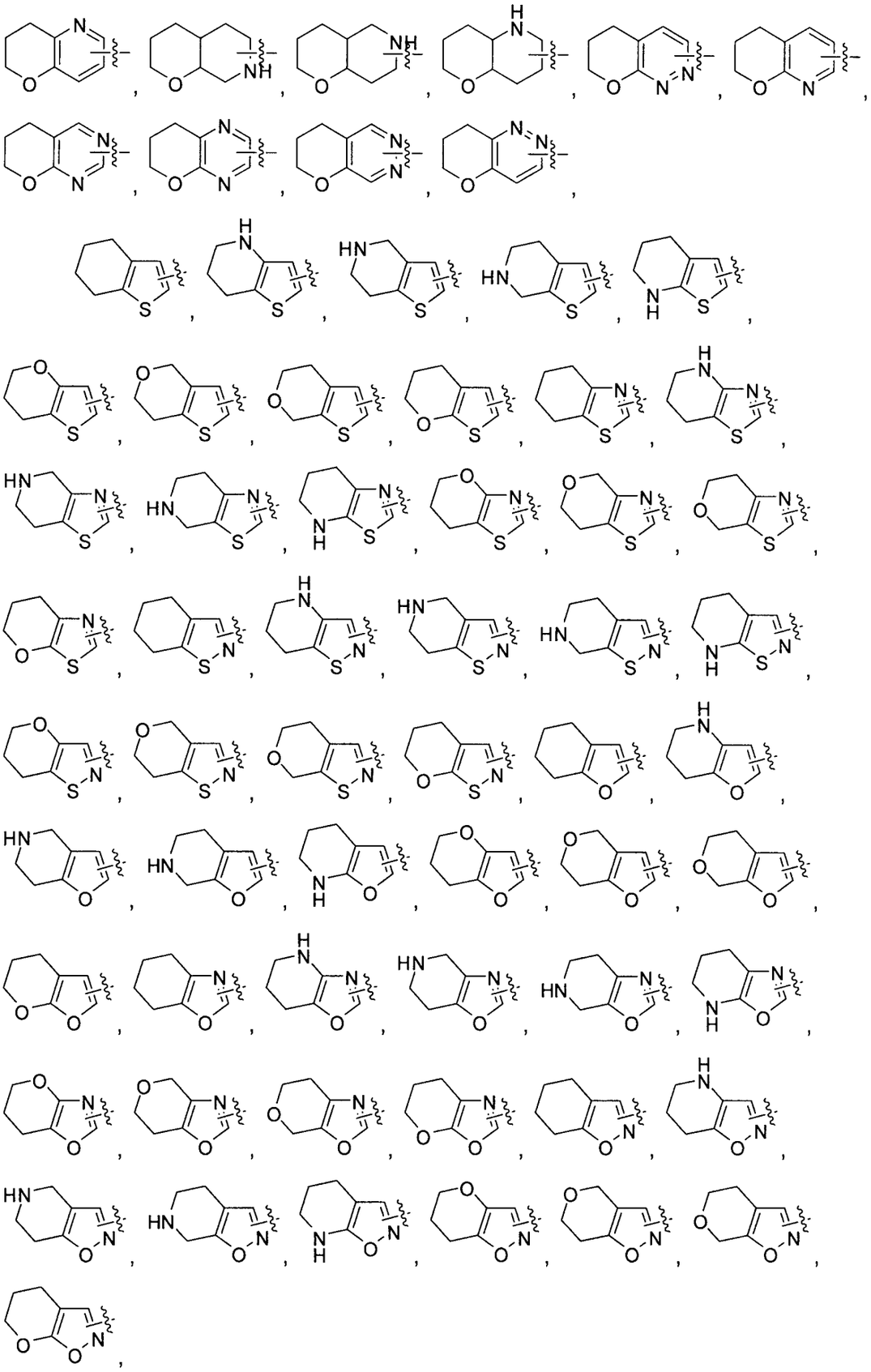
El término grupo multicíclico incluye grupos cicloalquilo bicíclicos parcialmente insaturados. Los ejemplos no limitativos de grupos multicíclicos los

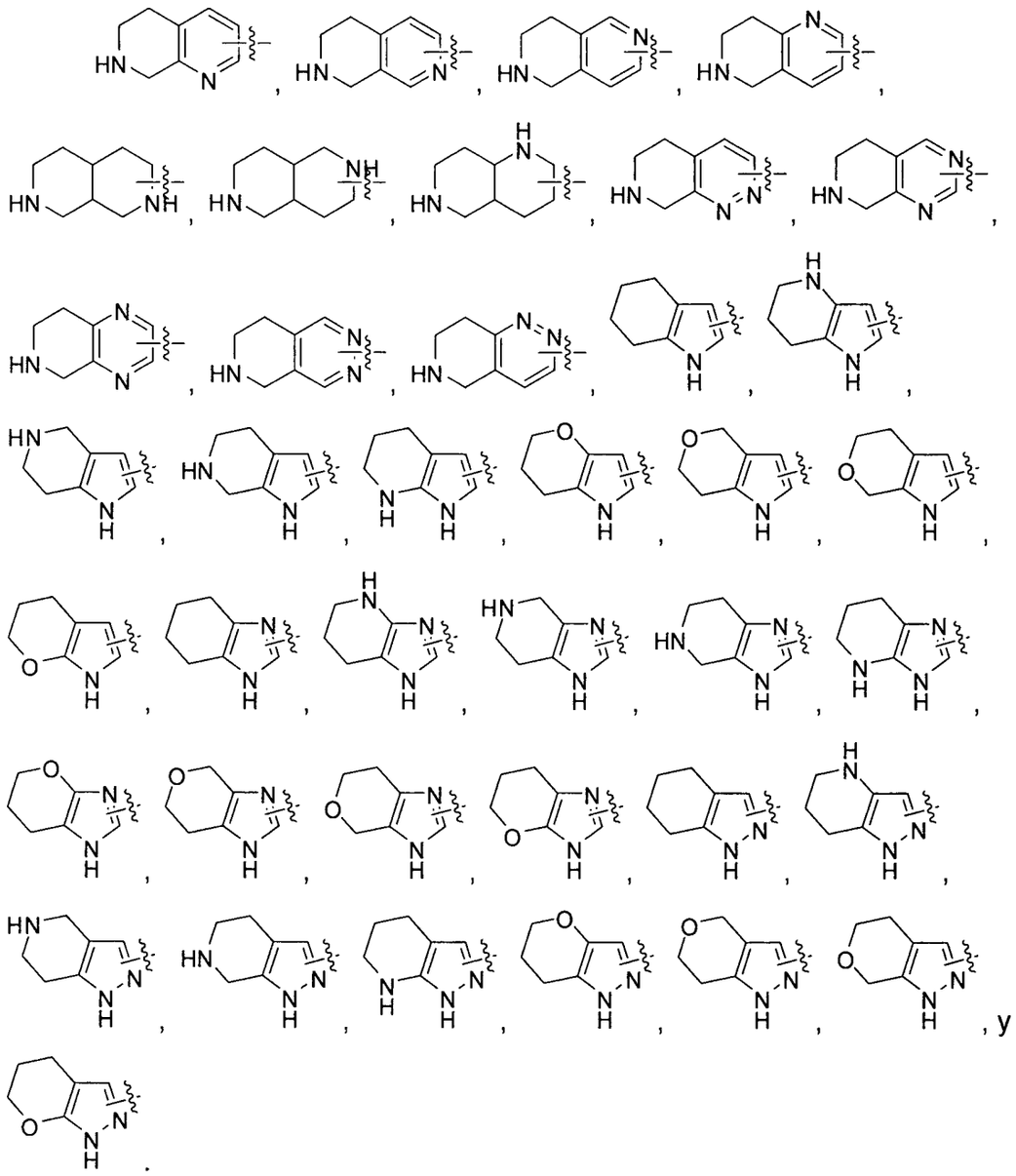
cuales comprenden grupos cicloalquilo bicíclicos parcialmente insaturados incluyen a los siguientes:



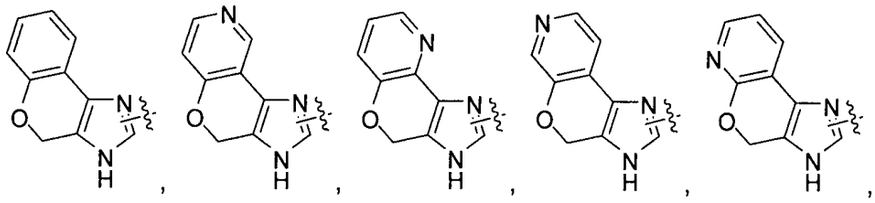
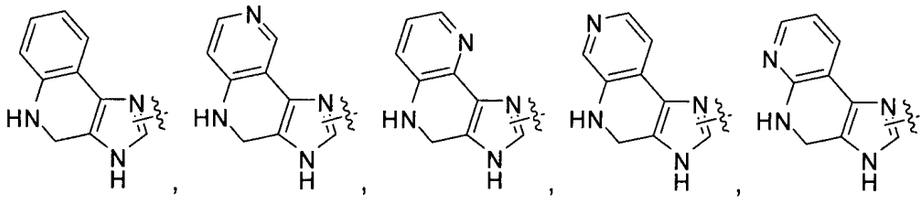
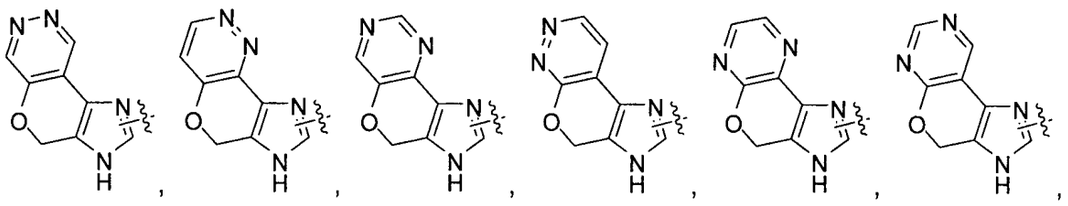
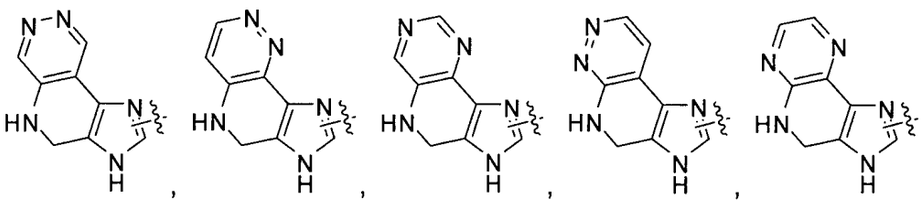
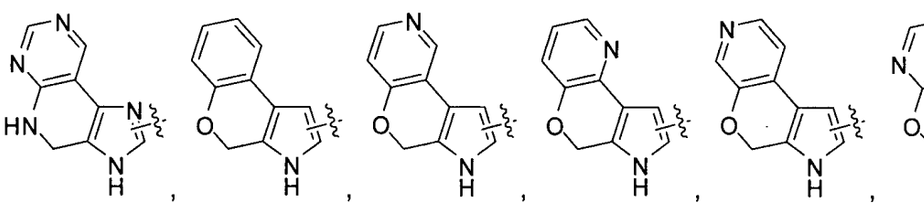
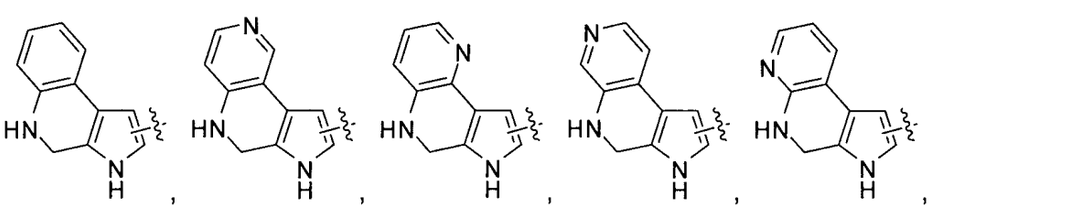
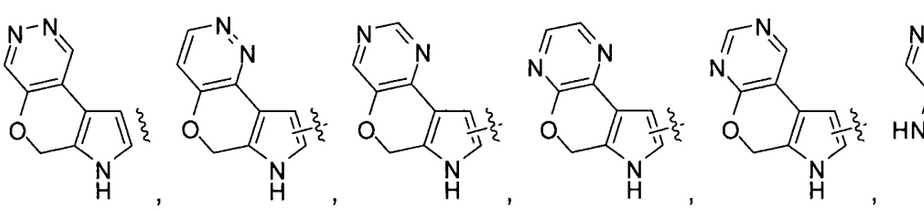
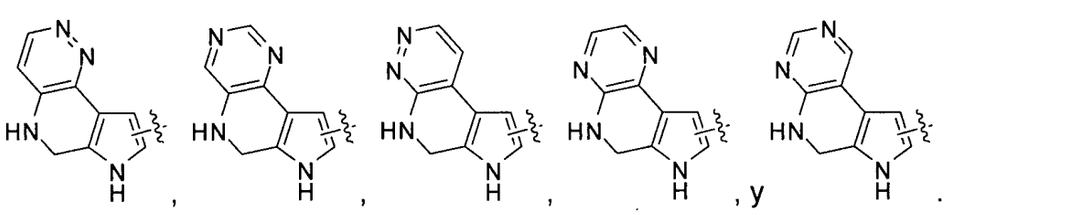
El término grupos multicíclicos incluye grupos bicíclicos parcial o totalmente saturados que comprenden entre 1 y 3 heteroátomos del anillo, cada uno de dicho heteroátomo del anillo se selecciona independientemente del grupo formado por N, O, y S, S(O), $S(O)_2$, y óxidos de N y S. Dichos anillos también pueden contener opcionalmente uno o más grupos oxo, según lo definido en esta invención. Los ejemplos no limitativos de grupos multicíclicos los cuales son grupos bicíclicos parcial o totalmente saturados que comprenden entre 1 y 3 heteroátomos del anillo, estado cada uno de dichos heteroátomos del anillo seleccionado independientemente entre N, O, y S incluyen a los siguientes, y sus óxidos:







El término grupos multicíclicos incluye grupos tricíclicos aromáticos, grupos tricíclicos cicloalquilo, así como también grupos heteroaromáticos y tricíclicos parcial o totalmente saturados. Para los grupos tricíclicos que comprenden heteroátomos del anillo, dichos grupos tricíclicos comprenden uno o más (por ej., entre 1 y 5) heteroátomos del anillo, donde cada uno de dicho heteroátomo del anillo se selecciona independientemente entre N, O, y S, S(O), $S(O)_2$, y óxidos de N, O, y S: Los ejemplos no limitativos de grupos multicíclicos tricíclicos incluyen a los siguientes, y, donde sea posible, sus óxidos:

y .

"Paciente" incluye tanto animales humanos como no humanos. Los animales no humanos incluyen aquellos animales de investigación y animales de compañía tales como ratones, primates, monos, simios grandes, canino (*por ej.,* perros), y felino (*por ej.,* gatos de hogar).

"Composición farmacéutica" (o "composición farmacéuticamente aceptable") significa una composición adecuada para la administración a un paciente. Dichas composiciones pueden contener el compuesto (o compuestos) puro de la invención o mezclas del mismo(s), o sus sales, solvatos, prodrogas, isómeros o tautómeros, o pueden contener uno o más portadores o diluyentes farmacéuticamente aceptables. El término "composición farmacéutica" tiene el propósito de abarcar tanto a la composición en masa como a unidades de dosificación individuales compuestas por más de uno (por ej., dos) agentes farmacéuticamente activos tales como, por ejemplo, un compuesto de la presente invención y un agente adicional seleccionado de las listas de los agentes adicionales descritos en esta invención, junto con cualquiera de los excipientes farmacéuticamente inactivos. La composición en masa y cada unidad de dosificación individual puede contener cantidades fijas de los "más de uno agente farmacéuticamente activo" antes mencionado. La composición en masa es material que aun no ha sido formado en unidades de dosificación individuales. Una unidad de dosificación ilustrativa es una unidad de dosificación oral tal como tabletas, píldoras y similares. Similarmente, el método descrito en esta invención para tratar a un paciente administrando una composición farmacéutica de la presente invención también tiene el propósito de abarcar la administración de la composición en masa antes mencionada y unidades de dosificación individuales.

"Halógeno" significa flúor, cloro, bromo o yodo.

Se prefieren flúor, cloro y bromo.

"Alquilo" significa un grupo hidrocarburo alifático el cual puede ser recto 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

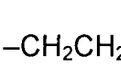
átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. "Alquilo" puede estar sin sustituir u opcionalmente sustituido con uno o más sustituyentes los cuales pueden ser iguales o diferentes, estando cada sustituyente según lo descrito en la presente invención o seleccionado independientemente del grupo formado por halo, alquilo, haloalquilo, espirocicloalquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, –NH(alquilo), –NH(cicloalquilo), $–N(alquilo)_2$, –O–C(O)–alquilo, –O–C(O)–arilo, –O–C(O)–cicloalquilo, carboxi y –C(O)O–alquilo. Los ejemplos no limitativos de grupos alquilo adecuados incluyen metilo, etilo, n–propilo, isopropilo y t–butilo.

"Haloalquilo" significa un alquilo según lo definido anteriormente donde uno o más átomos de hidrógeno en el alquilo es reemplazado por un grupo halo definido anteriormente.

"Heteroalquilo" significa un resto alquilo según lo definido anteriormente, que tiene uno o más átomos de carbono, por ejemplo uno, dos o tres átomos de carbono, reemplazados con uno o más heteroátomos, los cuales pueden ser iguales o diferentes, donde el punto de unión al resto de la molécula es a través de un átomo de carbono del radical heteroalquilo. Dichos heteroátomos adecuados incluyen O, S, S(O), $S(O)_2$, y –NH–, –N(alquilo)–. Los ejemplos no limitativos incluyen éteres, tioéteres, aminas, hidroximetilo, 3–hidroxipropilo, 1,2–dihidroxietilo, 2–metoxietilo, 2–aminoetilo, 2–dimetilaminoetilo, y similares.

"Alquenilo" significa un grupo hidrocarburo alifático que contiene por lo menos un enlace doble carbono- carbono y el cual puede ser recto o ramificado 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 más preferentemente aproximadamente 2 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 alquenilo lineal. "Alquenilo inferior" significa

aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. “Alquenilo" puede estar sin sustituir u opcionalmente sustituido con uno o más sustituyentes los cuales pueden ser iguales o diferentes, siendo cada sustituyente seleccionado independientemente del grupo formado por halo, alquilo, arilo, cicloalquilo, ciano, alcoxi y –S(alquilo). Los ejemplos no limitativos de grupos alquenilo adecuados incluyen etenilo, propenilo, n–butenilo, 3–metilbut–2–enilo, n–pentenilo, octenilo y decenilo.

“Alquileno” significa un grupo difuncional obtenido mediante remoción de un átomo de hidrógeno de un grupo alquilo que es definido anteriormente. Los ejemplos no limitativos de alquileno incluyen metileno, etileno y propileno. Más generalmente, el sufijo “eno” en alquilo, arilo, heterocicloalquilo, etc. indica un resto divalente, por ej., $-CH_2CH_2-$ es etileno, y  . es para–fenileno.

"Alquinilo" significa un grupo hidrocarburo alifático que contiene por lo menos un enlace triple carbono- carbono y el cual puede ser recto o ramificado y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y más preferentemente 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 recta o ramificada. Los ejemplos no limitativos de grupos alquinilo adecuados incluyen etinilo, propinilo, 2–butinilo y 3–metilbutinilo. “Alquinilo" puede estar sin sustituir u opcionalmente sustituido con uno o más sustituyentes los cuales pueden ser iguales o diferentes, siendo cada sustituyente independientemente seleccionado del grupo formado por alquilo, arilo y cicloalquilo.

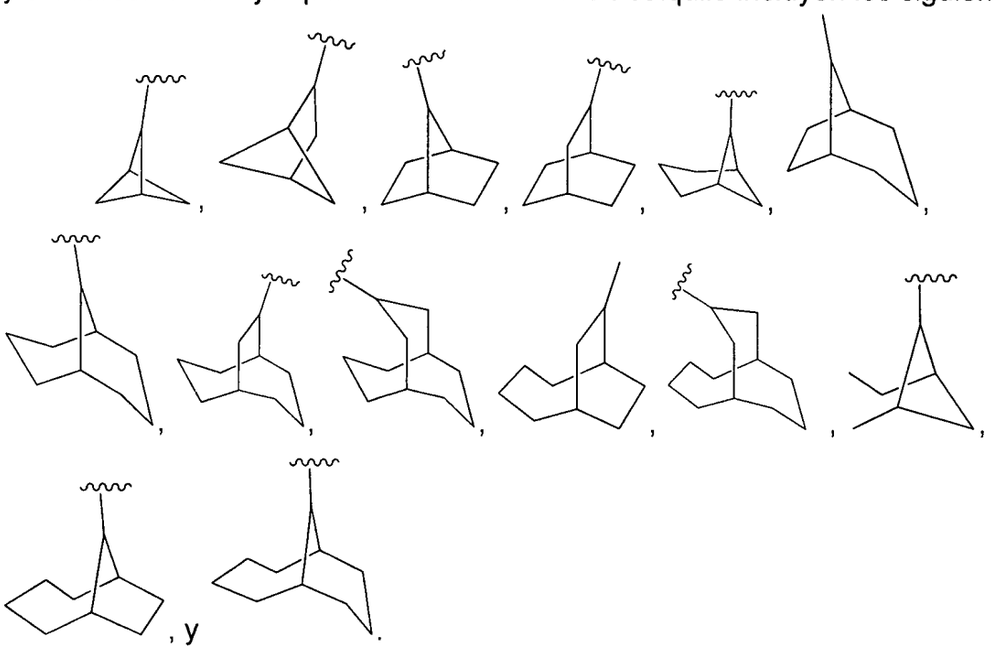
"Alquenileno" significa un grupo difuncional obtenido mediante remoción de un hidrógeno de un grupo alquenilo que es definido anteriormente. Los ejemplos no limitativos de alquenileno incluyen –CH=CH–, $–C(CH_3)=CH–$, y $–CH=CHCH_2–$.

"Arilo" significa un sistema de anillos monocíclicos o multicíclicos aromáticos que comprende aproximadamente 6 a aproximadamente 14 átomos de carbono, preferentemente aproximadamente 6 a aproximadamente 10 átomos de carbono. El grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" los cuales pueden ser iguales o diferentes, y son según lo definido en esta invención. Los ejemplos no limitativos de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema de anillos monocíclicos o multicíclicos aromáticos que comprende aproximadamente 5 a aproximadamente 14 átomos del anillo, preferentemente aproximadamente 5 a aproximadamente 10 átomos del anillo, en donde uno o más de los átomos del anillo es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos del anillo. El "heteroarilo" puede ser opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos " los cuales pueden ser iguales o diferentes, y son según lo definido en esta invención. El prefijo aza, oxa o tia antes del nombre de raíz heteroarilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como un átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede ser opcionalmente oxidado al N-óxido correspondiente. "Heteroarilo" puede incluir además un heteroarilo según lo definido anteriormente fusionado a un arilo según lo definido anteriormente. Los ejemplos no limitativos de heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo (alternativamente denominado tiofenilo), pirimidinilo, piridona (incluyendo 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, bencimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo,

pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4–triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere además a restos heteroarilo parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Cicloalquilo" significa un sistema de anillos mono- o multicíclicos no aromáticos que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, preferentemente aproximadamente 5 a aproximadamente 10 átomos de carbono. Los anillos preferidos cicloalquilo contienen aproximadamente 5 a aproximadamente 7 átomos del anillo. El cicloalquilo puede ser opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" los cuales pueden ser iguales o diferentes, y son según lo definido en esta invención. Los ejemplos no limitativos de cicloalquilos monocíclicos adecuados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Los ejemplos no limitativos de cicloalquilos multicíclicos adecuados incluyen 1–decalinilo, norbornilo, adamantilo y similares. Otros ejemplos no limitativos de cicloalquilo incluyen los siguientes:



, y

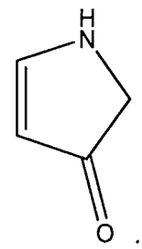
"Cicloalquenilo" significa un sistema de anillos mono o multicíclico no aromático que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, preferentemente aproximadamente 5 a aproximadamente 10 átomos de carbono el cual contiene por lo menos un enlace doble carbono- carbono. Los anillos cicloalquenilo preferidos contienen aproximadamente 5 a aproximadamente

7 átomos del anillo. El cicloalquenilo puede ser opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" los cuales pueden ser iguales o diferentes, y son según lo definido anteriormente. Los ejemplos no limitativos de cicloalquenilos monocíclicos adecuados incluyen ciclopentenilo, ciclohexenilo, ciclohepta–1,3–dienilo, y similares. Un ejemplo no limitativo de un cicloalquenilo multicíclico adecuado es norbornilenilo.

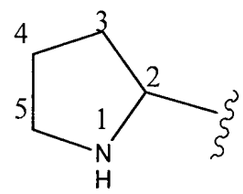
"Heterocicloalquilo" (o "heterociclilo") significa un sistema de anillos monocíclicos o multicíclicos saturados no aromáticos que comprende aproximadamente 3 a aproximadamente 10 átomos del anillo, preferentemente aproximadamente 5 a aproximadamente 10 átomos del anillo, en el cual uno o más de los átomos en el sistema de anillos es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. No existen átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillos. Los heterociclilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos del anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo del anillo. Cualquier –NH en un anillo heterociclilo puede existir protegido tales como, por ejemplo, un grupo –N(Boc), –N(CBz), –N(Tos) y similares; dichas protecciones son también consideradas parte de esta invención. El heterociclilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" los cuales pueden ser iguales o diferentes, y son según lo definido en esta invención. El átomo de nitrógeno o azufre del heterociclilo puede ser opcionalmente oxidado al correspondiente N–óxido, S–óxido o S,S–dióxido. Por lo tanto, el término "óxido," cuando aparece en una definición de una variable en una estructura general descrita en esta invención, se refiere al correspondiente N–óxido, S–óxido, o S,S–dióxido. Los ejemplos no limitativos de anillos heterociclilo monocíclicos adecuados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4–dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, y similares. "Heterociclilo" también incluye anillos donde =O reemplaza dos hidrógenos disponibles en el mismo átomo de carbono (es decir, heterociclilo

incluye anillos que tienen un grupo carbonilo en el anillo). Dichos grupos =O pueden ser denominados en esta invención "oxo," según lo descrito más abajo.

"Heterocicloalquenilo" (o "heterociclenilo") significa un sistema de anillos monocíclicos o multicíclicos no aromáticos que comprende aproximadamente 3 a aproximadamente 10 átomos del anillo, preferentemente aproximadamente 5 a aproximadamente 10 átomos del anillo, en el cual uno o más de los átomos en el sistema de anillos es un elemento que no es carbono, por ejemplo un átomo de nitrógeno, oxígeno o azufre, solo o en combinación, y el cual contiene por lo menos un enlace doble carbono- carbono o enlace doble carbono- nitrógeno. No existen átomos de oxígeno y/o azufre adyacentes en el sistema de anillos. Los anillos heterociclenilo preferidos contienen aproximadamente 5 a aproximadamente 6 átomos del anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclenilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo del anillo. El heterociclenilo puede estar opcionalmente sustituido con uno o más sustituyentes del sistema de anillos, donde "sustituyente del sistema de anillos" es según lo definido anteriormente. El átomo de nitrógeno o azufre del heterociclenilo puede ser opcionalmente oxidado al correspondiente N–óxido, S–óxido o S,S–dióxido. Los ejemplos no limitativos de grupos heterociclenilo adecuados incluyen 1,2,3,4–tetrahidropiridinilo, 1,2–dihidropiridinilo, 1,4–dihidropiridinilo, 1,2,3,6–tetrahidropiridinilo, 1,4,5,6–tetrahidropirimidinilo, 2–pirrolinilo, 3–pirrolinilo, 2–imidazolinilo, 2–pirazolinilo, dihidroimidazolilo, dihidrooxazolilo, dihidrooxadiazolilo, dihidrotiazolilo, 3,4–dihidro–2H–piranilo, dihidrofuranilo, fluordihidrofuranilo, 7–oxabiciclo[2.2.1]heptenilo, dihidrotiofenilo, dihidrotiopiranilo, y similares. "Heterociclenilo" también incluye anillos donde =O reemplaza dos hidrógenos disponibles en el mismo átomo de carbono (es decir, heterociclenilo incluye anillos que tienen un grupo carbonilo en el anillo). Ejemplo de dicho resto es pirrolidenona (o pirrolona):



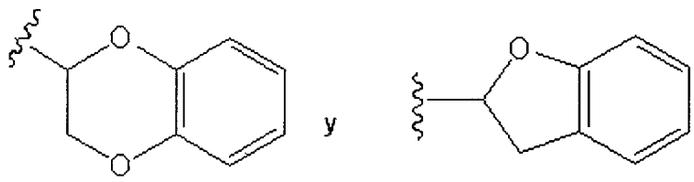
Debería señalarse que en sistemas de anillos que contienen heteroátomos de esta invención, no hay grupos hidroxilo en átomos de carbono adyacentes a un N, O u S, así como tampoco hay grupos N u S en carbono adyacente a otro heteroátomo. Por consiguiente, por ejemplo, en el anillo:



no hay –OH unido directamente a carbonos marcados 2 y 5.

"Arilcicloalquilo" (o "cicloalquilo fusionado a arilo") significa un grupo derivado de un arilo y cicloalquilo fusionados según lo definido en esta invención. Los arilcicloalquilos preferidos son aquellos donde arilo es fenilo (el cual puede ser denominado "benzofusionado") y cicloalquilo consiste en aproximadamente 5 a aproximadamente 6 átomos del anillo. El arilcicloalquilo puede ser opcionalmente sustituido según lo descrito en la presente invención. Los ejemplos no limitativos de arilcicloalquilos adecuados incluyen indanilo (un cicloalquilo benzofusionado) y 1,2,3,4–tetrahidronaftilo y similares. El enlace al resto principal es a través de un átomo de carbono no aromático.

"Arilheterocicloalquilo" (o "heterocicloalquilo arilfusionado") significa un grupo derivado de un arilo y heterocicloalquilo fusionados según lo definido en esta invención. Los arilheterocicloalquilos preferidos son aquellos donde arilo es fenilo (el cual puede ser denominado "benzofusionado") y heterocicloalquilo consiste en aproximadamente 5 a aproximadamente 6 átomos del anillo. El arilheterocicloalquilo puede ser opcionalmente sustituido, y/o puede contener el óxido u oxo, según lo descrito en la presente invención. Los ejemplos no limitativos de heterocicloalquilos arilfusionados adecuados incluyen:



El enlace al resto principal es a través de un átomo de carbono no aromático.

Se entiende además que los términos "arilo arilfusionado", "cicloalquilo arilfusionado", "cicloalquenilo arilfusionado", "heterocicloalquilo arilfusionado", heterocicloalquenilo arilfusionado", "heteroarilo arilfusionado", "arilo cicloalquilfusionado", "cicloalquilo cicloalquilfusionado", "cicloalquenilo cicloalquilfusionado", "heterocicloalquilo cicloalquilfusionado", "heterocicloalquenilo cicloalquilfusionado", "heteroarilo cicloalquilfusionado, "arilo cicloalquenilfusionado", " cicloalquilo cicloalquenilfusionado", " cicloalquenilo cicloalquenilfusionado", "heterocicloalquilo cicloalquenilfusionado", "heterocicloalquenilo cicloalquenilfusionado", " heteroarilo cicloalquenilfusionado", "arilo heterocicloalquilfusionado", "cicloalquilo heterocicloalquilfusionado", "cicloalquenilo heterocicloalquilfusionado", "heterocicloalquilo heterocicloalquilfusionado", "heteroarilo heterocicloalquilfusionado", "arilo heterocicloalquenilfusionado", "cicloalquilo heterocicloalquenilfusionado", "cicloalquenilo heterocicloalquenilfusionado", "heterocicloalquilo heterocicloalquenilfusionado", "heterocicloalquenilo heterocicloalquenilfusionado", "heteroarilo heterocicloalquenilfusionado", "arilo heteroarilfusionado", "cicloalquilo heteroarilfusionado", "cicloalquenilo heteroarilfusionado", "heterocicloalquilo heteroarilfusionado", "heterocicloalquenilo heteroarilfusionado", y "heteroarilo heteroarilfusionado" son similarmente representados por la combinación de los grupos arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, y heteroarilo, según lo descrito previamente. Cualquier grupo de ese tipo puede estar sin sustituir o sustituido con uno o más sustituyentes del sistema de anillos en cualquier posición disponible según lo descrito en la presente invención.

"Aralquilo" o "arilalquilo" significa un grupo aril–alquil– en el cual el arilo y alquilo son según lo previamente descrito. Los aralquilos preferidos comprenden un grupo alquilo inferior. Los ejemplos no limitativos de grupos aralquilo adecuados incluyen bencilo, 2–fenetilo y naftalenilmetilo. El enlace al resto principal es a través del alquilo. El término (y términos similares) puede ser escrito como "arilalquil–" para indicar el punto de unión al resto principal.

Similarmente, "heteroarilalquilo", "cicloalquilalquilo", "cicloalquenilalquilo", "heterocicloalquilalquilo", "heterocicloalquenilalquilo", etc., significan un heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, etc. según lo descrito en la presente invención unido a un resto principal a través de un grupo alquilo. Los grupos preferidos contienen un grupo alquilo inferior. Dichos grupos alquilo pueden ser rectos o ramificados, no sustituidos y/o sustituidos según lo descrito en la presente invención.

Similarmente, "arilalquil– arilfusionado", cicloalquilalquil– arilfusionado, etc., significa un grupo arilo arilfusionado, grupo cicloalquilo arilfusionado, etc. unido a un resto principal a través de un grupo alquilo. Los grupos preferidos contienen un grupo alquilo inferior. Dichos grupos alquilo pueden ser rectos o ramificados, no sustituidos y/o sustituidos según lo descrito en la presente invención.

"Alquilarilo" significa un grupo alquil–aril– en el cual el alquilo y arilo son según lo previamente descrito. Los alquilarilos preferidos comprenden un grupo alquilo inferior. Un ejemplo no limitativo de un grupo alquilarilo adecuado es tolilo. El enlace al resto principal es a través del arilo.

"Cicloalquiléter" significa un anillo no aromático de 3 a 7 miembros que comprende un átomo de oxígeno y de 2 a 7 átomos de carbono. Los átomos del anillo de carbono pueden ser sustituidos, siempre que los sustituyentes adyacentes al oxígeno del anillo no incluyan halo o sustituyentes unidos al anillo a través de un átomo de oxígeno, nitrógeno o azufre.

"Cicloalquilalquilo" significa un resto cicloalquilo según lo definido anteriormente ligado por medio de un resto alquilo (definido anteriormente) a un núcleo principal. Los ejemplos no limitativos de cicloalquilalquilos adecuados incluyen ciclohexilmetilo, adamantilmetilo, adamantilpropilo, y similares.

"Cicloalquenilalquilo" significa un resto cicloalquenilo según lo definido anteriormente ligado por medio de un resto alquilo (definido anteriormente) a un núcleo principal. Los ejemplos no limitativos de cicloalquenilalquilos adecuados incluyen ciclopentenilmetilo, ciclohexenilmetilo y similares.

"Heterociclilalquilo" (o "heterocicloalquilalquilo") significa un resto heterociclilo según lo definido anteriormente ligado por medio de un resto alquilo (definido anteriormente) a un núcleo principal. Los ejemplos no limitativos de heterociclilalquilos adecuados incluyen piperidinilmetilo, piperazinilmetilo y similares.

"Heterociclenilalquilo" significa un resto heterociclenilo según lo definido anteriormente ligado por medio de un resto alquilo (definido anteriormente) a un núcleo principal.

"Alquinilalquilo" significa un grupo alquinil–alquil– en el cual el alquinilo y alquilo son según lo previamente descrito. Los alquinilalquilos preferidos contienen un grupo alquinilo inferior y un grupo alquilo inferior. El enlace al resto principal es a través del alquilo. Los ejemplos no limitativos de grupos alquinilalquilo adecuados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril–alquil– en el cual el heteroarilo y alquilo son según lo previamente descrito. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Los ejemplos no limitativos de grupos adecuados aralquilo incluyen piridilmetilo, 2–piridinilmetilo, quinolinilmetilo, y quinolin–3–ilmetilo, y similares. El enlace al resto principal es a través del alquilo.

"Hidroxialquilo" significa un grupo HO–alquil– en el cual alquilo es como se ha definido previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Los ejemplos no limitativos de grupos hidroxialquilo adecuados incluyen hidroximetilo y 2–hidroxietilo.

"Cianoalquilo" significa un grupo NC–alquil– en el cual alquilo es según se ha definido previamente. Los cianoalquilos preferidos contienen alquilo inferior. Los ejemplos no limitativos de grupos cianoalquilo adecuados incluyen cianometilo y 2–cianoetilo.

"Acilo" significa un grupo H–C(O)–, alquil–C(O)– o cicloalquil–C(O)–, en el cual los diversos grupos son según lo previamente descrito. El enlace al resto principal es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Los ejemplos no limitativos de grupos acilo adecuados incluyen formilo, acetilo y propanoílo.

"Aroílo" significa un grupo aril–C(O)– en el cual el grupo arilo es según lo descrito previamente. El enlace al resto principal es a través del carbonilo. Los ejemplos no limitativos de grupos adecuados incluyen benzoílo y 1– naftoílo.

"Heteroaroílo" significa un grupo heteroaril–C(O)– en el cual el grupo heteroarilo es según lo descrito previamente. El enlace al resto principal es a través del carbonilo. Los ejemplos no limitativos de grupos adecuados incluyen piridoílo.

"Alcoxi" significa un grupo alquil–O– en el cual el grupo alquilo es según lo descrito previamente. Los ejemplos no limitativos de grupos alcoxi adecuados incluyen metoxi, etoxi, *n*–propoxi, isopropoxi y *n*–butoxi. El enlace al resto principal es a través del oxígeno de éter.

"Alquiloxialquilo" significa un grupo derivado de un alcoxi y alquilo según lo definido en esta invención. El enlace al resto principal es a través del alquilo.

"Ariloxi" significa un grupo aril–O– en el cual el grupo arilo es según lo descrito previamente. Los ejemplos no limitativos de grupos adecuados ariloxi incluyen fenoxi y naftoxi. El enlace al resto principal es a través del oxígeno de éter.

"Aralquiloxi" (o "arilalquiloxi") significa un grupo aralquil–O–(un grupo arilalquil–O–) en el cual el grupo aralquilo es según lo descrito previamente. Los ejemplos no limitativos de grupos adecuados aralquiloxi incluyen benciloxi y 1– o 2–naftalenmetoxi. El enlace al resto principal es a través del oxígeno de éter.

"Arilalquenilo" significa un grupo derivado de un arilo y alquenilo según lo definido en esta invención. Los arilalquenilos preferidos son aquellos donde arilo es fenilo y el alquenilo consiste en aproximadamente 3 a aproximadamente 6 átomos. El arilalquenilo puede ser opcionalmente sustituido con uno o más

sustituyentes. El enlace al resto principal es a través de un átomo de carbono no aromático.

"Arilalquinilo" significa un grupo derivado de un arilo y alquenilo según lo definido en esta invención. Los arilalquinilos preferidos son aquellos donde arilo es fenilo y el alquinilo consiste en aproximadamente 3 a aproximadamente 6 átomos. El arilalquinilo puede ser opcionalmente sustituido con uno o más sustituyentes. El enlace al resto principal es a través de un átomo de carbono no aromático.

"Alquiltio" significa un grupo alquil–S– en el cual el grupo alquilo es según lo descrito previamente. Los ejemplos no limitativos de grupos adecuados alquiltio incluyen metiltio y etiltio. El enlace al resto principal es a través del azufre.

"Ariltio" significa un grupo aril–S– en el cual el grupo arilo es según lo descrito previamente. Los ejemplos no limitativos de grupos ariltio adecuados incluyen feniltio y naftiltio. El enlace al resto principal es a través del azufre.

"Aralquiltio" significa un grupo aralquil–S– en el cual el grupo aralquilo es según lo descrito previamente. Un ejemplo no limitativo de un grupo aralquiltio adecuado es benciltio. El enlace al resto principal es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquil–O–CO–. Los ejemplos no limitativos de grupos adecuados alcoxicarbonilo incluyen metoxicarbonilo y etoxicarbonilo. El enlace al resto principal es a través del carbonilo.

"Ariloxicarbonilo" significa un grupo aril–O–C(O)–. Los ejemplos no limitativos de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace al resto principal es a través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil–O–C(O)–. Un ejemplo no limitativo de un grupo aralcoxicarbonilo adecuado es benciloxicarbonilo. El enlace al resto principal es a través del carbonilo.

"Alquilsulfonilo" significa un grupo alquil–S(O_2)–. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace al resto principal es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril–S(O_2)–. El enlace al resto principal es a través del sulfonilo.

"Espirocicloalquilo" significa un grupo cicloalquilo unido a un resto principal mediante reemplazo de dos átomos de hidrógeno disponibles en un único átomo de carbono. Los ejemplos no limitativos de espirocicloalquilo donde el resto principal es un cicloalquilo incluyen espiro [2.5] octano, espiro [2.4] heptano, etc. El resto puede opcionalmente ser sustituido según lo descrito en la presente invención. Los grupos espirocicloalquilo no limitativos incluyen espirociclopropilo, espirociclobutilo, espirocicloheptilo, y espirociclohexilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado se reemplaza con una selección del grupo indicado, siempre que la valencia normal del átomo designado bajo las circunstancias existentes no sea excedida, y que la sustitución de como resultado un compuesto estable. Las combinaciones de sustituyentes y/o variables son permisibles solamente si dichas combinaciones dan como resultado compuestos estables. Por "compuesto estable" o "estructura estable" se quiere decir un compuesto que es suficientemente robusto para sobrevivir al aislamiento hasta un grado útil de pureza de una mezcla de reacción, y formulación en un agente terapéutico eficaz.

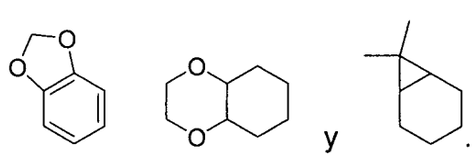
El término "opcionalmente sustituido" significa la sustitución opcional con los grupos, radicales o restos especificados. La sustitución en un resto cicloalquilalquilo, heterocicloalquilalquilo, arilalquilo, heteroarilalquilo, cicloalquilalquil– arilfusionado o similar incluye la sustitución en cualquier porción del anillo y/o en la porción alquilo del grupo.

Cuando una variable aparece más de una vez en un grupo, por ej., R^8 en –$N(R^8)_2$, o una variable aparece más de una vez en una estructura presentada en esta invención, las variables pueden ser iguales o diferentes.

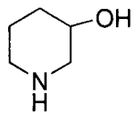
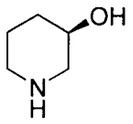
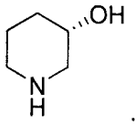
Con referencia a la cantidad de restos (por ej., sustituyentes, grupos o anillos) en un compuesto, a menos que se defina lo contrario, las frases "uno o más" y "por lo menos uno" significan que pueden haber tantos restos como sea permitido químicamente, y la determinación del número máximo de dichos restos es bien conocida por los expertos en la técnica. Con respecto a las composiciones y métodos que comprenden el uso de "por lo menos un compuesto de la invención, por ej., de fórmula (II)," se pueden administrar de uno a tres

compuestos de la invención, por ej., de fórmula (II) al mismo tiempo, preferentemente uno.

Los compuestos de la invención pueden contener uno o más anillos que tienen uno o más sustituyentes en el sistema de anillos. "Sustituyentes del sistema de anillos" significa un sustituyente unido a un sistema de anillos no aromáticos o aromáticos el cual, por ejemplo, reemplaza un hidrógeno disponible en el sistema de anillos. Los sustituyentes del sistema de anillos pueden ser iguales o diferentes, siendo cada uno según lo descrito en la presente invención o seleccionados independientemente del grupo formado por alquilo, alquenilo, alquinilo, haloalquilo, heteroalquilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, –O–C(O)–alquilo, –O–C(O)–arilo, –O–C(O)–cicloalquilo, –C(=N–CN)–NH_2, –C(=NH)–NH_2, –C(=NH)–NH(alquilo), Y_1Y_2N–, Y_1Y_2N–alquil–, $Y_1Y_2NC(O)$–, $Y_1Y_2NSO_2$– y $–SO_2NY_1Y_2$, donde Y_1 y Y_2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo formado por hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. “Sustituyente del sistema de anillos” también puede significar un resto único el cual reemplaza simultáneamente dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema de anillos. Los ejemplos de dichos restos son anillos tales como anillos heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, y heterocicloalquenilo. Los ejemplos no limitativos adicionales incluyen metilendioxi, etilendioxi, –$C(CH_3)_2$– y similares los cuales forman restos tales como, por ejemplo:

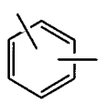


La línea —— como un enlace generalmente indica una mezcla de, o cualquiera de los dos de, los posibles isómeros, por ej., que contiene estereoquímica (R) y (S). Por ejemplo:

 indica una mezcla de, o cualquiera de,  y/o  .

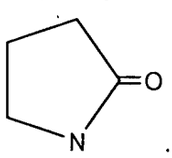
La línea ondulada ~~~~, como se emplea en esta invención, indica un punto de unión al resto del compuesto.

Las líneas dibujadas hacia dentro de los sistemas de anillos, tales como, por ejemplo:



indican que la línea indicada (enlace) puede estar unida a cualquiera de los átomos de carbono de anillo sustituibles.

"Oxo" se define como un átomo de oxígeno que está doblemente unido a un carbono de anillo en un cicloalquilo, cicloalquenilo, heterociclilo, heterociclenilo, u otro anillo descrito en esta invención, por ej.,

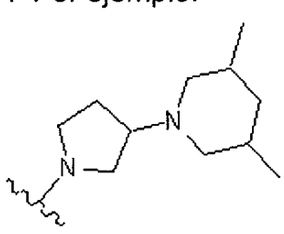
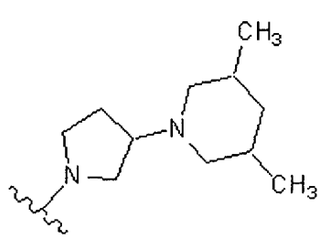
 .

En esta memoria descriptiva, donde hay múltiples átomos de oxígeno y/o azufre en un sistema de anillos, no puede haber ningún oxígeno y/o azufre adyacente presente en dicho sistema de anillos.

Se señala que los átomos de carbono para los compuestos de la invención pueden ser reemplazados con 1 a 3 átomos de silicio siempre y cuando se satisfagan todos los requerimientos de valencia.

Como es bien sabido en la técnica, un enlace dibujado desde un átomo en particular donde no se ilustra resto alguno en el extremo terminal del enlace indica un grupo metilo unido a través de ese enlace al átomo, a menos que se indique lo contrario

. Por ejemplo:

 representa 

En los compuestos de fórmula (I)

El término "purificado/a", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto después de ser aislado de un proceso sintético (por ej., de una mezcla de reacción) o fuente natural o combinación de los mismos. Por lo tanto, el término "purificado/a", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto (o un tautómero o estereoisómero del mismo, o una sal o solvato farmacéuticamente aceptable de dicho compuesto, dicho estereoisómero, o dicho tautómero) después de ser obtenido de un proceso o procesos de purificación descritos en esta invención o bien conocidos por el experto en la técnica (por ej., cromatografía, recristalización y similares), en pureza suficiente para ser adecuado para uso in vivo o medicinal y/o caracterizable por técnicas analíticas estándares descritas en esta invención o bien conocidas por los expertos en la técnica.

Cuando un grupo funcional en un compuesto es denominado "protegido", esto significa que el grupo está en forma modificada para excluir reacciones colaterales no deseadas en el sitio protegido cuando el compuesto es sujeto a una reacción. Los grupos protectores adecuados serán reconocidos por aquellos con experiencia en la técnica así como también por referencia a libros de textos estándares tales como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, Nueva York.

Como se emplea en esta invención, el término "composición" tiene el propósito de abarcar un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto el cual resulte, directa o indirectamente, de la combinación de los ingredientes especificados en las cantidades especificadas.

Las prodrogas y solvatos de los compuestos de la invención son también contemplados en esta invención. Una descripción de prodrogas es provista en T. Higuchi y V. Stella, *Pro–drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. El

término "prodroga" significa un compuesto (por ej., un precursor de droga) que es transformado *in vivo* para proporcionar un compuesto de la invención o una sal, hidrato o solvato farmacéuticamente aceptable del compuesto. La transformación puede ocurrir mediante diversos mecanismos (por ej., mediante procesos metabólicos o químicos), tales como, por ejemplo, a través de la hidrólisis en sangre. Una descripción del uso de prodrogas es proporcionada por T. Higuchi y W. Stella, "Pro–drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Por ejemplo, si un compuesto de la invención o una sal, hidrato o solvato farmacéuticamente aceptable del compuesto contiene un grupo funcional ácido carboxílico, una prodroga puede comprender un éster formado por el reemplazo del átomo de hidrógeno del grupo ácido con un grupo tal como, por ejemplo, alquilo(C_1–C_8), alcanoiloximetilo(C_2–C_{12}), 1–(alcanoiloxi)etilo que tiene entre 4 y 9 átomos de carbono, 1–metil–1–(alcanoiloxi)–etilo que tiene entre 5 y 10 átomos de carbono, alcoxicarboniloximetilo que tiene entre 3 y 6 átomos de carbono, 1–(alcoxicarboniloxi)etilo que tiene entre 4 y 7 átomos de carbono, 1–metil–1–(alcoxicarboniloxi)etilo que tiene entre 5 y 8 átomos de carbono, N–(alcoxicarbonil)aminometilo que tiene entre 3 y 9 átomos de carbono, 1–(N–(alcoxicarbonil)amino)etilo que tiene entre 4 y 10 átomos de carbono, 3–ftalidilo, 4–crotonolactonilo, gamma–butirolacton–4–ilo, di–N,N–alquilamino(C_1–C_2) alquilo(C_2–C_3) (tal como β–dimetilaminoetilo), carbamoil–alquilo(C_1–C_2), N,N–di alquilcarbamoil(C_1–C_2)–alquilo(C1–C2) y piperidino–, pirrolidino– o morfolinoalquilo(C_2–C_3), y similares.

Similarmente, si un compuesto de la invención contiene un grupo funcional alcohol, se puede formar una prodroga mediante el reemplazo del átomo de hidrógeno del grupo alcohol con un grupo tal como, por ejemplo, alcanoiloximetilo(C_1–C_6), 1–(alcanoiloxi(C_1–C_6))etilo, 1–metil–1–(alcanoiloxi(C_1–C_6))etilo, alcoxicarboniloximetilo(C_1–C_6), N–alcoxicarbonilaminometilo(C_1–C_6), succinoilo, alcanoilo(C_1–C_6), □–aminoalcanilo(C_1–C_4), arilacilo y α–aminoacilo, o □–aminoacil–□–aminoacilo, donde cada grupo □–aminoacilo se selecciona

independientemente de los L–aminoácidos naturales, $P(O)(OH)_2$, $-P(O)(Oalquilo(C_1–C_6))_2$ o glicosilo (el radical es un resultado de la remoción de un grupo hidroxilo de la forma hemiacetal de un carbohidrato), y similares.

Si un compuesto de la invención incorpora un grupo funcional amina, se puede formar una prodroga mediante el reemplazo de un átomo de hidrógeno en el grupo amina con un grupo tal como, por ejemplo, R–carbonilo, RO–carbonilo, NRR'–carbonilo donde R y R' son cada uno independientemente alquilo($C_1–C_{10}$), cicloalquilo($C_3–C_7$), bencilo, o R–carbonilo es un □–aminoacilo natural o □–aminoacilo natural, —C(OH)C(O)OY^1 donde Y^1 es H, alquilo($C_1–C_6$) o bencilo, —$C(OY^2)Y^3$ donde Y^2 es alquilo($C_1–C_4$) y Y^3 es alquilo($C_1–C_6$), carboxi alquilo($C_1–C_6$), aminoalquilo($C_1–C_4$) o mono–N—o di–N,N–alquilaminoalquilo($C_1–C_6$), —$C(Y^4)Y^5$ donde Y^4 es H o metilo y Y^5 es mono–N— o di–N,N–alquilamino($C_1–C_6$) morfolino, piperidin–1–ilo o pirrolidin–1–ilo, y similares.

Uno o más compuestos de la invención pueden existir en formas no solvatadas así como también en formas solvatadas con solventes farmacéuticamente aceptables tales como agua, etanol, y similares, y se pretende que la invención abarque tanto a las formas solvatadas como a las no solvatadas. "Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas solventes. Esta asociación física involucra grados variables de enlace iónico y covalente, incluyendo enlace a hidrógeno. En ciertas circunstancias, el solvato será capaz de aislamiento, por ejemplo cuando una o más moléculas solventes se incorporan en el reticulado cristalino del sólido cristalino. "Solvato" abarca tanto solvatos en fase de solución como aislables. Los ejemplos no limitativos de solvatos adecuados incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato donde la molécula solvente es H_2O.

Uno o más compuestos de la invención pueden ser convertidos, opcionalmente, en un solvato. La preparación de solvatos es generalmente conocida. Por lo tanto, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601–611 (2004) describen la preparación de los solvatos del antifúngico fluconazol en acetato de etilo así como también a partir de agua. Se describen preparaciones similares de solvatos, hemisolvatos, hidratos y similares en E. C. van Tonder *et al*,

AAPS PharmSciTech., 5(1), artículo 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603–604 (2001). Un proceso típico, no limitativo involucra disolver el compuesto inventivo en cantidades deseadas del solvente deseado (orgánicos o agua o mezclas de los mismos) a una temperatura superior a la temperatura ambiente, y enfriar la solución a una velocidad suficiente para formar cristales los cuales son luego aislados mediante métodos estándares. Las técnicas analíticas tales como, por ejemplo espectroscopia I. R., muestran la presencia del solvente (o agua) en los cristales como un solvato (o hidrato).

"Cantidad eficaz" o "cantidad terapéuticamente eficaz" tiene el propósito de describir una cantidad de compuesto o una composición de la presente invención eficaz para inhibir las enfermedades antes mencionadas y así producir el efecto terapéutico, mejorador, inhibidor o preventivo deseado.

Los compuestos de la invención pueden formar sales las cuales también se encuentran dentro del alcance de esta invención. La referencia a un compuesto de la invención en este documento se entiende que incluye la referencia a sus sales, a menos que se indique lo contrario. El término "sale(s)", como se emplea en este documento, denota sales ácidas formadas con ácidos inorgánicos y/u orgánicos, así como también sales básicas formadas con bases inorgánicas y/u orgánicas. Adicionalmente, cuando un compuesto de la invención contiene tanto un resto básico, tal como, aunque sin limitarse a una piridina o imidazol, y un resto ácido, tal como, aunque sin limitarse a un ácido carboxílico, pueden formarse zwiteriones ("sales internas") y son incluidas dentro del término "sale(s)" como se emplea en esta invención. Las sales farmacéuticamente aceptables (es decir, no tóxicas, fisiológicamente aceptables) son preferidas, si bien otras sales son también útiles. Las sales de los compuestos de la invención pueden formarse, por ejemplo, haciendo reaccionar un compuesto de la invención con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el cual la sal precipita o en un medio acuoso seguido por liofilización.

Los ejemplos de sales de adición de ácido incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos, canforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos,

maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartaratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos) y similares. Adicionalmente, los ácidos los cuales son generalmente considerados adecuados para la formación de sales farmacéuticamente útiles de compuestos farmacéuticos básicos son descritos, por ejemplo, por 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, Nueva York; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su página en Internet). Estas descripciones son incorporadas a modo de referencia a la presente invención.

Los ejemplos de sales básicas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalinotérreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t–butilaminas, y sales con aminoácidos tales como arginina, lisina y similares. Los grupos que contienen nitrógeno básicos pueden ser cuaternizados 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.

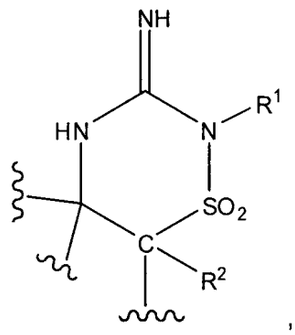
Todas esas sales ácidas y sales básicas tienen el propósito de ser sales farmacéuticamente aceptables dentro del alcance de la invención y todas las sales de ácido y base son consideradas equivalentes a las formas libres de los correspondientes compuestos para propósitos de la invención.

Los ésteres farmacéuticamente aceptables de los presentes compuestos incluyen los siguientes grupos: (1) ésteres de ácido carboxílico obtenidos por esterificación de los grupos hidroxi, en los cuales el resto no carbonilo de la porción ácido carboxílico del agrupamiento éster se selecciona entre alquilo de

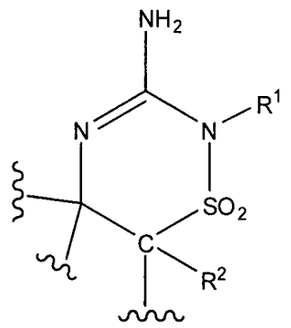
cadena recta o ramificada (por ejemplo, acetilo, n–propilo, t–butilo, o n–butilo), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), ariloxialquilo (por ejemplo, fenoximetilo), arilo (por ejemplo, fenilo opcionalmente sustituido con, por ejemplo, halógeno, alquilo C_{1-4}, o alcoxi C_{1-4} o amino); (2) ésteres de sulfonato, tales como alquil– o aralquilsulfonil (por ejemplo, metansulfonilo); (3) ésteres de aminoácidos (por ejemplo, L–valilo o L–isoleucilo); (4) ésteres de fosfonato y (5) ésteres de mono–, di– o trifosfato. Los ésteres de fosfato pueden ser adicionalmente esterificados mediante, por ejemplo, un alcohol C_{1-20} o su derivado reactivo, o mediante un 2,3–diacil (C_{6-24}) glicerol.

Las mezclas diastereoméricas pueden ser separadas en sus diastereómeros individuales sobre la base de sus diferencias físico- químicas mediante métodos bien conocidos por los expertos en la técnica, tales como, por ejemplo, por cromatografía y/o cristalización fraccional. Los enantiómeros pueden ser separados convirtiendo la mezcla enantiomérica en una mezcla diastereomérica mediante reacción con un compuesto apropiado ópticamente activo (por ej., auxiliar quiral tal como un alcohol quiral o cloruro ácido de Mosher), separando los diastereómeros y convirtiendo (por ej., hidrolizando) los diastereómeros individuales en los enantiómeros puros correspondientes. Asimismo, algunos de los compuestos de la invención pueden ser atropisómeros (por ej., biarilos sustituidos) y son considerados como parte de esta invención. Los enantiómeros también pueden ser separados mediante el uso de columna de HPLC quiral.

También es posible que los compuestos de la invención puedan existir en diferentes formas tautoméricas, y todas esas formas son abarcadas dentro del alcance de la invención. Asimismo, por ejemplo, todas las formas de ceto–enol e imina–enamina de los compuestos son incluidas en la invención. Por lo tanto, por ejemplo, los compuestos de la invención que se conforman a la fórmula:



y sus tautómeros:



son ambos contemplados como estando dentro del alcance de los compuestos de la invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos, ésteres y prodrogas de los compuestos así como también las sales, solvatos y ésteres de las prodrogas), tales como aquellos los cuales pueden existir debido a carbonos asimétricos en diversos sustituyentes, incluyendo formas enantioméricas (las cuales pueden existir incluso en ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros, y formas diastereoméricas, son contemplados dentro del alcance de esta invención, como lo son los isómeros posicionales (tales como, por ejemplo, 4–piridilo y 3–piridilo). (Por ejemplo, si un compuesto de la invención incorpora un enlace doble o un anillo fusionado, tanto las formas cis– como trans–, así como también las mezclas, son abarcadas dentro del alcance de la invención. Asimismo, por ejemplo, todas las formas de ceto–enol e imina–enamina de los compuestos son incluidas en la invención).

Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, estar sustancialmente libres de otros isómeros, o pueden

estar mezclados, por ejemplo, como racematos o con todos los otros estereoisómeros u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R según lo definido por the *IUPAC* 1974 Recommendations. El uso de los términos "sal", "solvato", "éster", "prodroga" y similares, tiene el propósito de ser aplicable igualmente a la sal, solvato, éster y prodroga de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o prodrogas de los compuestos inventivos.

La presente invención también abarca compuestos isotópicamente rotulados de los compuestos de la presente invención los cuales son idénticos a aquellos mencionados en esta invención, salvo por el hecho de que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa generalmente encontrado en la naturaleza. Los ejemplos de isótopos que pueden ser incorporados en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente.

Ciertos compuestos isotópicamente rotulados de la invención (por ej., aquellos rotulados con ^{3}H y ^{14}C) son útiles en ensayos de distribución de tejido de sustrato y/o compuesto. Los isótopos tritiados (es decir, ^{3}H) y carbono–14 (es decir, ^{14}C) son particularmente preferidos por su facilidad de preparación y detectabilidad. Adicionalmente, la sustitución con isótopos más pesados tales como deuterio (es decir, ^{2}H o D) puede proporcionar ciertas ventajas terapéuticas que son el resultado de la mayor estabilidad metabólica (por ej., mayor vida media in vivo o requerimientos reducidos de dosificación) y, por ende, pueden ser preferidos en ciertas circunstancias. Los compuestos isotópicamente rotulados de la invención pueden ser generalmente preparados siguiendo procedimientos análogos a aquellos descritos en los Esquemas y/o en los Ejemplos que aparecen más adelante, sustituyendo un reactivo isotópicamente rotulado apropiado por un reactivo no isotópicamente rotulado. Los ejemplos no limitativos de compuestos deuterados de la invención son descritos en la presente más adelante.

Las formas polimórficas de los compuestos de la invención, y de las sales, solvatos, ésteres y prodrogas de los compuestos de la invención, tienen el propósito de ser incluidas en la presente invención.

Las dosis adecuadas para administrar los compuestos de la invención a pacientes pueden ser determinadas fácilmente por los expertos en la técnica, por ej., por un médico interviniente, farmacéutico, y otra persona experimentada, y pueden variar de acuerdo con la salud, edad, peso, del paciente, frecuencia de administración, uso con otros ingredientes activos, y/o indicación para la cual se administran los compuestos. Las dosis pueden oscilar entre aproximadamente 0,001 y 500 mg/kg de peso corporal/ día del compuesto de la invención. En una realización, la dosificación es entre aproximadamente 0,01 y aproximadamente 25 mg/kg de peso corporal/ día de un compuesto de la invención, o una sal o solvato farmacéuticamente aceptable de dicho compuesto. En otra realización, la cantidad de compuesto activo en una dosis unitaria de preparación puede variar o ajustarse entre aproximadamente 1 mg y aproximadamente 100 mg, preferentemente entre aproximadamente 1 mg y aproximadamente 50 mg, más preferentemente entre aproximadamente 1 mg y aproximadamente 25 mg, de acuerdo con la aplicación en particular. En otra realización, un régimen de dosificación diaria recomendado típico para la administración oral puede oscilar entre aproximadamente 1 mg/día y aproximadamente 500 mg/día, preferentemente 1 mg/día y 200 mg/día, en dos a cuatro dosis divididas.

Según lo descrito anteriormente, la cantidad y frecuencia de administración de los compuestos de la invención y/o sus sales farmacéuticas aceptables serán reguladas de acuerdo con el criterio del clínico interviniente considerando factores tales como la edad, condición y tamaño del paciente así como también la severidad de los síntomas que se están tratando.

Cuando se emplean en combinación con uno o más agentes terapéuticos adicionales, los compuestos de esta invención pueden ser administrados en forma conjunta o en forma consecutiva. Cuando se administran en forma consecutiva, los compuestos de la invención pueden ser administrados antes o después de uno

o más agentes terapéuticos adicionales, según lo determinado por aquellos expertos en la técnica o según la preferencia del paciente.

Si se formulan como una dosis fija, dichos productos de combinación emplean los compuestos de esta invención dentro del rango de dosificación descrito en esta invención y el otro agente farmacéuticamente activo o tratamiento dentro de su rango de dosificación.

Por lo tanto, en un aspecto, esta invención incluye combinaciones que comprenden una cantidad de por lo menos un compuesto de la invención, o una sal, solvato, éster o prodroga del mismo farmacéuticamente aceptable, y una cantidad eficaz de uno o más agentes adicionales descritos anteriormente.

Las propiedades farmacológicas de los compuestos de esta invención pueden ser confirmadas mediante una cantidad de ensayos farmacológicos. Ciertos ensayos son ejemplificados en otra parte en este documento.

Para preparar composiciones farmacéuticas a partir de los compuestos descritos por esta invención, los portadores inertes, farmacéuticamente aceptables, pueden ser sólidos o líquidos. Las preparaciones en forma sólida incluyen polvos, tabletas, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y tabletas pueden estar compuestos por entre aproximadamente 5 y aproximadamente 95 por ciento de ingrediente activo. Los portadores sólidos adecuados son conocidos en la técnica, por ej., carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Se pueden emplear tabletas, polvos, sellos y cápsulas como formas de dosificación sólidas adecuadas para la administración oral. Los ejemplos de portadores farmacéuticamente aceptables y métodos de manufactura para diversas composiciones pueden encontrarse en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pensilvania.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. Como un ejemplo puede mencionarse agua o soluciones de agua-propilenglicol para inyección parenteral o adición de edulcorantes y agentes de la opacidad para soluciones, suspensiones y emulsiones orales. Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, las cuales pueden estar en combinación con un portador farmacéuticamente aceptable, tal como un gas comprimido inerte, por ej. nitrógeno.

También se incluyen las preparaciones en forma sólida que tienen el propósito de ser convertidas, brevemente antes del uso, 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 pueden ser administrados por vía transdérmica. Las composiciones transdérmicas pueden adoptar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden ser incluidas en un parche transdérmico del tipo matriz o reservorio según lo convencional en la técnica para este propósito.

Los compuestos de esta invención también pueden ser administrados por vía subcutánea.

En una realización, el compuesto es administrado por vía oral.

En algunas realizaciones, puede ser ventajoso para la preparación farmacéutica que comprende uno o más compuestos de la invención que sea preparada en una forma unitaria de dosificación. En dichas formas, la preparación es subdividida en dosis unitarias con tamaño adecuado que contienen cantidades apropiadas del componente activo, por ej., una cantidad eficaz para lograr el propósito deseado.

EJEMPLOS PREPARATIVOS

Los compuestos de la invención pueden ser preparados utilizando procedimientos conocidos en la técnica. Los siguientes esquemas de reacción muestran procedimientos típicos, aunque los expertos en la técnica reconocerán que también pueden ser adecuados otros procedimientos.

Se puede hacer referencia a las técnicas, solventes y reactivos mediante sus siguientes abreviaturas:

Cromatografía de capa fina: (Thin layer chromatography): TLC

Cromatografía de alto rendimiento (High performance liquid chromatography): HPLC

acetato de etilo: AcOEt o EtOAc

metanol: MeOH

éter o éter dietílico: Et_2O

tetrahidrofurano: THF

Acetonitrilo: MeCN o ACN

1,2–dimetoxietano: DME

ácido trifluoracético: TFA

Dimetilacetamida: DMA

Dimetilformamida: DMF

Sulfóxido de dimetilo: DMSO

trietilamina: Et_3N o TEA

terc–Butoxicarbonilo: t–Boc o Boc

2–(Trimetilsilil)etoxicarbonilo: Teoc

cromatografía líquida espectrometría de masas (liquid chromatography mass spectrometry): LCMS

mililitros: mL

milimoles: mmol

micromoles : µmol

microlitros: µl

gramos: g

miligramos: mg

N–yodosuccinimida: NIS

temperatura ambiente (aproximadamente 25ºC): t.a. (o TA)

Tiempo de retención: t_R

N–bromosuccinimida: NBS

Bromuro de metilmagnesio: MeMgBr

acetilacetonato de hierro (III): $Fe(acac)_3$

Difenilfosforil azida: DPPA

Clorhidrato de 1–(3–dimetilaminopropil)–3–etilcarbodiimida: EDCI

Diisopropiletilamina: DIEA o iPr_2NEt

Diisopropilamina: iPr_2NH

2–(Trimetilsilil)etanol: TMSetanol

ácido 3–cloroperoxibenzoico: mCPBA

n–Butilitio: nBuLi

diisopropilamida de litio: LDA

[1,1'Bis(difenilfosfino)ferroceno]di–cloropaladio(II): $PdCl_2dppf$

Acetato de paladio(II): $Pd(OAc)_2$

Cloruro de metansulfonilo: $MeSO_2Cl$

Bencilol: Bn

4–metoxi bencilo: PMB

Fenilo: Ph

Etanol: EtOH

Litro: L

Minutos: min

Fase inversa (Reverse phase): RP

Hexanos: Hex

Cloruro de Metileno: DCM

ácido acético: HOAc o AcOH

Saturado: Sat (o sat)

Cloruro de bis(2–oxo–3–oxazolidinil) fosfínico: BOPCl

4–(dimetilamino)piridina: DMAP

Molar: M

2–((trimetilsilil)etoxi)metilo: SEM

Diisopropil azodicarboxilato: DIAD

Trietilborano: Et_3B

Tris(dibencilidenacetona)dipaladio(0): Pd_2dba_3

Piridina: Pir

(2–Bifenil)di–*ter*–butilfosfina: John–Phos

2–diciclohexilfosfino–2',4',6'–triisopropil bifenilo: X–Phos

Hexafluorfosfato de 2–(1H–7–azabenzotriazol–1–il)–1,1,3,3–tetrametiluronio: HATU

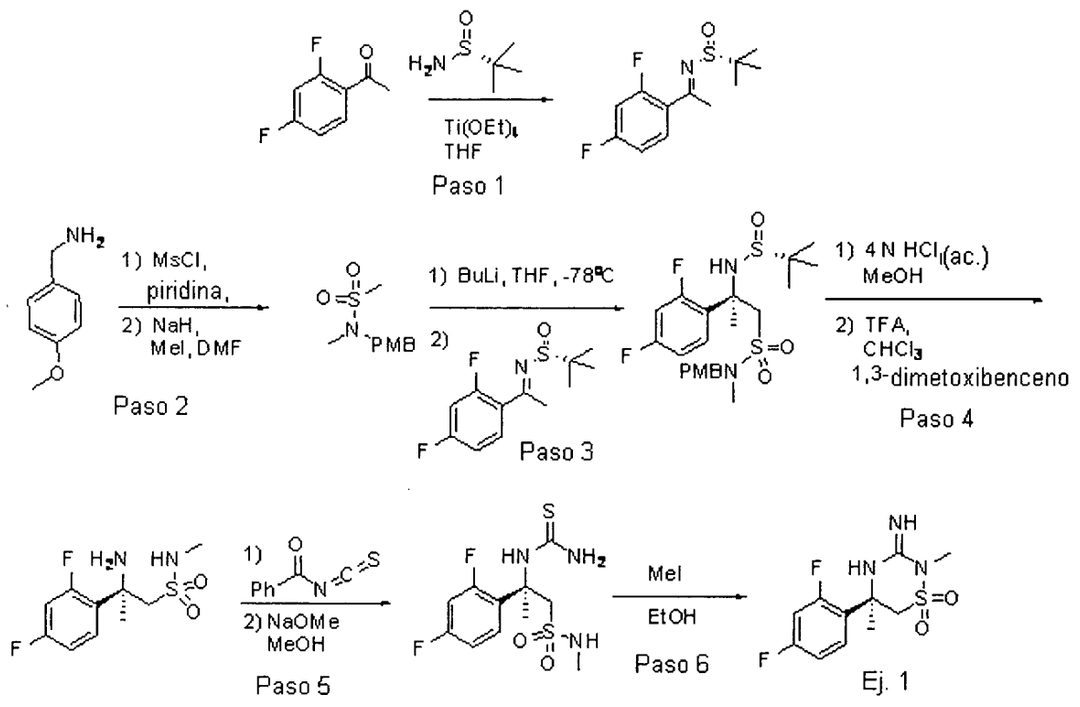
Concentrado: conc.

Fluoruro de tetrabutilamonio: TBAF

168

2–Diciclohexilfosfino–2',6'–diisopropoxi–1,1'–bifenilo: RuPhos	Tetrakis(trifenilfosfina)paladio: $Pd(PPh_3)_4$

Esquema 1a



Paso 1: A una solución de 2,4–difluoracetofenona (15,0 g, 96 mmol) en THF (100 mL) se agregó (R)–2–metil–2–propansulfinamida (12,8 g, 106 mmol) y $Ti(OEt)_4$, (32,0 g, 120 mmol). La solución resultante se calentó hasta reflujo durante la noche. Después de ese tiempo, la solución se enfrió hasta TA y se vertió sobre hielo. A esta mezcla se agregó CH_2Cl_2 y la mezcla resultante se agitó a TA durante 10 min. Luego, la mezcla se filtró a través de Celite. La torta de filtro se lavó con CH_2Cl_2. Las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante cromatografía

flash (SiO_2: elución de gradiente 100:0 a 45:55 hexanos:EtOAc) para dar la ketimina (12,3 g).

Paso 2: A una solución agitada de 4–metoxibencilamina (198,9 g, 1,45 mol) en piridina anhidra (400 mL) a 0°C se agregó por goteo por medio de embudo de adición cloruro de metansulfonilo (116 mL, 1,45 mol) durante 45 min. Luego de completada la adición, se extrajo el baño de enfriamiento y la solución resultante se agitó a TA durante la noche. La reacción se concentró *in vacuo* (baño de agua 60–65°C) para extraer la mayor parte de la piridina. El residuo se absorbió en CH_2Cl_2 (1 L). La solución orgánica se lavó con $HCl_{(ac.)}$ 1 N (2 x 1 L), $NaHCO_3$ (ac) sat. (2 x 1 L) y salmuera (1 x 500 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró para proporcionar un sólido en bruto. Este sólido se disolvió en 95% EtOH (430 mL) empleando un baño de vapor para calentar la solución. La solución se dejó enfriar, haciendo que el producto precipitara de solución. El producto se extrajo por filtración y el sólido se lavó con EtOH frío (3 x 150 mL). Se obtuvo un segundo cultivo después de dejar el licor madre en agitación a TA durante la noche. El rendimiento general del producto fue 246,5 g (79% de rendimiento).

Este producto se disolvió en DMF anhidro (3,0 L), se enfrió hasta 0°C y se colocó bajo una atmósfera de N_2. A esta solución se le agregó en pequeñas porciones hidruro sódico (60% en aceite mineral, 60,2 g, 1,51 mol, 1,3 eq.). Después de completada la adición, la mezcla se agitó durante 10 min. adicionales. A esta mezcla se le agregó por goteo por medio de un embudo de adición yoduro de metilo (250 g, 1,76 mol, 1,5 eq.). Luego de completada la adición, el baño de enfriamiento se extrajo y la mezcla se dejó agitando a TA durante la noche. Luego, la mezcla se concentró *in vacuo* (p = 10 torr, temp del baño = 55–60°C) para extraer cerca de 2,5 L de DMF. Algunos sólidos precipitaron de la solución. La mezcla remanente se repartió entre agua helada 5 L, 5 L de Et_2O y 500 mL de EtOAc. La capa orgánica se separó. La capa acuosa se extrajo con Et_2O (2 x 1 L). Las capas orgánicas combinadas se lavaron con salmuera (2 x 1 L), se secaron sobre Na_2SO_4, se filtraron y concentraron. El sólido se agitó con hexanos empleando una cuchilla de agitación de alambre para pulverizar el sólido. El sólido

fue extraido mediante filtración y lavado con hexanos (2 x 250 mL). El sólido se disolvió en hexanos/EtOAc (1:1, 450 mL) empleando un baño de vapor para calentar la mezcla. Se formó un precipitado blancuzco con el enfriamiento y se separó por filtración (182 g). El licor madre remanente se purificó mediante cromatografía flash (SiO_2: 1:1 hexanos:EtOAc) para dar producto adicional (51,8 g) para un rendimiento general de 233,8g (89% de rendimiento).

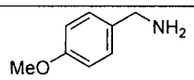
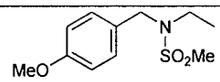
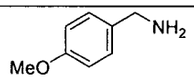
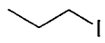
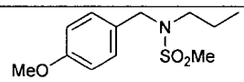
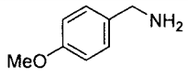
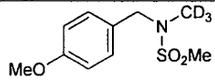
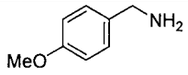
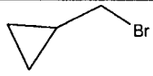
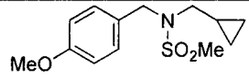
Paso 3: A una solución de la sulfonamida del paso 2 (4,18 g, 18,2 mmol) en THF anhidro (50 mL) a –78°C bajo una atmósfera de N_2 se le agregó por goteo una solución de *n*–BuLi (1,6 M en hexanos, 11,4 mL, 18,2 mmol). La solución resultante se agitó a –78°C durante 30 min. Luego de ese tiempo, una solución de la ketimina del paso 1 (3,15 g, 12,1 mmol) en THF (50 mL) preenfriada hasta –78°C en un frasco de fondo redondo separado se transfirió por medio de una cánula a la solución antes mencionada. La solución resultante se agitó a –78°C durante 3,5 horas. Se agregó agua y la mezcla se dejó calentar hasta TA. La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 40:60 hexanos:EtOAc) para proporcionar la sulfinamida (3,95 g, 67% de rendimiento).

Paso 4: A una solución de la sulfinamida del paso 3 (3,80 g, 7,6 mmol) en CH_2Cl_2/MeOH (3:1 80 mL) se agregó una solución de 4 M HCl $_{(dioxano)}$ (11,4 mL, 45,4 mmol). La solución resultante se agitó a TA durante 1,5 horas. La solución se concentró. El residuo se reconcentró a partir de tolueno (1x). El residuo se absorbió en $CHCl_3$ y TFA (26 mL, 1:1). A esta solución se le agregó 1,3–dimetoxibenceno (6,5 mL, 50 mmol). La solución resultante se agitó a TA durante la noche. La solución resultante se concentró. El aceite resultante se repartió entre Et_2O y 1 M HCl $_{(ac.)}$. La capa acuosa se extrajo con Et_2O (2x). Luego, la capa acuosa se ajustó hasta pH 10 con la adición de Na_2CO_3 sat. $_{(ac.)}$. La capa acuosa se extrajo con CH_2Cl_2 (3x). Las capas orgánicas se extrajeron de la capa acuosa básica, se combinaron, se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar la amina (1,88 g, 85%).

Paso 5: A una solución de la amina del paso 4 (1,80 g, 6,8 mmol) en CH_2Cl_2 (30 mL) se agregó isotiocianato de benzoílo (1,01 mL, 7,49 mmol). La solución resultante se agitó a TA durante la noche. Luego, la solución se concentró. El residuo se redisolvió en MeOH (20 mL). A esta solución se le agregó una solución de NaOMe en MeOH (25%, 3,9 mL). La solución resultante se agitó a TA durante 45 min. La solución se concentró *in vacuo*. Luego, el residuo se repartió entre CH_2Cl_2 y agua. El pH de la capa acuosa se ajustó hasta casi 11 con la adición de $NaHCO_3$ (ac.). La capa acuosa se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar la tiourea (1,90 g, 86%).

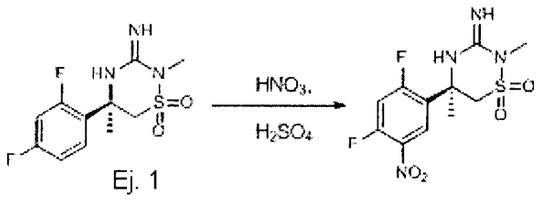
Paso 6: A la tiourea del paso 5 (1,90 g, 5,88 mmol) en EtOH (40 mL) se le agregó yoduro de metilo (0,42 mL, 6,7 mmol). La solución resultante se calentó hasta reflujo durante 3 horas. La solución se enfrió hasta TA y se concentró *in vacuo*. El residuo se repartió entre EtOAc y $Na_2CO_{3\ (ac.)}$. La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 92:8 CH_2Cl_2:MeOH) para proporcionar **Ej. 1** (1,12 g, 66% de rendimiento). LCMS (condiciones D): t_R = 1,73 min, *m/e* = 290,2 (M+H).

Tabla I: Las siguientes sulfonamidas se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 1a paso 2.

Entrada	Amina	Haluro de alquilo	sulfonamida
1			
2			
3*		CD_3I	
4*			

* Se utilizó carbonato de cesio como la base en lugar de NaH para las entradas 3 y 4.

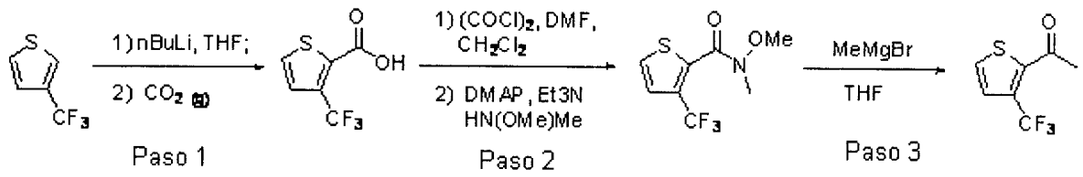
Esquema 1b:



Ej. 1

Paso 1: A una mezcla de **Ej. 1** (8,00 g, 28,0 mmol) y ácido sulfúrico concentrado (16 mL) se le agregó ácido nítrico humeante (2,24 mL) a 0°C. La mezcla de reacción se agitó desde 0ºC hasta temperatura ambiente durante 2 h. Después de este tiempo, la mezcla de reacción se basificó con carbonato sódico hasta pH 10 y se extrajo con acetato de etilo (2 × 200 mL). Los extractos combinados se secaron sobre Na_2SO_4 anhidro, se filtraron y concentraron bajo presión reducida para proporcionar el compuesto nitro (8,81 g, 94%).

Esquema 2:



Paso 1 Paso 2 Paso 3

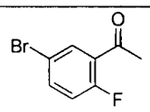
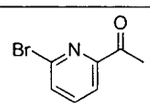
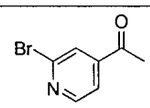
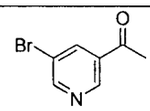
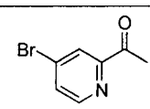
Paso 1: A una solución de 3–trifluormetil tiofeno (3,75g, 24,6 mmol) en THF anhidro (60 mL) a –78°C se agregó una solución de n–BuLi (2,5 M en hexanos, 13 mL, 32,5 mmol). La solución resultante se agitó a –78°C durante 10 min. A la solución se le introdujo burbujas de $CO_{2\ (g)}$ durante 20 min a –78°C. La solución se dejó calentar hasta TA y se agitó durante 40 min. más a TA mientras se introducían burbujas de $CO_{2\ (g)}$ a través de la solución. Luego de ese tiempo,se agregó $HCl_{\ (ac.)}$ 1 M a la solución. La capa acuosa se extrajo luego con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y concentró. El producto en bruto se purificó mediante cromatografía flash (SiO_2: 85:15:1 CH_2Cl_2:MeOH:AcOH) para proporcionar el ácido carboxílico (4,33 g, 90%).

Paso 2: A una solución de una porción del ácido del paso 1 (465 mg, 2,37 mmol) en CH_2Cl_2 (12 mL) y DMF (0,20 mL) a 0°C se agregó por goteo una solución de cloruro de oxalilo (2 M en CH_2Cl_2, 3,5 mL, 3 eq.). La solución resultante se agitó a 0°C durante 15 min seguido por 1 hora adicional a TA. La solución se concentró. Al residuo se le agregó clorhidrato de N,O–dimetilhidroxilamina (470 mg, 2 eq.) seguido por CH_2Cl_2 (18 mL). La mezcla resultante se enfrió hasta 0°C. A esta mezcla se le agregó Et_3N (1,4 mL) y DMAP (10 mg). La solución se agitó a 0°C durante 1 hora. A la solución se le agregó $HCl_{(ac.)}$ 1 M (60 mL) y CH_2Cl_2 (60 mL). Las capas se separaron. La capa orgánica se lavó con salmuera, se secó y concentró. El residuo en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 60:40 heptano:EtOAc) para proporcionar la amida (426 mg, 75%).

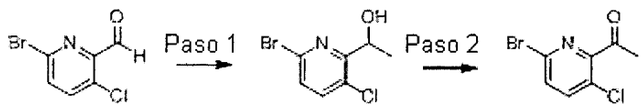
Paso 3: A una solución de la amida del paso 2 (4,10 g, 17,1 mmol) en THF (70 mL) a 0°C se le agregó lentamente una solución de bromuro de metilmagnesio (3 M en Et_2O, 7 mL). La solución resultante se agitó a 0°C durante 3 horas. Luego de

ese tiempo, se agregó HCl $_{(ac.)}$ 1 M. Luego, la mezcla se extrajo con Et_2O. La capa orgánica se secó, se filtró y concentró. El residuo se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 60:40 pentano:EtOAc) para proporcionar la cetona (3,22 g, 97%) en forma de un aceite incoloro.

Tabla Ib: Las siguientes cetonas se prepararon utilizando procedimientos similares a aquel descrito en el Esquema 2, Pasos 2 y 3 utilizando los ácidos carboxílicos apropiados.

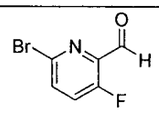
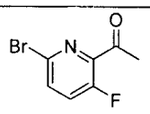
Esquema 2b:



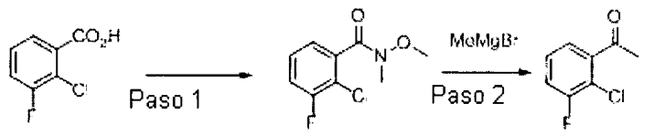
Paso 1: A una solución de 6–bromo–3–cloropicolinaldehído (10,0 g, 45,45 mmol) en 200 mL THF agitación a –78°C bajo N_2 se agregó lentamente bromuro de metilmagnesio (3,0 M en éter dietílico, 16,63 mL, 50 mmol). La reacción se agitó a esta temperatura durante 3 horas, y luego se agregó cloruro de amonio saturado. La mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y concentraron *in vacuo*. El residuo se purificó mediante cromatografía en gel de sílice (0–10% EtOAc/hexanos durante 20 minutos) para proporcionar 1–(6–bromo–3–cloropiridin–2–il)etanol (8,4 g, 78%).

Paso 2: El material preparado anteriormente (8,4 g, 35,5 mmol) se agitó durante la noche a temperatura ambiente en 100 mL de DCM junto con clorocromiato de piridinio (15 g, 71 mmol) y aproximadamente 5 g de celite. La reacción se filtró a través de celite y se lavó con DCM. El filtrado se concentró hasta sequedad *in vacuo* y el residuo se purificó mediante cromatografía en gel de sílice (0–10% EtOAc/hexanos durante 22 minutos) para proporcionar 1–(6–bromo–3–cloropiridin–2–il)etanona (6,85 g, 82%).

Tabla Ic: La siguiente cetona se preparó utilizando métodos similares a aquellos descritos en el Esquema 2b:

Entrada	Aldehído	Cetona
1		

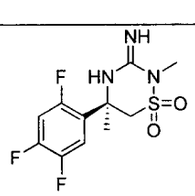
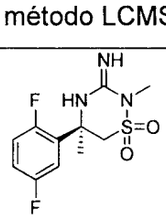
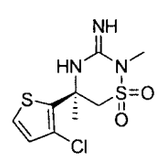
Esquema 2c:

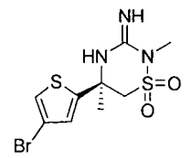
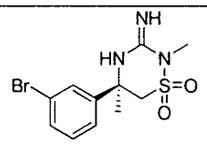
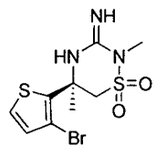
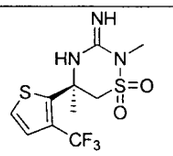
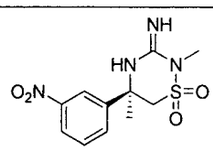
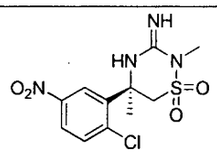
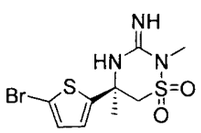
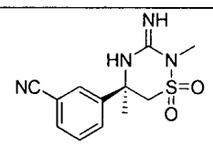
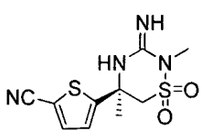
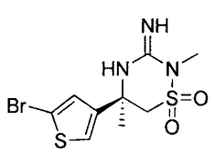
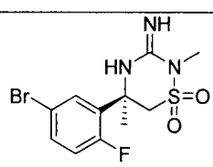
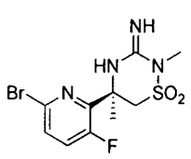
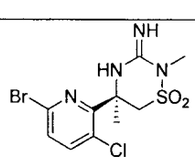
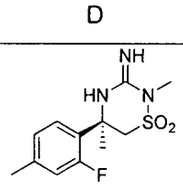


Paso 1: A una solución de ácido 2–cloro–3–fluorbenzoico (30 g, 172 mmol) en 300 mL de DCM se agregó carbonildiimidazol (CDI) (32,0 g, 198 mmol) en porciones. Después de la adición y luego agitación a TA durante 1 h, se agregó sal N,O–dimetilhidroxilamina HCl (18,5 g, 189 mmol) en la mezcla seguido por Et_3N (20 mL). La mezcla se agitó a TA durante la noche. Después la reacción se templó con agua, la capa acuosa se extrajo con DCM (2x). Las capas orgánicas se lavaron con HCl (ac) 2N, agua, $NaHCO_3$ (ac.) sat. y salmuera. La solución se secó ($MgSO_4$) y concentró. El producto 2–cloro–3–fluor–N–metoxi–N–metilbenzamida (32,0 g) se obtuvo mediante cromatografía en gel de sílice (elución con 0–30% EtOAc/Hex).

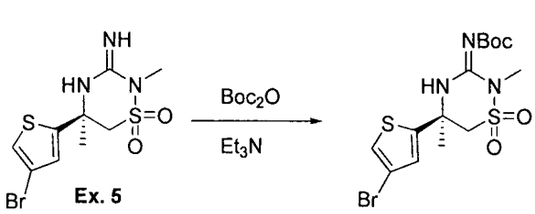
Paso 2: El material antes mencionado se trató de acuerdo con el Esquema 2, Paso 3 para proporcionar el producto cetona (89% de rendimiento).

Tabla II: Los siguientes ejemplos se prepararon empleando procedimientos similares a aquel descrito en el Esquema 1a empleando los materiales de partida apropiados.

Ejemplos (Datos de LCMS enlistados con cada compuesto: MH^+ observado, tiempo de retención de HPLC y método LCMS)					
2	 MH^+: 308.2, 1.64 min, D	**3**	 MH^+: 290.0, 1.99 min, B	**4**	 MH^+: 294.2, 1.43 min, A

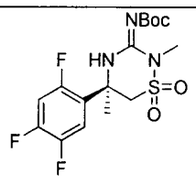
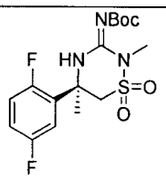
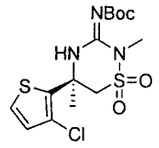
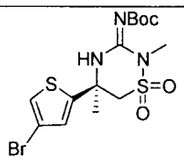
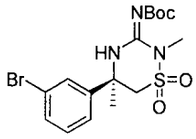
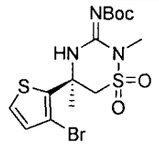
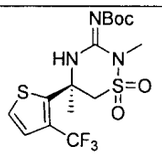
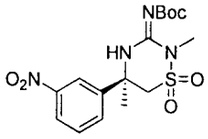
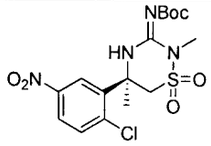
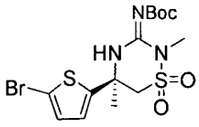
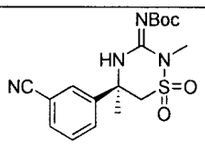
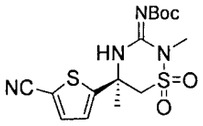
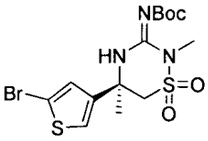
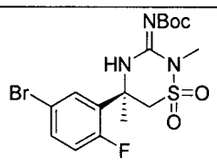
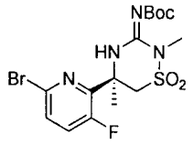
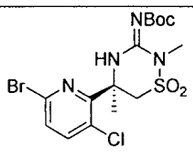
5	 MH^+: 340.2, 2.64 min, A	**6**	 MH^+: 331.9, 1.95 min, B	**7**	 MH^+: 340.2, 2.19 min, A
8		**9**		**10**	
11	 MH^+: 339.8, 1.87 min, A	**12**	 MH^+: 278.9, 1.73 min, B	**13**	 MH^+: 285.0, 1.54 min, B
14	 MH^+: 340.2, 2.44 min, A	**14a**	 MH^+: 350.0, 1.72 min, D	**14b**	
14c		**14d**			

Esquema 3:



A una solución de **Ej. 5** (1,60 g, 5,53 mmol) en CH_2Cl_2 se le agregó Boc_2O (1,24 g, 5,68 mmol) y Et_3N (0,82 mL, 5,91 mmol). La solución resultante se agitó a TA durante la noche. La solución se lavó con $NaHCO_{3\ (ac.)}$ 1/2 saturado. La capa acuosa se retroextrajo con CH_2Cl_2 (2x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 70:30 hexanos:EtOAc) para proporcionar el *terc*–butil carbamato (1,74 g, 84% de rendimiento).

Tabla IIb: Los siguientes carbamatos se prepararon empleando procedimientos similares a aquel descrito en el Esquema 3 empleando los materiales de partida apropiados.

Entradas					
1		**2**		**3**	
4		**5**		**6**	
7		**8**		**9**	
10		**11**		**12**	
13		**14**		**15**	
16					

5

Tabla IIc: El siguiente ejemplo se preparó empleando un procedimiento similar a aquel descrito en el Esquema 1b, empleando el siguiente perfil de temperatura modificado: adición de ácido nítrico a –40 grados C, luego calentando hasta 0 grados C.

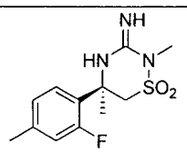
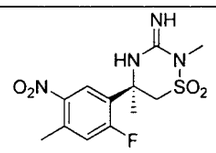
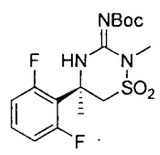
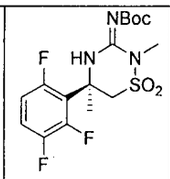
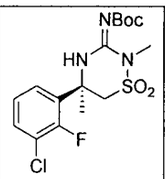
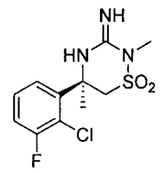
Ejemplo	Material de partida	Producto
14e	 Ejemplo 14d	

Tabla IId: Los siguientes dióxidos de tiadiazina se prepararon de acuerdo con métodos similares a aquellos en los Esquemas 1a y 3, con las excepciones señaladas:

Entradas							
1[a,b]		**2**[a,b]		**3**[c]		**Ej. 14f**[d, e]	

a: (S)–2–Metil–2–propansulfinamida se empleó en el Paso 1 Esquema 1a en lugar de (R)–2–metil–2–propansulfinamida.

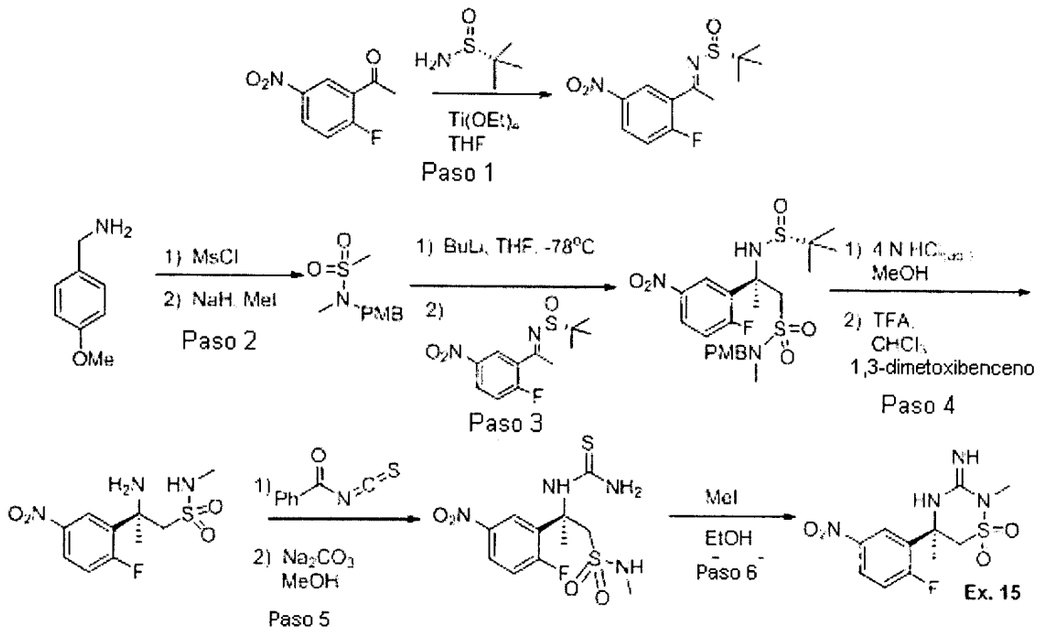
b: La recristalización a partir de 95% MeOH / 5% agua se empleó para eliminar un producto diastereomérico después de la purificación en gel de sílice en el Paso 3 Esquema 1a.

c: cromatografía SFC (TharSFC80, Chiralpak OD–H, 50 x 250 mm, 5 μm, 150 bar con 30% iPrOH, 250 g/min, 40 °C) empleada para eliminar un producto diastereomérico después de purificación en gel de sílice en el Paso 3 Esquema 1a.

d: cromatografía SFC (TharSFC80, Chiralpak OJ–H, 50 x 250 mm, 5 μm, 150 bar con 25% iPrOH, 250 g/min, 40 °C) empleada para eliminar un producto diastereomérico después de purificación en gel de sílice en el Paso 3 Esquema 1a.

e: El producto del Esquema 1a Paso 4 se trató de acuerdo con el Esquema 3b para proporcionar el Ejemplo 14f directamente, en lugar de empleando el Esquema 1a, Pasos 5 y 6.

Esquema 3a:



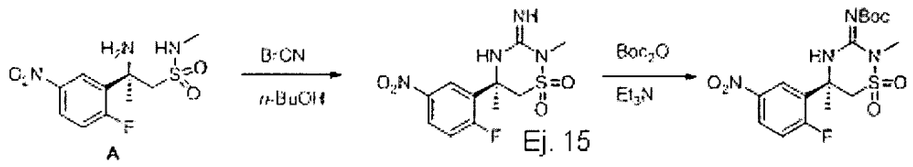
Pasos 1–4: Estos pasos se llevaron a cabo empleando procedimientos similares a aquellos descritos en los pasos 1–4 del Esquema 1a.

Paso 5: A una solución de la amina del paso 4 (10,5 g, 36 mmol) en CH_2Cl_2 (200 mL) se le agregó isotiocianato de benzoílo (4,3 mL, 1,1 eq.). La solución resultante se agitó a TA durante 2,5 días. Se agregó más isotiocianato de benzoílo (0,86 mL, 0,2 eq.) y la solución se agitó a TA durante 2 horas más. Luego, la solución se concentró *in vacuo*.

Se disolvió una porción de este material (6,5 g, ~14 mmol) en MeOH (200 mL). A esta solución se agregó $Na_2CO_{3\,(s)}$ (1,52 g, 14 mmol). La mezcla resultante se agitó a TA durante 45 min. Luego de ese tiempo, se agregó un ligero exceso de HOAc a la solución. Luego, la mezcla se concentró. El residuo se repartió entre CH_2Cl_2 y $NaHCO_{3\,(ac.)}$ ½ sat. La capa acuosa se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. La tiourea (~ 4,9 g) se empleó en la siguiente reacción sin más purificación.

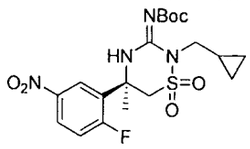
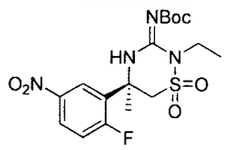
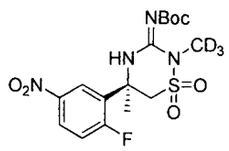
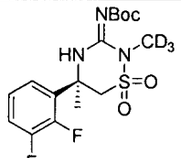
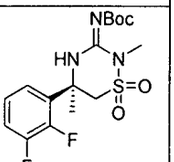
Paso 6: El **Ejemplo 15** se preparó empleando un método similar a aquel descrito en el Esquema 1a paso 6.

Esquema 3b:

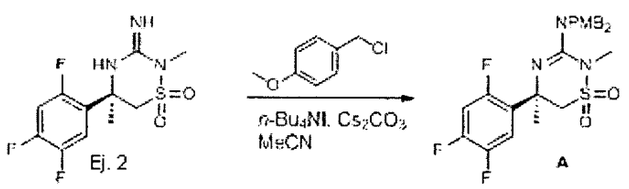


A una suspensión de la amina **A** (Esquema 3a paso 4) (13,7 gramos) en n–butanol (150 mL) se agregó una solución de bromuro de cianógeno (5M en MeCN). La mezcla resultante se calentó hasta reflujo durante 4 horas. La mezcla se concentró hasta 1/3 del volumen original. A la mezcla se le agregó Et_2O (200 mL). El sólido resultante se eliminó por filtración y el sólido se lavó con Et_2O (2x). El sólido se repartió entre EtOAc y Na_2CO_3 (ac.) sat.. La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar 10,6 gramos de **Ej. 15**. Este material se convirtió en el t–butilcarbamato empleando un procedimiento similar a aquel descrito en el Esquema 3.

Tabla IIe: Los siguientes dióxidos de tiadiazina se prepararon empleando procedimientos similares a aquellos descritos en los Esquemas 3a (entrada 1), 3b (entradas 2–5) y 3 empleando las sulfonamidas mostradas en la Tabla I y en el Esquema 1a.

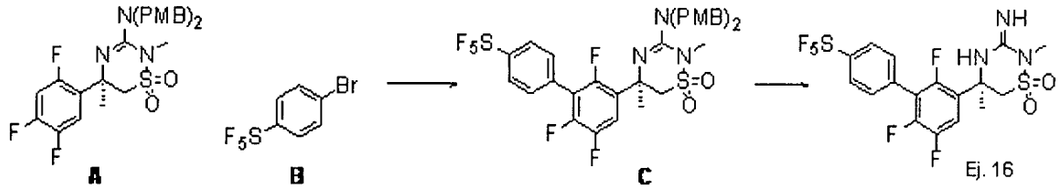
Entrada				
				
1	**2**	**3**	**4**	**5**

Esquema 4:



A una solución de **Ej. 2** (3,8 g, 12,2 mmol) en MeCN (40 mL) se le agregó cloruro de 4–metoxibencilo (4,6 g, 29 mmol), Cs_2CO_3 (9,9 g, 31 mmol) y n–Bu_4NI (450 mg, 1,2 mmol). La mezcla resultante se calentó hasta reflujo durante 16 horas. Luego de ese tiempo, se agregaron cloruro de 4–metoxibencilo adicional (1,9 g, 12 mmol) y Cs_2CO_3 (4,4 g, 12 mmol) y la mezcla se calentó hasta reflujo durante 4 horas más. Luego, la mezcla se concentró *in vacuo* a TA. El residuo se repartió entre agua y CH_2Cl_2. La capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El residuo en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 80:20 hexanos:EtOAc) para proporcionar el compuesto bis–PMB **A** (4,9 g, 73%).

Esquema 5:

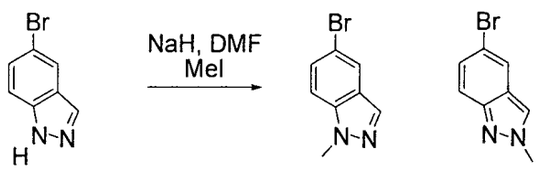


Un recipiente de microondas de 20 mL se secó a la llama y se enfrió bajo vacío, luego de cargó nuevamente con N_2, seguido por dos ciclos de vacío /N_2 retrocarga. Se agregó NaHMDS (1 M en THF, 2,2 mL, 2,2 mmol) a una solución de dióxido de tiadiazina **A** ((Esquema 4) 547 mg, 1,0 mmol) en dioxano (5 mL) a TA, y se agitó durante 30 min. Se agregó una solución recientemente preparada de $ZnCl_2$ (1,2 M en THF, 2,0 mL, 2,4 mmol), y la agitación continuó durante 30 min a TA. Se agregaron $Pd(OAc)_2$ (45 mg, 0,2 mmol), X–Phos (190 mg, 0,4 mmol) y bromuro de arilo **B** (509 mg 1,80 mmol) y la mezcla de reacción se desgasificó (4 x vacío/N_2), se tapó y colocó en un baño de aceite precalentado a 100°C durante 3h. La reacción se bruto se enfrió hasta TA, se diluyó con EtOAc/agua, se filtró a través de una almohadilla de celite, y la capa acuosa se extrajo con EtOAc (2x). Las capas orgánicas combinadas se lavaron con salmuera (1x), se secaron sobre

Na_2SO_4, se filtraron y concentraron bajo presión reducida para dar un residuo en bruto el cual fue sometido a cromatografía en gel de sílice (0→30 % EtOAc/hexanos) seguido por condiciones de RP–HPLC (monitoreo a 220 nm) para proporcionar el compuesto intermedio **C** (73 mg, 97 umol).

Una solución del compuesto intermedio **C** (73 mg, 97 umol) en CH_3CN (4 mL) se calentó hasta 75°C, y se agregó una solución de K_2HPO_4 (26 mg, 147 umol), KH_2PO_4 (20 mg, 147 umol) y $K_2S_2O_8$ (158 mg, 588 umol) en agua (2 mL) por pipeta. Después de 60 min a 75°C, la mezcla de reacción se enfrió hasta TA y se concentró bajo vacío. El residuo se sometió a condiciones de RP–HPLC para proporcionar el **Ej. 16** (sal TFA, 26 mg). Datos LCMS: (método D): t_R = 2,17 min, *m/e* = 510,0 (M+H).

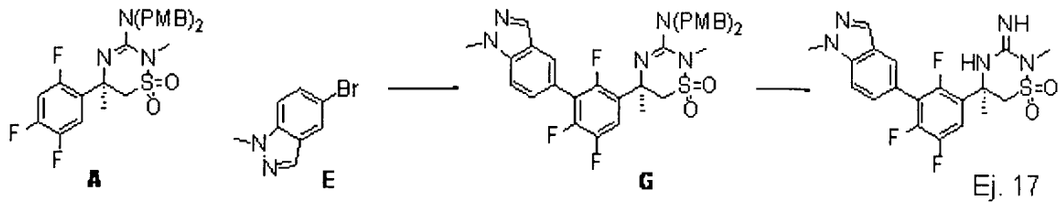
Esquema 6a:



D **E** R = Me **F**

Se agregó hidruro de sodio (60% en aceite, 1,5 g, 37,5 mmol) a una solución de 5–bromoindazol **D** (6 g, 30,6 mmol) en DMF (60 mL) a TA. Después de agitación durante 30 min, se agregó yoduro de metilo (2,83 mL, 45,9 mmol) y la reacción se agitó durante otras 2 h a TA. La reacción se templó con $NaHCO_3$ (ac) sat., se extrajo con EtOAc (1x), se secó sobre $MgSO_4$, se filtró y concentró bajo presión reducida para dar una mezcla de 5–bromoindazoles *N*–1 y *N*–2 metilado **E** y **F**, los cuales se separaron mediante cromatografía en gel de sílice empleando 0→30 % EtOAc/hexanos.

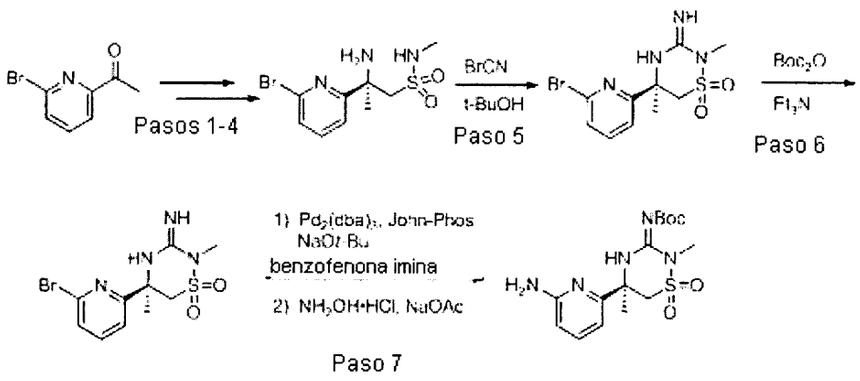
Esquema 6b:



Ej. 17

Ejemplo 17 se preparó según lo descrito para el ejemplo **16** en el Esquema 5, sustituyendo el bromuro de arilo **E** por **B**. Datos de LCMS: (método C): t_R = 3,12 min, *m/e* = 438,2 (M+H).

Esquema 7a:



Pasos 1–4: Estos pasos se llevaron a cabo empleando procedimientos similares a aquellos descritos en los pasos 1–4 del Esquema 1a.

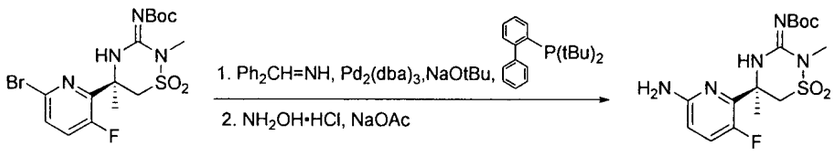
Paso 5: Este paso se llevó a cabo empleando un procedimiento similar a aquel descrito en el Esquema 3b excepto que se empleó *t*–BuOH como el solvente en lugar de n–BuOH.

Paso 6: Se introdujo el *t*–butil carbamato utilizando un procedimiento similar a aquel descrito en el Esquema 3.

Paso 7: Una mezcla del bromuro (3,00 g, 6,92 mmol), benzofenona imina (1,39 mL, 8,30 mmol), $Pd_2(dba)_3$ (0,634 g, 0,692 mmol), John–Phos (0,413 g, 1,38 mmol), terc-butóxido de sodio (2,13 g, 22,1 mmol), y tolueno (51 mL) se desgasificó (vacío/N_2). Luego, la mezcla se agitó a 65°C bajo nitrógeno durante 3 h. Después de este tiempo, la mezcla de reacción se enfrió hasta temperatura ambiente y se filtró a través de una almohadilla de Celite y se enjuagó con acetato de etilo (100 mL). El líquido filtrado se concentró bajo presión reducida. Luego el

residuo se disolvió en metanol (76 mL) y la solución resultante se cargó con clorhidrato de hidroxilamina (2,16 g, 31,1 mmol) y acetato sódico (2,55 g, 31,1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 40 min. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El residuo resultante se disolvió en acetato de etilo (200 mL) y se lavó con bicarbonato sódico acuoso saturado (100 mL), agua (100 mL), y salmuera (100 mL). Luego, la capa orgánica se secó sobre sulfato sódico anhidro, se filtró y concentró bajo presión reducida. El residuo se purificó mediante cromatografía en columna (sílice, 0–100% acetato de etilo /heptano) para proporcionar la amino piridina (0,880 g, 34%) .

Esquema 7b:



A un frasco secado a la llama se agregó un bromuro de piridilo (Tabla IIb, Entrada 15, 1,5 g, 3,3 mmol), $Pd_2(dba)_3$ (305 mg, 0,3 mmol), (2–bifenil)di–*terc*–butilfosfina (200 mg, 0,7 mmol), terc-butóxido sódico (1,02 g, 0,011 mmol), benzofenona imina (670ul, 4 mmol), y tolueno (21 mL). La mezcla se evacuó bajo vacío y se retro-cargó con N_2 (3X). La mezcla se agitó a 60°C durante 1 h. Luego de filtración a través de celite, el líquido filtrado se concentró. El residuo en bruto se disolvió en 36 mL de metanol, y se agregaron clorhidrato de hidroxil amina (458 mg, 6,6 mmol) y acetato sódico (541 mg, 6,6 mmol). La reacción se agitó durante 35 min y luego se templó con bicarbonato sódico acuoso saturado. La mezcla se extrajo con acetato de etilo, y las porciones orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron. El residuo en bruto se purificó mediante una columna de sílice flash (50% acetato de etilo /hexano) para obtener un producto de aminopiridina (730 mg, 68%).

Tabla IIIa: Las siguientes amino–piridinas se prepararon empleando procedimientos similares a aquellos descritos en el Esquema 7a empleando las cetonas apropiadas de la Tabla Ib.

Entrada

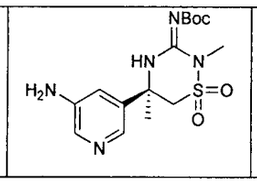
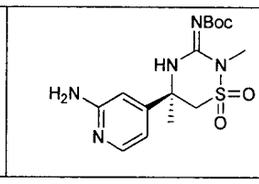
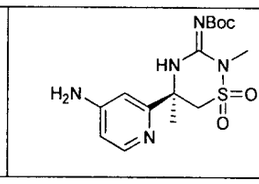
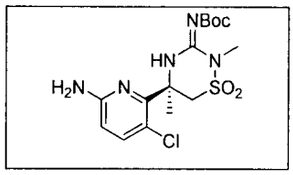
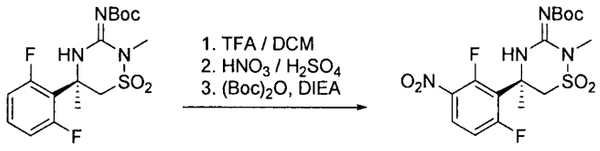
1		2		3	

Tabla IIIb: El siguiente compuesto se preparó a partir del bromuro (Tabla IIb entrada 16) empleando métodos similares a aquellos descritos en el Esquema 7b:



Esquema 7c:



A una solución de una halofeniltiadiazina (Tabla IId, entrada 1: 2,31 g, 5,9 mmol) en 5 mL de DCM se agregó 1 mL de TFA. La mezcla se agitó durante 4 h y luego se concentró. A 0°C, a una solución de este residuo en bruto en 4 mL de ácido sulfúrico se agregó cuidadosamente una mezcla de 0,5 mL de ácido nítrico humeante y 1,2 mL de ácido sulfúrico. La mezcla se agitó a 0 °C durante 2 h y luego se vertió en 150 mL de hielo. La mezcla se neutralizó agregando cuidadosamente solución de bicarbonato sódico saturado e hidróxido sódico sólido. La mezcla resultante se extrajo con acetato de etilo, y las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron. Este residuo en bruto se disolvió en 20 mL de DCM, y se agregaron $(Boc)_2O$ (1,29g, 5,9 mmol), y DIEA (2,56 mL, 14,75 mmol). La reacción se agitó durante la noche, y luego se templó con HCl 1N. La mezcla se extrajo con DCM, las porciones orgánicas se combinaron, se secaron sobre sulfato de magnesio, y se concentraron. El residuo en bruto se purificó mediante una columna de sílice flash (25% de acetato de etilo /hexano) para dar un producto de nitrofenil tiadiazina (1,93 g, 76% de rendimiento).

Tabla IIIc: Los siguientes compuestos se prepararon empleando métodos similares a aquellos descritos en el Esquema 7c comenzando a partir de los materiales de partida apropiados mostrados en la Tabla IIb:

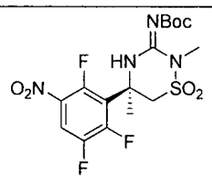
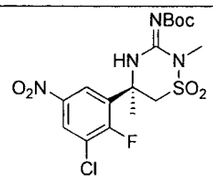
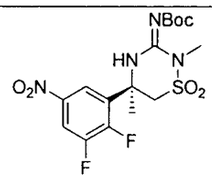
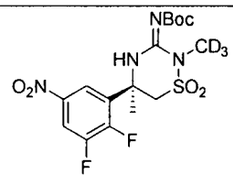
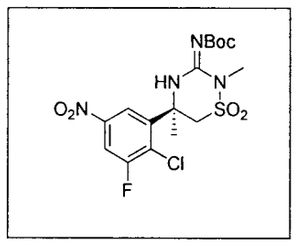
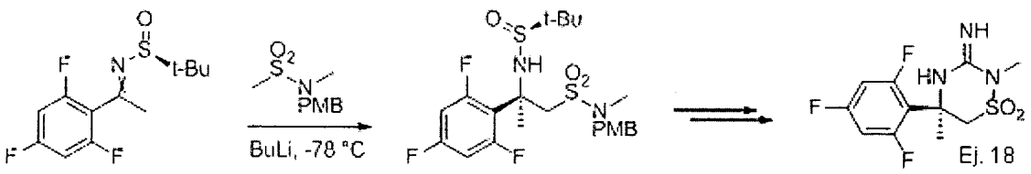
Entradas			
			
1	2	3	4

Tabla IIId: El siguiente compuesto se preparó a partir del Ej. 14f empleando métodos similares a aquellos descritos en el Esquema 7c, omitiendo el tratamiento inicial con TFA:



Esquema 8:



A una solución de N–(4–metoxibencil)–N–metilmetansulfonamida (26,8 g, 117 mmol) en THF (200 mL) a –78°C se agregó n–butillitio (2,5 M en hexanos, 47 mL, 118 mmol) durante 10 minutes. Luego de completada la adición, la mezcla se dejó agitando a –78 °C durante 1h.

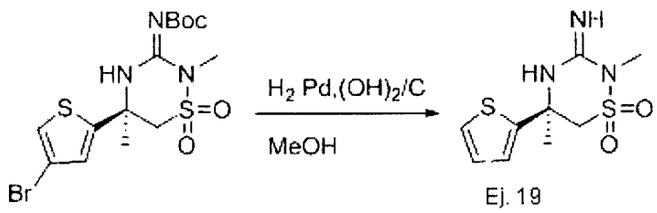
Luego, a esta mezcla se le agregó una solución de (S)–2–metil–N–(1–(2,4,6–trifluorfenil)etiliden)propan–2–sulfinamida (21,6 g, 77,9 mmol, preparada a partir de 2,4,6–trifluoracetofenona y (S)–2–metil–2–propansulfinamida de acuerdo con el Esquema 1a, Paso 1) en THF (150 mL) a –78°C. La mezcla resultante se dejó agitar a –78°C durante 4h. En ese momento, la reacción se templó mediante

la rápida dilución con agua (~ 400 mL). Luego, la mezcla se calentó hasta TA, luego se diluyó con EtOAc y salmuera. Las fases se separaron, y la capa acuosa se extrajo con EtOAc (4X). Las porciones orgánicas se combinaron, se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y concentraron. Este residuo en bruto se sometió a cromatografía en columna (600g de sílice, 100 mL/min, 0% a 60% EtOAc/hexanos) para dar (R)–2–((S)–1,1–dimetiletilsulfinamido)–N–(4–metoxibencil)–N–metil–2–(2,4,6–trifluorfenil)propan–1–sulfonamida como una mezcla 4:1 con su diastereómero (14,5 g de masa total, 37%).

Este material se sometió adicionalmente a cromatografía SFC (TharSFC80, Chiralpak OJ–H, 21 x 250 mm, 5 µm, 200 bar con 5% MeOH, 55 g/min, 35°C) para proporcionar (R)–2–((S)–1,1–dimetiletilsulfinamido)–N–(4–metoxibencil)–N–metil–2–(2,4,6–trifluorfenil)propan–1–sulfonamida).

El material antes mencionado se trató de acuerdo con el Esquema 1a, Pasos 4–6 para proporcionar el Ejemplo 18, dihidro–2,5(R)–dimetil–5–(2,4,6–trifluorfenil)–2H–1,2,4–tiadiazin–3(4H)–imina–1,1–dióxido. LCMS (condiciones A): t_R = 1,45 min, *m/e* = 308,2 (M+H).

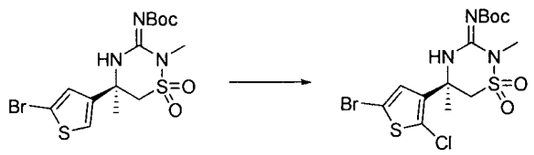
Esquema 9:



Ej. 19

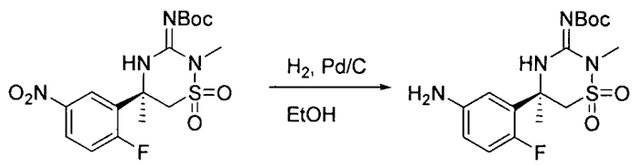
A una solución desgasificada del *terc*–butil carbamato (Esquema 3) (348 mg, 0,794 mmol) en MeOH (10 mL) se agregó 20% $Pd(OH)_2/C$ (50% agua) (52 mg, 0,074 mmol). El frasco se purgó con H_2 y se dejó agitar a TA bajo un balón de H_2 durante 2,75 horas. La mezcla se purgó con N_2, se filtró a través de Celite y se concentró. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 95:5 CH_2Cl_2:MeOH) para proporcionar **Ej. 19** (69 mg). LCMS (condiciones A): t_R = 2,00 min, *m/e* = 260,1 (M+H).

Esquema 9a:



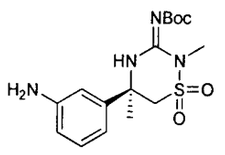
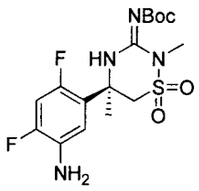
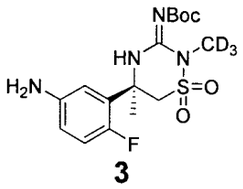
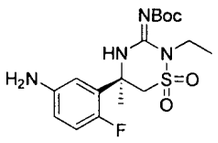
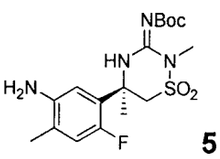
Al bromuro (Tabla IIb, entrada 13) (0,8 g, 1,8 mmol) en DMF (6 mL) se le agregó *N*–clorosuccinimida (0,7 g, 5,5 mmol). La reacción se calentó hasta 60°C y se agitó durante 5 h. Se agregó acetato de etilo y la mezcla se lavó con $NaHCO_3$ (ac.) saturado, agua y salmuera. La capa orgánica se secó ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se purificó mediante cromatografía en gel de sílice (0–30% EtOAc/hex durante 30 minutos) para proporcionar una espuma blanca la cual fue adicionalmente purificada mediante cromatografía en fase inversa (C18: elución de gradiente, 90:10:0,1 a 0:100:0,1 de agua:MeCN:ácido fórmico) para proporcionar el clorotiofeno (0,63 g, 1,3 mmol).

Esquema 10:

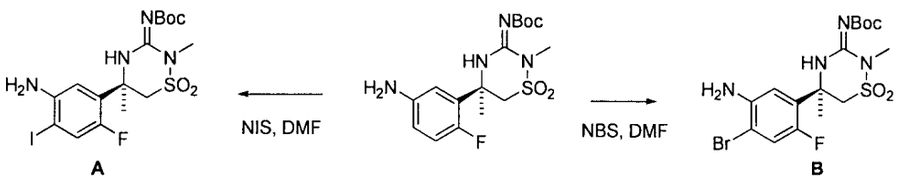


Una solución del compuesto nitro (Esquema 3b) (2,50 g, 6,0 mmol) en EtOH (150 mL) se desgasificó burbujeando N_2 a través de la solución durante 3 min. A esta solución se le agregó Pd/C (10% p/p, 50% H_2O, 698 mg.). La mezcla se colocó bajo una atmósfera de N_2. La atmósfera se evacuó y se retro-cargó con H_2 (3x). La mezcla resultante se agitó a TA bajo un balón de H_2 durante 2 h. La mezcla se purgó burbujeando N_2 a través de la misma, se filtró a través de Celite y se concentró. El producto se purificó por filtración a través de un pequeño tapón de columna de gel de sílice eluyendo con EtOAc para proporcionar la anilina (2,2g, 97%) .

Tabla IV: Las siguientes anilinas se prepararon a partir de los correspondientes compuestos nitro utilizando un procedimiento similar a aquel descrito en el Esquema 10.

Entradas				
 1	 2	 3	 4	 5

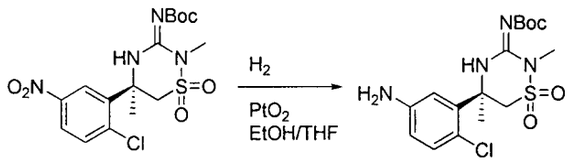
Esquema 10a:



Preparación de yodoanilina **A**: se agregó NIS (2,52 g, 11,2 mmol) a 0°C a una solución de la anilina (3,6 g, 9,31 mmol, Esquema 10) en DMF (40 mL). Después de 60 minutos a 0°C y 60 min a TA, la reacción se templó con $NaHCO_3$ (ac.) saturado, se extrajo con EtOAc (3 x), y las capas orgánicas combinadas se secaron sobre Na_2SO_4. Luego de la remoción de los volátiles bajo presión reducida, el residuo se sometió a cromatografía en gel de sílice (elución de gradiente 100:0 a 70:30 hexanos:EtOAc) para dar la yodoanilina (3,2 g, 67%).

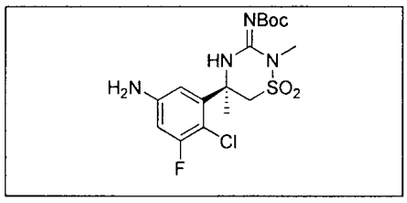
Preparación de bromoanilina **B**: Se agregó NBS (1,05 g, 6,21 mmol) a TA a una solución de la anilina (2,0 g, 5,17 mmol, Esquema 10) en DMF (21 mL). Luego de 30 minutos, la reacción se templó con Na_2SO_3 (ac.) ac. al 10%, se diluyó con EtOAc, y la capa orgánica se lavó con $NaHCO_3$ ac. saturado (2 x), salmuera (1x) y se secó sobre Na_2SO_4. Después de la remoción de los volátiles bajo presión reducida, el residuo (2,57 g) se sometió a cromatografía en gel de sílice (elución de gradiente 100:0 a 50:50 hexanos:EtOAc) para dar la bromoanilina (2,065 g, 86%).

Esquema 11a:

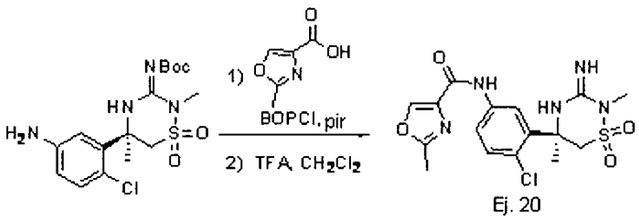


Una solución del compuesto nitro (Entrada 9, Tabla IIb) (515 mg, 1,19 mmol) en 1:1 EtOH:THF (24 mL) en un recipiente de presión se desgasificó burbujeando N_2 a través de la misma durante 5 min. A esta solución se le agregó PtO_2 (27 mg, 0,12 mmol). El recipiente se cerró herméticamente. Luego, el recipiente se evacuó y se retrocargó con N_2 (3x). A continuación, el recipiente se evacuó y se purgó con H_2 (3x). El recipiente se presurizó hasta 408 kPa (60 psi) con H_2 y se agitó a TA durante la noche. Luego de ese tiempo, el recipiente se purgó con N_2. Luego, la mezcla se filtró a través de Celite. El solvente se eliminó *in vacuo* para proporcionar la anilina (500 mg, 100%).

Tabla IVa: Se preparó el siguiente compuesto a partir del correspondiente compuesto nitro (Tabla IIId) de acuerdo con los métodos descritos en el Esquema 11a:



Esquema 11b:

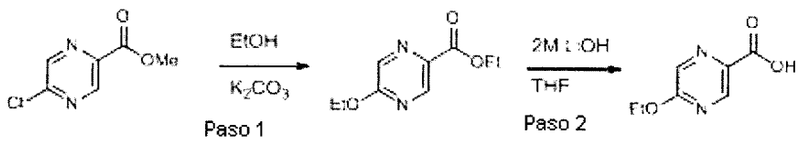


Ej. 20

Paso 1: A un frasco que contiene la anilina (Esquema 11a) (100 mg, 0,25 mmol) y ácido 2–metil–1,3–oxazol–4–carboxílico (47 mg, 0,37 mmol) se agregó BOPCl (145 mg, 0,57 mmol). El frasco se cerró herméticamente y se purgó con N_2. Al frasco se le agregó piridina (1,0 mL). La solución resultante se agitó a TA durante 1 hora. Luego de ese tiempo, la solución se repartió entre EtOAc y agua. La mezcla se filtró a través de Celite para eliminar los sólidos. La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 65:35 hexanos:EtOAc) para proporcionar la amida (81 mg, 64%).

Paso 2: A una solución de la amida del paso 1 (81 mg, 0,16 mmol) en CH_2Cl_2 (1,5 mL) se le agregó TFA (1,5 mL). La solución resultante se agitó a TA durante 2 horas. La solución se concentró *in vacuo* para proporcionar **Ej. 20** (83 mg) como la sal trifluoracetato. Datos de LCMS: (método D): t_R = 1,75 min, *m/e* = 412,0 (M+H).

Esquema 11c:

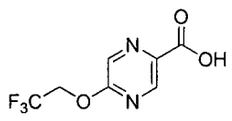
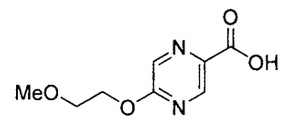
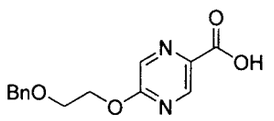
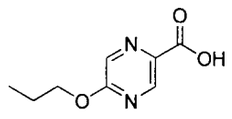
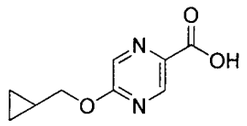
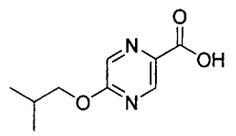
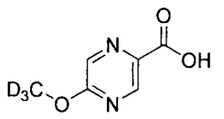


Paso 1: A una suspensión de 5–cloropirazina–2–carboxilato de metilo (250 mg, 1,45 mmol) en EtOH (5 mL) se le agregó carbonato de potasio (300 mg, 2,18 mmol). La solución resultante se agitó a TA durante 2 horas. La mezcla se concentró. El residuo se repartió entre agua y CH_2Cl_2. La capa acuosa se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar 5–etoxipirazin–2–carboxilato de etilo (110 mg, 39%) en forma de un sólido amarillo.

Paso 2: A una solución del material del paso 1 (110 mg, 0,60 mmol) en THF (3 mL) se le agregó una solución de LiOH (2M en agua, 0,90 mL, 1,8

mmol). La solución se agitó a TA durante 1 h. La solución se ajustó hasta pH 1 utilizando HCl 1M (ac.). La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar el ácido (75 mg, 74%).

Tabla IVb: Los siguientes ácidos carboxílicos de pirazina se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 11c utilizando el alcohol apropiado en el paso 1. Las modificaciones para los ejemplos específicos son enlistadas a continuación de la tabla.

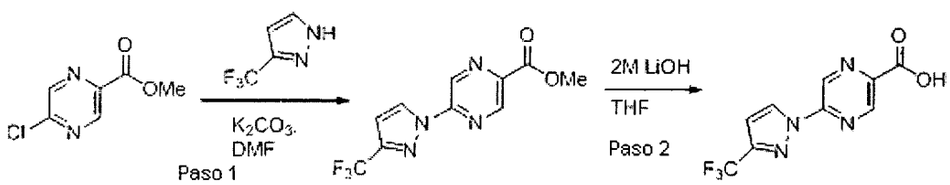
Entradas					
1		**2**[a]		**3**[b]	
4[a]		**5**[b]		**6**[c]	
7					

[a] Modificación del Paso 1: el éter se purificó mediante cromatografía flash (SiO_2 elución de gradiente 100:0 a 70:30 hexanos:EtOAc).

[b] Modificación del Paso 1: el éter se purificó por medio de cromatografía flash (C_{18} elución de gradiente 90:10:0,1 a 0:100:0,1 agua:MeCN:ácido fórmico).

[c] Modificación del paso 2: el ácido de pirazina se purificó por medio de cromatografía flash (C_{18} elución de gradiente 90:10:0,1 a 0:100:0,1 de agua:MeCN: ácido fórmico).

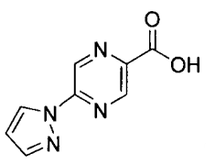
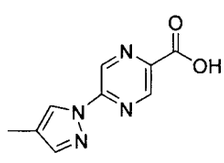
Esquema 11d:



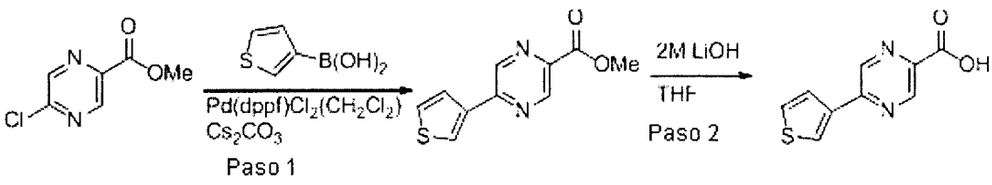
Paso 1: A una solución de 5–cloropirazin–2–carboxilato de metilo (500 mg, 2,90 mmol) y 3–(trifluormetil)–1H–pirazol (591 mg, 4,35 mmol) en DMF (7 mL) se agregó carbonato de potasio (591 mg, 4,35 mmol). La solución resultante se agitó a TA durante la noche. La mezcla se repartió entre agua y EtOAc y se separó. La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró para proporcionar el éster de biarilo (560 mg, 71%).

Paso 2: El ácido se formó utilizando un procedimiento similar a aquel descrito en el Esquema 11c paso 2.

Tabla IVc: Los siguientes ácidos carboxílicos de pirazina se prepararon empleando un procedimiento similar a aquel descrito en el Esquema 11d utilizando el pirazol apropiado.

Entradas	
 1	 2

Esquema 11e:

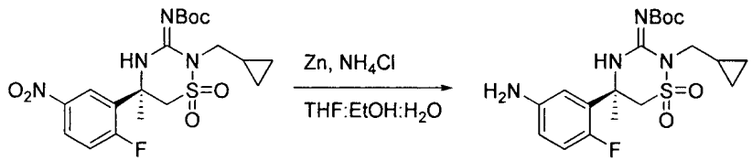


Paso 1: Una mezcla desgasificada de 5–cloropirazina–2–carboxilato (500 mg, 2,90 mmol), Cs_2CO_3 (1,1 g, 3,5 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (237 mg, 0,29 mmol) y ácido tiofen–3–ilborónico (445 mg, 3,5 mmol) en dioxano (10 mL) se calentó hasta reflujo durante 2 horas. La mezcla se concentró. El residuo se repartió entre agua y CH_2Cl_2 y se filtró a través de Celite. La capa acuosa del líquido filtrado se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El residuo se purificó por medio

de cromatografía flash (SiO_2 elución de gradiente 100:0 a 10:90 hexanos:EtOAc) para proporcionar el éster de biarilo (560 mg, 88%).

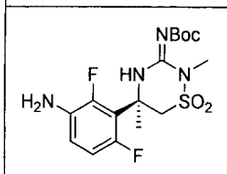
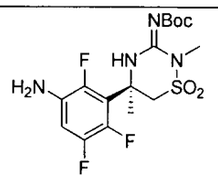
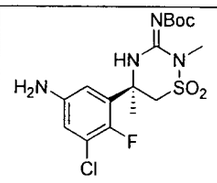
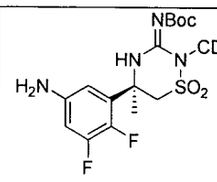
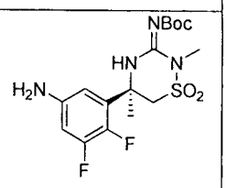
Paso 2: El ácido se formó utilizando un procedimiento similar a aquel descrito en el Esquema 11c paso 2.

Esquema 11f:

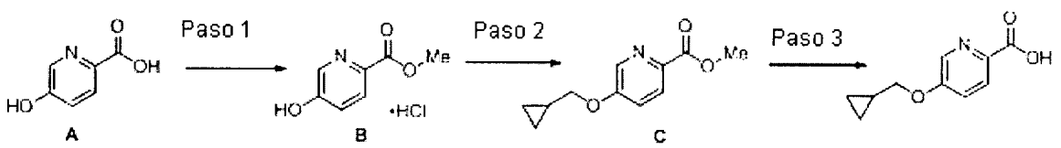


Una solución del compuesto nitro (Tabla IIe, entrada 1, 1,70 gramos, 3,7 mmol) en THF:EtOH:H_2O (30 mL, 3:1:0,3) se desgasificó burbujeando N_2 a través de la solución durante 3 min. A la solución se le agregó Zn (2,4 g, 37 mmol) y NH_4Cl (996 mg, 18 mmol). La mezcla resultante se calentó hasta reflujo bajo una atmósfera de N_2 durante 3 horas. La mezcla se filtró a través de célite y se concentró. El residuo se purificó mediante cromatografía flash en fase inversa (C_{18}, elución de gradiente 90:10:0,1 a 0:100:0,1 H_2O:MeCN:ácido fórmico). La sal formiato resultante se repartió entre EtOAc y $NaHCO_3$ (ac.) sat. La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar la anilina (847 mg, 54%).

Tabla IVd: Los siguientes compuestos se prepararon de acuerdo con los métodos descritos en el Esquema 11f excepto que se purificaron por medio de cromatografía flash de SiO_2:

Entradas				
				
1	2	3	4	5

Esquema 11g:



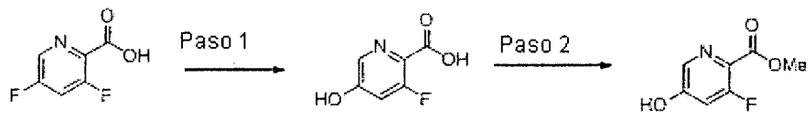
Paso 1: Al ácido 5–hidroxipiridina–2–carboxílico (4,40 g, 32 mmol) suspendido en metanol (77 mL) se le agregó cloruro de tionilo (6,9 mL, 95 mmol) por goteo. La reacción se calentó hasta reflujo y se agitó durante 22 h. Después de enfriamiento hasta temperatura ambiente, la mezcla se concentró *in vacuo* para proporcionar el éster de metilo (5,71 g, 95%).

Paso 2: Al éster de metilo (0,40 g, 2,1 mmol) formado en el paso 1 en DMF (3 mL) se le agregó carbonato de potasio (0,88 g, 6,3 mmol) y bromuro de ciclopropilmetilo (0,41 mL, 4,2 mmol). La reacción se calentó hasta 65°C y se agitó durante 18 h. La reacción se enfrió hasta temperatura ambiente y luego se concentró *in vacuo*. El residuo se trituró con EtOAc y se filtró lavando con EtOAc. El líquido filtrado se concentró *in vacuo* para proporcionar un producto en bruto el cual se purificó mediante cromatografía sobre gel de sílice (0–50% EtOAc/hex durante 30 minutos) para proporcionar el ciclopropilmetiléter (0,27 g, 61%).

Paso 3: Al producto del paso 2 (0,27 g, 1,3 mmol) en THF (2 mL) se le agregó $LiOH_{(ac.)}$ 2N (1,9 mL, 3,9 mmol). La reacción se agitó a temperatura ambiente durante 2 h. El pH se ajustó hasta pH 4 empleando ácido cítrico acuoso saturado. La mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se

lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo* para proporcionar el ácido carboxílico (0,23 g, 94%).

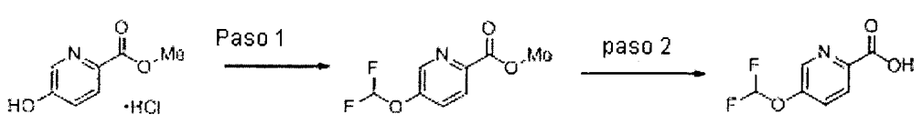
Esquema 11h:



Paso 1: Al ácido 3,5–difluorpiridina–2–carboxílico (3,0 g, 19 mmol) en THF (30 mL) en un recipiente de reacción de tubo de vidrio se le agregó $LiOH_{(ac)}$ 2N. La mezcla de reacción se tapó y se calentó hasta 100°C. La reacción se agitó durante 18 h y luego se enfrió hasta temperatura ambiente. Se agregó TFA (5 mL) y la reacción se concentró *in vacuo*. El residuo se purificó mediante cromatografía en fase inversa [C18 (360g) ácido fórmico al 0,1% /agua durante 20 minutos seguido por 0–100% ácido fórmico al 0,1% /acetonitrilo//ácido fórmico al 0,1% /agua] para proporcionar la hidroxipiridina (2,1 g) en forma de una mezcla ~1:1 de material de partida y producto. La mezcla se utilizó en el siguiente paso de reacción directamente.

Paso 2: A la hidroxipiridina preparada en el paso previo (2,1 g) en metanol (20 mL) se le agregó cloruro de tionilo (2,2 mL, 31 mmol). La reacción se calentó hasta 70°C y se agitó durante 18 h. La reacción se enfrió hasta temperatura ambiente y se concentró *in vacuo*. El residuo se purificó mediante cromatografía en fase inversa [C18 (205 g), 0–100% en el lapso de 20 minutos ácido fórmico al 0,1% /acetonitrilo//ácido fórmico al 0,1% /agua] para proporcionar el éster de metilo (1,0 g, 31% en 2 pasos).

Esquema 11i:

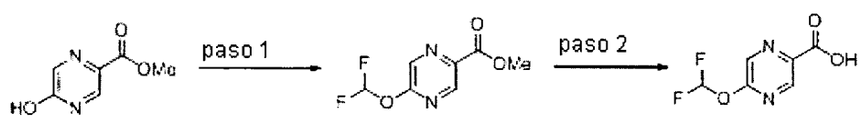


Paso 1: Al clorhidrato de metil 5–hidroxipicolinato preparado en el paso 1 del Esquema 11g (0,21 g, 1,1 mmol) en un reactor de tubo de vidrio en

acetonitrilo (4 mL) se le agregó agua (4 mL), carbonato de potasio (5,5 g, 40 mmol) y 2–cloro–2,2–difluoracetofenona (1,0 g, 5,5 mmol). El recipiente de reacción se tapó y se calentó hasta 80°C. La reacción se agitó a 80°C durante 3h y se enfrió hasta temperatura ambiente. La mezcla se filtró lavando con éter. El líquido filtrado se lavó con éter. Los lavados con éter se combinaron y lavaron con agua y salmuera, se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo* para proporcionar un aceite tostado. El aceite se purificó mediante cromatografía sobre gel de sílice (0–40% EtOAc/hex en el lapso de tiempo de 30 minutos) para proporcionar el éter (0,13 g, 60%).

Paso 2: Utilizando el procedimiento descrito en el paso 3 del Esquema 11g, el producto del paso 1 se convirtió en el ácido carboxílico.

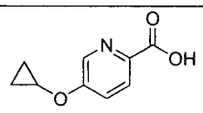
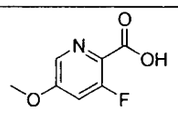
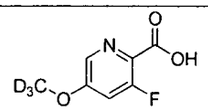
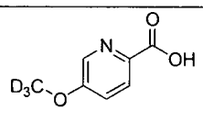
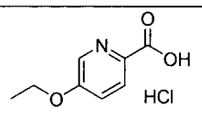
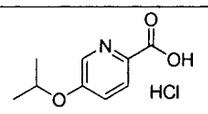
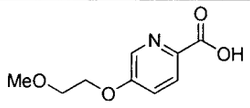
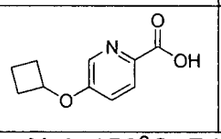
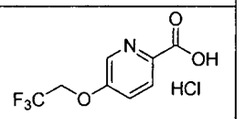
Esquema 11j:



Paso 1: Al éster metílico del ácido 5–hidroxipirazina–2–carboxílico (2,0 g, 13 mmol) en un recipiente de reacción de tubo de vidrio en DMF (26 mL) se agregó carbonato de potasio (5,3 g, 39 mmol) y 2–cloro–2,2–difluoracetato sódico (4,0 g, 26 mmol). El recipiente de reacción se tapó y se calentó hasta 100 °C. La reacción se agitó durante 30 minutos y se enfrió hasta temperatura ambiente. La reacción se filtró lavando con EtOAc. El líquido filtrado se concentró *in vacuo*. El residuo se absorbió en EtOAc y se lavó con salmuera. La capa orgánica se secó ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se purificó mediante cromatografía sobre gel de sílice (0–40% EtOAc/hex) para dar meti–5–(difluormetoxi)pirazina–2–carboxilato (0,09 g, 0,46 mmol) (0,40 g, 20%).

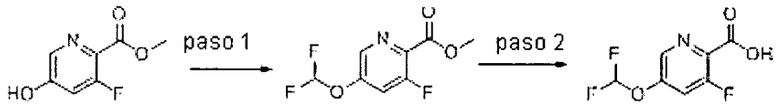
Paso 2: Al producto del paso 1 (0,09 g, 0,46 mmol) se le agregó $HCl_{(ac)}$ 3N. La reacción se calentó en un frasco de reactor de microondas cerrado herméticamente hasta 100°C durante 2 h. La reacción se concentró in vacuo para proporcionar el ácido carboxílico (0,88 g, 100%).

Tabla IVf: Los siguientes ácidos piridina- carboxílicos se prepararon a partir del compuesto intermedio **B**, Esquema 11g o de la hidroxipiridina del Esquema 11h utilizando condiciones similares a aquellas descritas en el Esquema 11g pasos 2 y 3. Las modificaciones de las condiciones experimentales son señaladas a continuación de la tabla.

Entrada		Entrada		Entrada	
1 [a]		**2** [b]		**3** [b]	
4 [b]		**5** [c, g]		**6** [c, g]	
7 [f]		**8** [d]		**9** [e]	

Condiciones de alquilación: a: Cs_2CO_3, NaI, 150°C, 7 h; b: ta; c: 45°C; d: 100°C; e:130°C, microondas, 1 h; f: 70°C.
Condiciones de hidrólisis: g: *Véase el* Esquema 11j, paso 2.

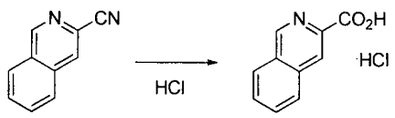
Esquema 11k:



Paso 1: A la hidroxipiridina preparada en el Esquema 11h (0,19 g, 1,1 mmol) en acetonitrilo (4 mL) y agua (4 mL) se le agregó carbonato de potasio (5,5 g, 40 mmol) y 2–cloro–2,2–difluoracetofenona. El tubo de reacción de vidrio se cerró herméticamente y se calentó hasta 80°C. Después de 3,5 h, la reacción se enfrió hasta temperatura ambiente y se filtró lavando con EtOAc. El líquido filtrado se extrajo con éter. Las capas de éter combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron, y concentraron *in vacuo*. El residuo se purificó mediante cromatografía sobre gel de sílice (0–30% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el producto (0,15 g, 60%).

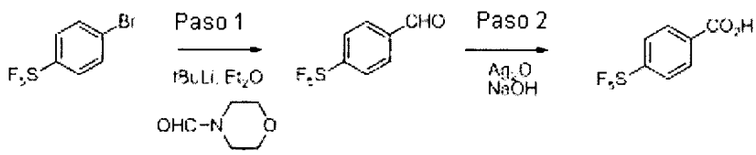
Paso 2: El producto del paso 1 se convirtió en el ácido carboxílico empleando las condiciones encontradas en el paso 3 del Esquema 11g.

Esquema 11l:



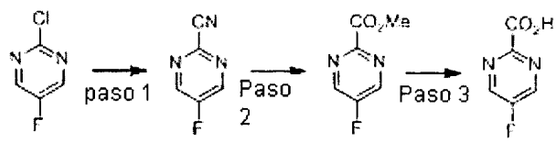
Se suspendió 3–cianoisoquinolina (1,047 g, 6,79 mmol) en HCl (ac.) 6 M (50 mL) y se sometió a reflujo a 95°C durante 18 h. La reacción se enfrió hasta TA, y los volátiles se eliminaron bajo vacío para proporcionar el ácido carboxílico (2,07 g) el cual se empleó como estaba.

Esquema 11m:



Se obtuvo el ácido 4–pentafluorazufre benzoico en dos pasos a partir de pentafluoruro de 4–bromofenilazufre de acuerdo con el procedimiento de la bibliografía técnica por Zarantonello et al., *J. Fluor. Chem.* **2007**, *128*, 1449–1453.

Esquema 11n:



Paso 1: A 2–cloro–5–fluorpirimidina (2 g, 15 mmol) en un frasco de fondo redondo de 250 mL se agregó DMA (8 mL), tris(dibencilidenacetona)dipaladio (0,544 g, 0,6 mmol), 1,1'–bis(difenilfosfino)ferroceno (0,67 g, 1,2 mmol), cianuro de zinc (1,15 g, 9,8 mmol), y polvo de zinc (0,237 g, 3,62 mmol). El frasco se tapó, se lavó con nitrógeno, y se agitó durante 2,5 h a 100°C. La reacción se enfrió hasta temperatura ambiente, se filtró a través de célite, y se lavó con DCM. El líquido filtrado se vertió en agua y se extrajo con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y concentraron *in vacuo*. El residuo se purificó mediante cromatografía sobre gel de sílice (0–10% EtOAc/hexanos en el transcurso de 20 minutos) para proporcionar el compuesto de nitrilo (0,58 g, 31%).

Paso 2: Al compuesto de nitrilo preparado en el Paso 1 (0,51 g, 4,14 mmol) agitación en 5 mL de MeOH se le agregó 5 mL de HCl conc.. La reacción contaba con un condensador de reflujo y se calentó a 80°C durante 2 horas, luego se enfrió hasta temperatura ambiente. Se agregó bicarbonato sódico acuoso saturado y se agitó durante 1 hora a temperatura ambiente. La mezcla se acidificó hasta pH 4 empleando HCl (ac.) 1 N y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron ($MgSO_4$), filtraron y concentraron *in vacuo* para proporcionar el éster de metilo (0,256 g, 40%).

Paso 3: Al compuesto éster metílico preparado en el Paso 2 (0,256 g, 1,64 mmol) en 6 mL 1:1:1 THF: H_2O: MeOH se le agregó LiOH hidrato (0,272 g, 4,04 mmol), y la mezcla se agitó a temperatura ambiente durante 1 hora. La reacción se acidificó hasta pH 4 empleando HCl (ac.) 1 N y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron ($MgSO_4$), filtraron y concentraron *in vacuo* para proporcionar el ácido carboxílico (0,136 g, 58%).

Tabla IVg: Los siguientes ácidos se prepararon empleando métodos similares a aquellos descritos en el Esquema 11n utilizando el cloruro de arilo apropiado (entradas 1–3) o el bromuro (entradas 4 y 5):

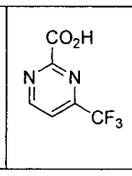
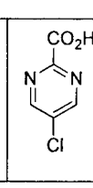
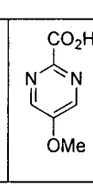
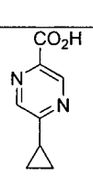
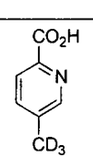
Entradas									
1		**2**		**3**		**4**		**5**	

Tabla IVh: El siguiente ácido se preparó empleando métodos similares a aquellos descritos en el Esquema 11n, Paso 3:

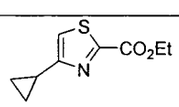
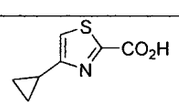
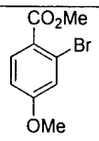
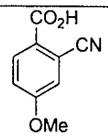
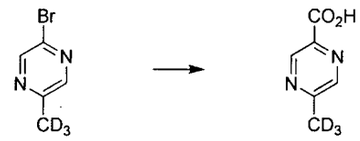
Entrada	Material de partida	Ácido
1		

Tabla IVi: El siguiente ácido se preparó de acuerdo con métodos similares a aquellos descritos en el Esquema 11n, utilizando el Paso 1 y luego el Paso 3, omitiendo el Paso 2:

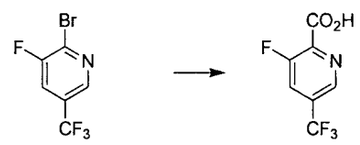
Entrada	Material de partida	Ácido
1		

Esquema 11o:

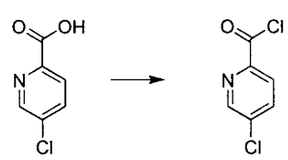


A 2–bromo–5–(metil–D_3)–pirazina (400 mg, 2,27 mmol) agitando en 8 mL de THF anhidro a –78°C bajo atmósfera de N_2 se agregó lentamente *n*–BuLi (2,5 M en hexanos, 1,14 mL, 2,85 mmol). La reacción se agitó durante 30 minutos a esta temperatura, luego de lo cual se introdujeron burbujas de dióxido de carbono a través de la solución durante 15 minutos por medio de aguja de canulación. Se retiró el baño frío y la reacción se dejó llegar a temperatura ambiente lentamente en el transcurso de 1 hora. A continuación se agregó agua y la reacción se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se secaron ($MgSO_4$), y concentraron *in vacuo* para proporcionar un aceite (120 mg, 38%) el cual se empleó sin más purificación.

Se preparó ácido 3–Fluor–5–(trifluormetil)picolínico a partir de 2–bromo–3–fluor–5–(trifluormetil)piridina utilizando un procedimiento similar a aquel descrito anteriormente en el Esquema 11o.



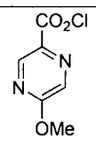
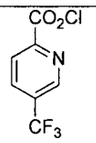
Esquema 11p:



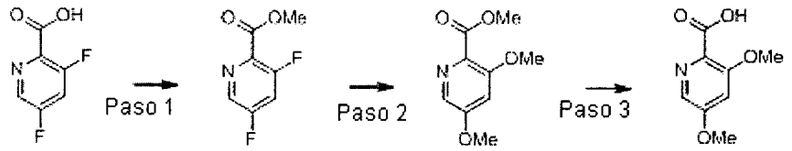
A ácido 5–cloropicolínico (0,3 g, 1,9 mmol) agitando a temperatura ambiente en 6 mL de THF y 1 gota de DMF se le agregó lentamente por goteo cloruro de oxalilo (0,48 mL, 5,7 mmol). Se observó una desgasificación vigorosa.

La reacción se agitó a temperatura ambiente durante 1,5 horas, luego se concentró hasta sequedad *in vacuo* y el producto se empleó sin más purificación.

Tabla IVj: Los siguientes cloruros ácidos se prepararon empleando métodos similares a aquellos descritos en el Esquema 11p a partir del ácido carboxílico apropiado.

Entradas	
	
1	**2**

Esquema 11q:



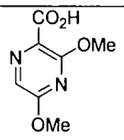
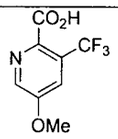
Paso 1: Al ácido 3,5–difluorpiridina–2–carboxílico (2 g, 12,6 mmol) agitando en 20 mL 4:1 tolueno:MeOH a temperatura ambiente se le agregó lentamente por goteo trimetilsilildiazometano (2,0 M en hexanos, 15,1 mmol, 7,5 mL). La reacción se dejó agitar durante 30 minutos, y luego se concentró hasta sequedad *in vacuo* y se empleó sin más purificación.

Paso 2: Al éster metílico preparado en el paso 1 (1,09 g, 6,3 mmol) agitando a temperatura ambiente en 20 mL de MeOH en un recipiente sellado de 350 mL se le agregó metóxido sódico 25% en peso en metanol (3,4 g metóxido sódico, 13,6 g de solución, 63 mmol). La reacción se lavó a chorro con nitrógeno, se cerró herméticamente, y se agitó durante 16 horas en un baño de aceite a 100°C. La día siguiente, la reacción se enfrió hasta temperatura ambiente y se acidificó hasta pH 4 empleando HCl 1 N. La solución se extrajo con 1:1 EtOAc:THF (250 mL). La capa orgánica se secó ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se purificó mediante cromatografía sobre gel de sílice (0–60%

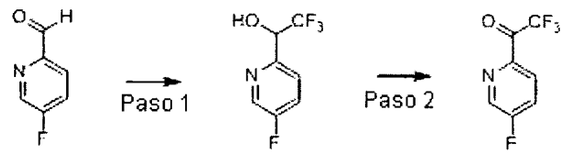
EtOAc/hexanos en el transcurso de 20 minutos) para proporcionar el compuesto *bis*–metoxi deseado (0,53 g, 43%).

Paso 3: El éster metílico se convirtió en el ácido carboxílico empleando métodos similares a aquellos descritos en el Esquema 11n, Paso 3.

Tabla IVk: Los siguientes ácidos se prepararon empleando métodos similares a aquellos descritos en el Esquema 11q utilizando el cloruro de arilo apropiado:

Entradas	
	
1	**2**

Esquema 11r:

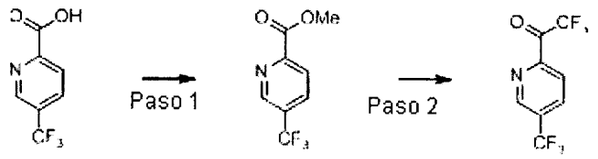


Paso 1: A 2–fluor–5–formilpiridina (1,57 g, 12,55 mmol) agitando en THF anhidro (20 mL) a 0°C ajo atmósfera de nitrógeno se agregó lentamente (trifluormetil)–trimetilsilano (2,67 g, 18,78 mmol). La mezcla se agitó a 0°C durante 15 minutos, y luego se agregó lentamente por goteo fluoruro de tetrabutilamonio (1,0 M en THF, 31,38 mL, 31,38 mmol) después de lo cual se extrajo el baño de hielo, y la reacción se dejó agitar a temperatura ambiente durante la noche (tiempo de reacción total 16 horas). Luego, la reacción se vertió en agua y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó mediante cromatografía sobre gel de sílice (0–20% EtOAc/hexanos en el transcurso de 20 minutos) para proporcionar el producto de alcohol de trifluormetilo (2,01 g, 82%).

Paso 2: Al alcohol de trifluormetilo preparado en el paso 1 (1 g, 5,12 mmol) agitando en DCM anhidro (20 mL) se le agregó peryodinano Dess–Martin (2,63 g,

6,14 mmol). La reacción se agitó a temperatura ambiente durante la noche (tiempo de reacción total 16 horas). Se agregaron hexanos después de lo cual se formó un precipitado. El sólido se separó por filtración y se lavó con DCM. El líquido filtrado se absorbió y se vertió en bicarbonato sódico acuoso saturado y se extrajo con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo*. El residuo se purificó mediante cromatografía sobre gel de sílice (0–20% EtOAc/hexanos durante 20 minutos) para proporcionar el producto trifluormetil cetona (0,453 g, 46%).

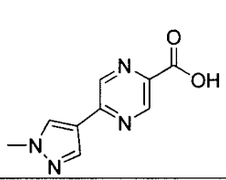
Esquema 11s:



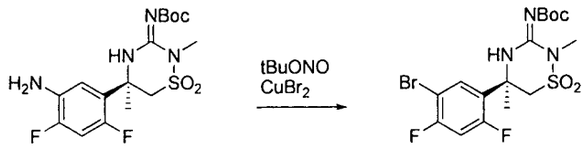
Paso 1: El ácido carboxílico (1,5 g, 7,84 mmol) se convirtió en el éster metílico utilizando métodos similares a aquellos descritos en el Esquema 11q, Paso 1. La reacción en bruto se evaporó hasta sequedad *in vacuo*, y se purificó por medio de cromatografía en gel de sílice (0–30% EtOAc/hexanos en el transcurso de 20 minutos, 30–40% EtOAc/hexano de 20–30 minutos) para proporcionar el producto de éster metílico en forma de un sólido (1,02 g, 63%).

Paso 2: A una mezcla de 5–(trifluormetil)piridin–2–carboxilato de metilo preparada anteriormente (0,2 g, 0,97 mmol) y (trifluormetil)trimetilsilano (0,173 g, 1,22 mmol) agitando a –78°C en pentano (3 mL) bajo atmósfera de nitrógeno se agregó lentamente fluoruro de tetrabutilamonio (1,0 M en THF, 25 µL, 0,024 mmol). La reacción se dejó llegar a temperatura ambiente y se agitó durante la noche (tiempo de reacción total 16 horas). En ese momento, se agregó HCl 2 N, y la mezcla se agitó vigorosamente a temperatura ambiente durante 2 horas. La solución se extrajo con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–20% EtOAc/hexanos durante 20 minutos) para proporcionar el producto de trifluormetilcetona (0,084 g, 35%).

Tabla IVI: Se preparó el siguiente ácido carboxílico de pirazina utilizando un procedimiento similar a aquel descrito en el Esquema 11e.

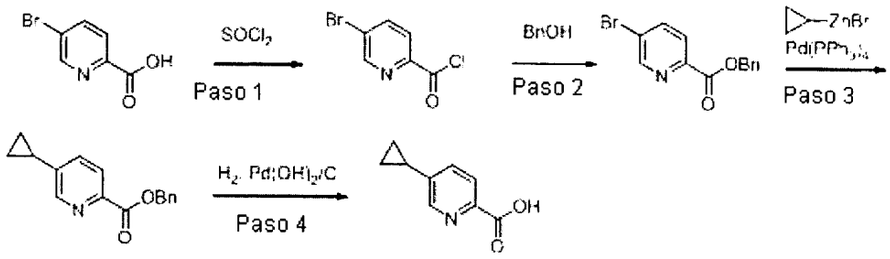
Entrada	
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Esquema 11t:



Se cargó un tubo de microondas grande consecutivamente con MeCN (9 mL), *terc*–butil nitrito (0,15 mL, 1,2 mmol), y bromuro de cobre (II) (0,331 g, 1,48 mmol). El tubo se cerró herméticamente y se sumergió en un baño de aceite a 60°C. A la mezcla resultante de color verde – negro se le agregó una solución de 1,1–dimetiletil [5(R)–(5–amino–2,4–difluorfenil)dihidro–2,5–dimetil–1,1–dioxido–2H–1,2,4–tiadiazin–3(4H)–iliden]carbamato (Tabla IV, Entrada 2, 500 mg, 1,24 mmol) en MeCN (3 mL) por medio de una jeringa durante ~ 2 min. Luego de completada la adición, la reacción se agitó a 60°C durante 20 min. En ese momento, la reacción se enfrió, se diluyó con EtOAc, y se filtró a través de Celite. El líquido filtrado se diluyó con agua y EtOAc. Las fases se separaron y la capa acuosa se extrajo 2X con EtOAc. Las porciones orgánicas se combinaron, se lavaron con $NaHCO_3$ ac. sat. y salmuera, se secaron sobre $MgSO_4$, se filtraron y concentraron. Esta muestra en bruto fue sometida a cromatografía en columna (80 g de sílice, 60 mL/min, 0% a 50% EtOAc/hexanos) para dar el producto 1,1–dimetiletil [5(R)–(5–bromo–2,4–difluorfenil)dihidro–2,5–dimetil–1,1–dioxido–2H–1,2,4–tiadiazin–3(4H)–iliden]carbamato (0,30 g, 52%).

Esquema 11u:



Paso 1: A una suspensión de ácido 5–bromopicolínico (20,2 g, 100 mmol) en 200 mL de tolueno se le agregó cloruro de tionilo (11 mL, 150 mmol). La mezcla se agitó a temperatura ambiente durante 20 min y luego se calentó hasta reflujo durante 30 min. La solución resultante se enfrió hasta temperatura ambiente y se concentró hasta sequedad. El producto en bruto cloruro de 5–bromopicolinoílo se empleó directamente en el siguiente paso.

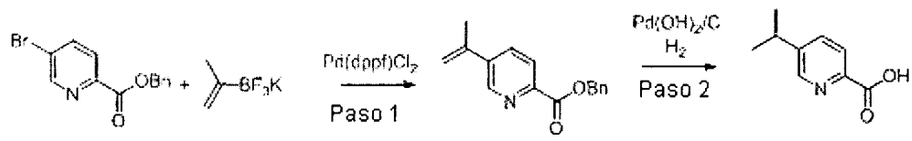
Paso 2: Luego de la adición de THF (200 mL) y Et_3N (42 mL) al residuo antes mencionado, la mezcla se enfrió en un baño de agua helada. Se agregó lentamente alcohol bencílico (31,1 mL, 300 mmol). La mezcla se calentó hasta temperatura ambiente y se agitó durante la noche.

La mezcla de reacción se diluyó con éter, se lavó con $NaHCO_{3(ac.)}$ sat., H_2O, salmuera y luego se secó ($MgSO_4$). Después de la concentración y cristalización, se obtuvo el producto deseado 5–bromopicolinato de bencilo (20,6 g).

Paso 3: A una solución de 5–bromopicolinato de bencilo (876 mg, 3,0 mmol) en THF (10 mL) se le agregó $Pd(PPh_3)_4$ (173 mg, 0,15 mmol) bajo N_2. Luego de la adición de una solución de bromuro de ciclopropilzinc en THF (0,5 M, 10 mL), la mezcla se calentó a 80°C durante 3 horas y luego se enfrió hasta temperatura ambiente. La mezcla de reacción se templó con NH_4Cl (ac.) sat. y se extrajo con EtOAc (3x). La capa orgánica se lavó con $NaHCO_{3(ac.)}$ sat., salmuera, y se secó ($MgSO_4$). El producto 5–ciclopropilpicolinato de bencilo (510 mg) fue obtenido por medio de cromatografía en gel de sílice (elución con 0–15% EtOAc/Hex, luego 15% EtOAc/Hex).

Paso 4: A una solución de 5–ciclopropilpicolinato de bencilo en MeOH (15 mL) se le agregó 20% $Pd(OH)_2/C$ (100 mg). La hidrogenólisis con H_2 se llevó a cabo a temperatura ambiente bajo un balón de H_2. Se obtuvo el producto deseado ácido 5–ciclopropilpicolínico (305 mg) luego de filtración y concentración.

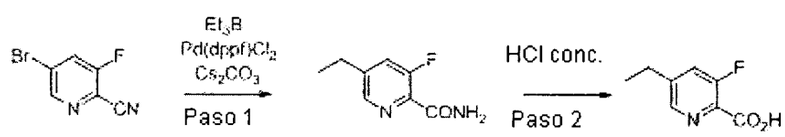
Esquema 11v:



Paso 1: Una mezcla de 5–bromopicolinato de bencilo (2,92 g, 10 mmol), trifluorborato de isopropenilo potasio (3,05 g, 21 mmol), $Pd(dppf)Cl_2$ (445 mg, 0,54 mmol), y Et_3N (1,4 mL) en alcohol isopropílico (20 mL) se desgasificó con N_2 y se calentó a 80°C durante 7 h. La mezcla se enfrió hasta temperatura ambiente y se diluyó con EtOAc. La capa orgánica se lavó con H_2O, ácido cítrico al 5%, $NaHCO_3$ (ac.) sat. y salmuera, luego se secó ($MgSO_4$) y concentró. Se obtuvo el producto 5–isopropenilpicolinato de bencilo (1,27 g) por medio de cromatografía en gel de sílice (elución con 0–16% EtOAc/Hex).

Paso 2: Una solución de 5–isopropenilpicolinato de bencilo (1,27 g, 5 mmol) en MeOH (25 mL) fue sometida a hidrogenación con 20% $Pd(OH)_2/C$ (200 mg) con un balón de H_2 durante 2h. Se obtuvo el producto ácido 5–isopropenilpicolínico (780 mg) mediante filtración y concentración.

Esquema 11w:

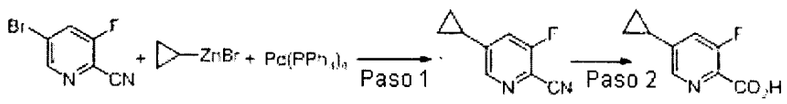


Paso 1: Una mezcla de 5–bromo–3–fluorpicolinonitrilo (1,0 g, 5 mmol), $Pd(dppf)Cl_2$ (82 mg, 0,1 mmol) y carbonato de cesio (3,26, 10 mmol) en THF (20 mL) se desgasificó con N_2. Luego de la adición de una solución de trietilborano (1,0 M THF, 10 mL), la mezcla se calentó a 65°C durante 5 h. La mezcla se enfrió

hasta temperatura ambiente, y luego se enfrió adicionalmente en un baño de hielo. Se agregó en la mezcla una solución de NaOH (1,2 g) en 20 mL de H_2O, seguido por H_2O_2 (30% acuoso 7 mL). La mezcla se agitó a 0°C durante 30 min y se extrajo con éter (4x). La capa orgánica se lavó con salmuera y se secó ($MgSO_4$), y se concentró. Se obtuvo el producto 5–etil–3–fluorpicolinamida (370 mg) a través de cromatografía en gel de sílice (elución con 0–40% EtOAc/Hex).

Paso 2: Una mezcla de amida (475 mg, 2,8 mmol) en 10 mL de HCl conc. se calentó a reflujo durante 5 h. La mezcla se concentró y se secó *in vacuo* para dar el producto ácido 5–etil–3–fluorpicolínico.

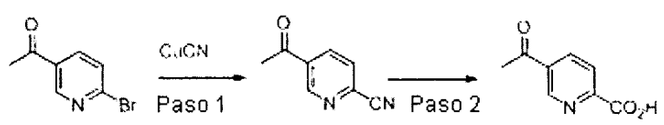
Esquema 11x:



Paso 1: A una solución de 5–bromo–3–fluorpicolinonitrilo (603 mg, 3,0 mmol) y $Pd(PPh_3)_4$ (173 mg, 0,15 mmol) en 10 mL de THF se agregó bromuro de ciclopropil zinc (0,5 M, 10 mL) bajo N_2. Luego de calentamiento a 80°C durante 4 h, la mezcla se enfrió hasta temperatura ambiente y se templó con NH_4Cl (ac). sat.. La mezcla se extrajo con EtOAc (3x) y las capas orgánicas combinadas se lavaron con $NaHCO_{3\ (ac.)}$ sat. y salmuera, se secaron ($MgSO_4$), y concentraron. El producto en bruto se purificó por medio de cromatografía en gel de sílice (elución con 0–8% EtOAc/Hex) para proporcionar 5–ciclopropil–3–fluorpicolinonitrilo (406 mg).

Paso 2: El producto del paso 1 se calentó a reflujo en 10 mL de HCl conc. durante la noche. Luego de concentración, el producto sólido ácido 5–ciclopropil–3–fluorpicolínico (400 mg) se lavó con agua fría y se secó *in vacuo*.

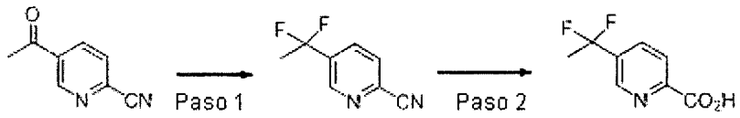
Esquema 11y:



Paso 1: Una mezcla de 1–(6–bromopiridin–3–il)etanona (200 mg, 1,0 mmol) y CuCN (179 mg, 2,0 mmol) en DMF anhidra (5 mL) se calentó a 110°C durante 18 h bajo N_2. La mezcla se enfrió hasta temperatura ambiente y se diluyó con agua. Después de la adición de EtOAc y filtración, la capa acuosa se extrajo con EtOAc. La capa orgánica se lavó con $NaHCO_3$ (ac.) sat., salmuera, y luego se secó ($MgSO_4$) y concentró. Se obtuvo el producto 5–acetilpicolinonitrilo (120 mg) por medio de cromatografía en gel de sílice (elución con 0–20% EtOAc/Hex).

Paso 2: Se calentó 5–Acetilpicolinonitrilo (146 mg, 1,0 mmol) en 5 mL de HCl conc. a reflujo durante 2,5 h. La mezcla se concentró y se secó *in vacuo*. El producto en bruto ácido 5–acetilpicolínico se empleó sin más purificación.

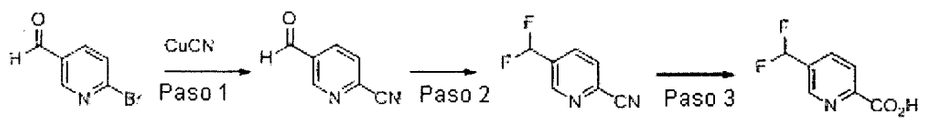
Esquema 11z:



Paso 1: Una mezcla de 5–acetilpicolinonitrilo (146 mg, 1,0 mmol) y Deoxo–Fluor™ (1,0 mL, 50% en tolueno) se calentó a 80°C durante 3h bajo N_2. La mezcla se enfrió hasta temperatura ambiente y se diluyó con DCM. La capa orgánica se lavó con $NaHCO_{3\,(ac.)}$ sat., y salmuera, se secó ($MgSO_4$) y concentró. El residuo se purificó por medio de cromatografía en gel de sílice (elución con 0–15% EtOAc/Hex) para proporcionar 5–(1,1–difluoretil)picolinonitrilo (120 mg).

Paso 2: 5–(1,1–Difluoretil)picolinonitrilo (120 mg, 0,71 mmol) en 9 mL de HCl conc. se calentó a 110°C durante 5 h. La mezcla se concentró. Al residuo se le agregó diisopropiletilamina (2 mL) y la mezcla se concentró. El residuo se secó *in vacuo* y se empleó sin más purificación.

Esquema 11aa:



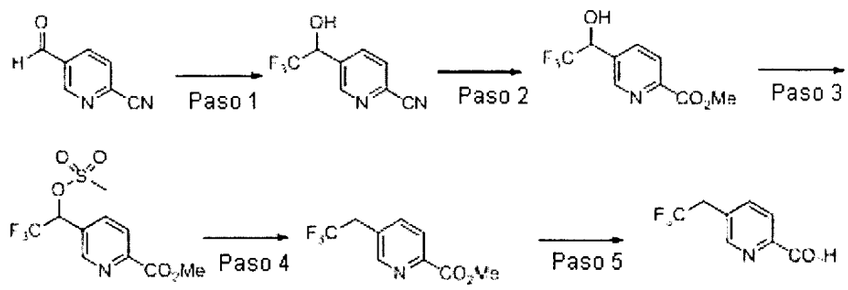
Paso 1: Una mezcla de 6–bromonicotinaldehído (11,2 g, 60 mmol) y CuCN (8,06 g, 90 mmol) en DMF (100 mL) se calentó a 120°C durante 3 h bajo N_2. La mezcla se enfrió hasta t.a. y se diluyó con EtOAc y se filtró a través de una almohadilla de célite. La capa orgánica se lavó con agua y salmuera y luego se secó ($MgSO_4$) y concentró. Se obtuvo el producto 5–formilpicolinonitrilo (4,55 g) por medio de cromatografía en gel de sílice (elución con 0–20% EtOAc/Hex).

Paso 2: Una mezcla de 5–formilpicolinonitrilo (132 mg, 1,0 mmol) y Deoxo–Fluor ® (1,0 mL, 50% en tolueno) se agitó a temperatura ambiente durante 16 h. Luego de la dilución con DCM, la solución se lavó con $NaHCO_3$ sat., salmuera, luego se secó ($MgSO_4$) y concentró.

Se obtuvo el producto 5–(difluormetil)picolinonitrilo (118 mg) por medio de cromatografía en gel de sílice (elución con 0–10% EtOAc/Hex).

Paso 3: 5–(Difluormetil)picolinonitrilo (118 mg, 0,75 mmol) en 9 mL de HCl conc. se calentó a 110°C durante 2,5 h. La mezcla se enfrió, se concentró y se trató con diisopropiletilamina (2 mL). La mezcla se reconcentró y se secó *in vacuo* para dar ácido 5–(difluormetil)picolínico la cual se empleó sin purificación.

Esquema 11ab:



Paso 1: A una solución a –78°C de 5–formilpicolinonitrilo (1,0 g, 7,58 mmol) y trifenildifluorsilicato de tetrabutilamonio (4,9 g, 9,10 mmol) en 60 mL de THF se le agregó una solución de trimetil(trifluormetil)silano (1,62 g, 114 mmol). La mezcla se agitó durante 20 min a –78°C. Luego, el baño de enfriamiento se cambió a un baño de hielo. Después de agitación durante otros 30 min, la reacción se templó con NH_4Cl $_{(ac.)}$ sat. La mezcla se extrajo con EtOAc (3x). La capa orgánica se lavó con $NaHCO_3$ $_{(ac.)}$ sat., salmuera, luego se secó ($MgSO_4$) y

concentró. Se obtuvo el producto 5–(2,2,2–trifluor–1–hidroxietil)picolinonitrilo (600 mg) por medio de cromatografía en gel de sílice (elución con 0–40% EtOAc/Hex).

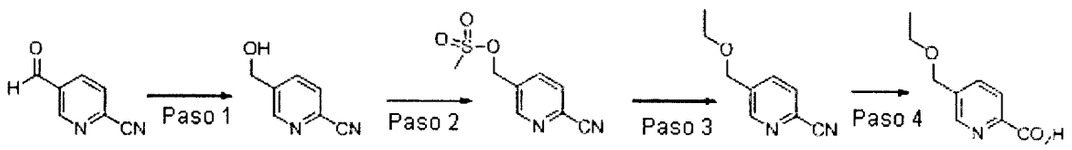
Paso 2: Una mezcla de 5–(2,2,2–trifluor–1–hidroxietil)picolinonitrilo (202 mg, 1,0 mmol), HCl conc. (0,5 mL) y H_2SO_4 conc. (0,25 mL) en 10 mL de MeOH anhidro se calentó a reflujo durante 19 h. La solución se concentró y neutralizó con $NaHCO_{3\,(ac.)}$ sat. La extracción con EtOAc seguida por concentración de la capa orgánica y purificación del residuo por medio de cromatografía en gel de sílice (elución con 0–45% EtOAc/Hex) proporcionó 5–(2,2,2–trifluor–1–hidroxietil)picolinato de metilo (76 mg).

Paso 3: A una solución de 5–(2,2,2–trifluor–1–hidroxietil)picolinato de metilo (76 mg, 0,32 mmol) en 3mL de DCM se le agregó trietilamina (0,22 mL), seguido por una solución de cloruro de metansulfonilo (45 mg, 0,39 mmol) en 1 mL de DCM. La mezcla se agitó a temperatura ambiente durante 7h y luego se diluyó con DCM. La solución se lavó con ácido cítrico al 5% y $NaHCO_{3\,(ac.)}$ sat., se secó ($MgSO_4$), y concentró. El producto 5–(2,2,2–trifluor–1–(metilsulfoniloxi)etil)picolinato de metilo (95 mg) se purificó por cromatografía.

Paso 4: A una solución de 5–(2,2,2–trifluor–1–(metilsulfoniloxi)etil)picolinato de metilo (95 mg, 0,3 mmol) en 5 mL de MeOH se le agregó 10% Pd/C (45 mg). La hidrogenación con 1 atm H_2 se llevó a cabo a temperatura ambiente durante 2h. Luego de la extracción del catalizador por filtración, el filtrado se concentró. El residuo se disolvió en DCM y se lavó con $NaHCO_{3\,(ac.)}$ sat. y salmuera. La solución se secó ($MgSO_4$) y concentró para dar 5–(2,2,2–trifluoretil)picolinato de metilo el cual se empleó sin purificación.

Paso 5: Una mezcla de 5–(2,2,2–trifluoretil)picolinato de metilo (57 mg, 0,26 mmol) y LiOH (12,5 mg, 0,52 mmol) en 6 mL de MeOH/agua (5:1) se agitó a temperatura ambiente durante 3,5 h. La mezcla de reacción se acidificó con ácido cítrico al 5%, y luego se concentró. El residuo se extrajo con DCM (4x). La capa orgánica se lavó con salmuera y se secó (Na_2SO_4). Luego de la concentración, se secó el producto ácido 5–(2,2,2–trifluoretil)picolínico *in vacuo* y se utilizó sin más purificación.

Esquema 11ac:



Paso 1: A una solución a 0°C de 5–formilpicolinonitrilo (490 mg, 3,71 mmol) en 15 mL de MeOH se agregó $NaBH_4$ (140 mg, 3,71 mmol). La mezcla de reacción se agitó a 0°C durante 1 h y se templó con ácido cítrico al 5%. Luego de la extracción de la mayor parte del MeOH por concentración, el residuo se repartió entre DCM y $NaHCO_{3\ (ac.)}$ sat. La capa acuosa se extrajo con DCM (10x). La capa orgánica se lavó con salmuera y se secó (Na_2SO_4). Se obtuvo el producto 5–(hidroximetil)picolinonitrilo (431 mg) por concentración bajo vacío.

Paso 2: A una solución de 5–(hidroximetil)picolinonitrilo (1,59 g, 11,9 mmol) en 80 mL de DCM se le agregó diisopropiletilamina (3,2 mL), seguido por una solución de cloruro de metansulfonilo (1,49 g, 13,0 mmol) en 20 mL de DCM a 0°C. La solución se agitó a 0°C durante 40 min y se lavó con ácido cítrico 5%, $NaHCO_{3\ (ac.)}$ sat. y salmuera. Luego de la concentración, el residuo se purificó por medio de cromatografía en gel de sílice (elución con 0–30% EtOAc/Hex) para proporcionar (6–cianopiridin–3–il)metil metansulfonato (2,33 g).

Paso 3: (6–Cianopiridin–3–il)metil metansulfonato (199 mg, 0,94 mmol) en 2 mL de EtOH anhidro se calentó a 85°C en un tubo sellado durante 3,5 h. La mezcla se concentró y purificó por medio de cromatografía en gel de sílice (elución con 0–25% EtOAc/Hex) para proporcionar 5–(etoximetil)picolinonitrilo (104 mg).

Paso 4: Una solución de 5–(etoximetil)picolinonitrilo (104 mg) en 10 mL de HCl conc. se calentó a reflujo durante 3,5 h. Luego de la concentración, se agregó diisopropiletilamina (3mL) en el residuo. La mezcla se concentró y secó *in vacuo*. El producto ácido 5–(etoximetil)picolínico se utilizó sin más purificación.

Tabla IVm: Los siguientes ácidos se prepararon utilizando procedimientos similares a los descritos en el Esquema 11ac, sustituyendo el alcohol apropiado en el Paso 3.

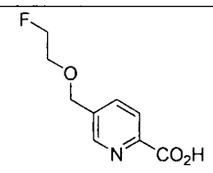
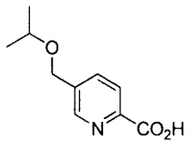
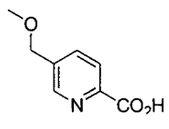
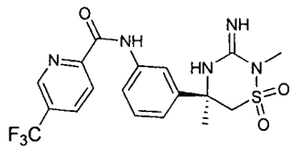
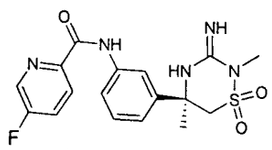
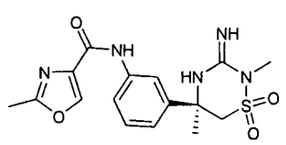
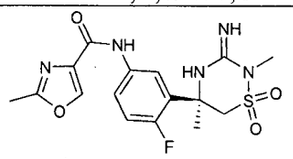
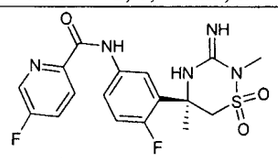
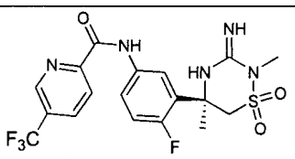
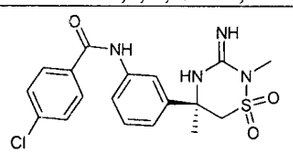
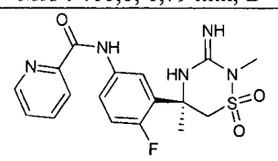
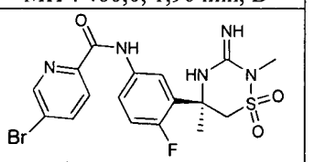
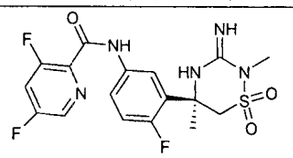
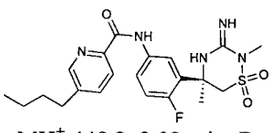
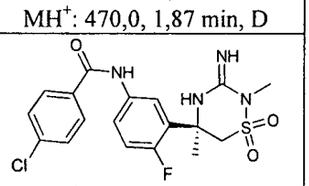
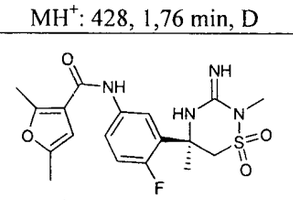
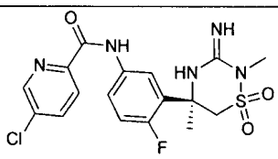
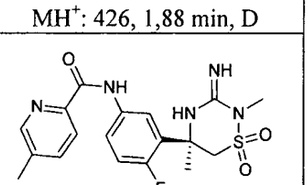
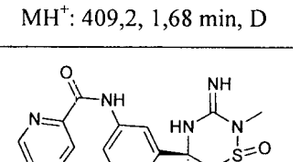
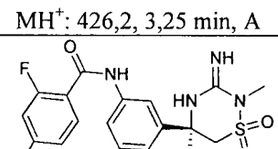
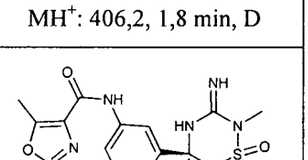
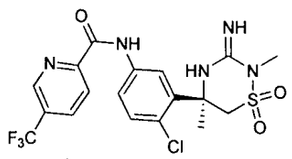
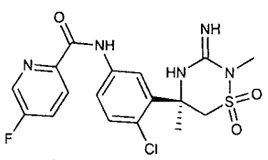
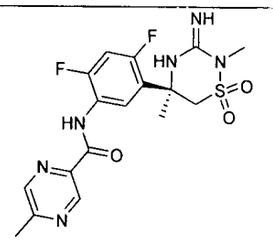
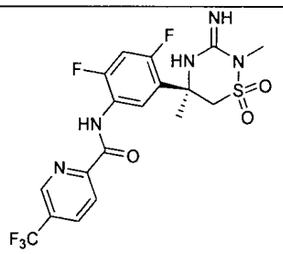
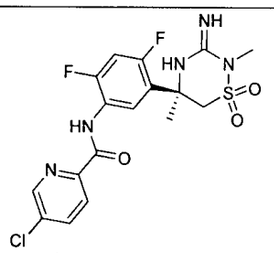
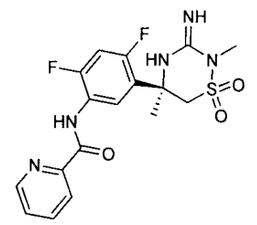
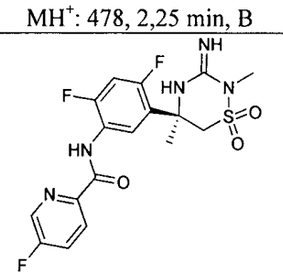
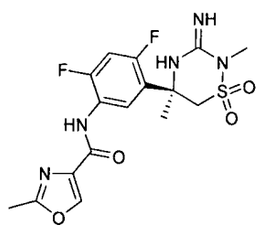
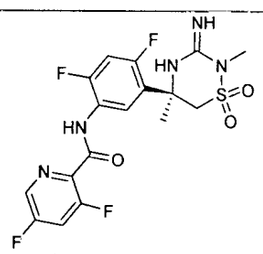
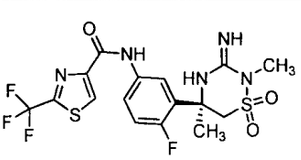
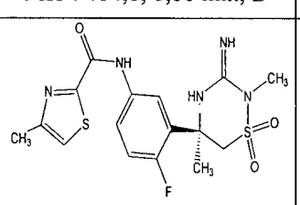
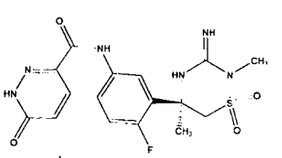
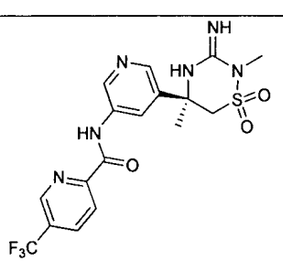
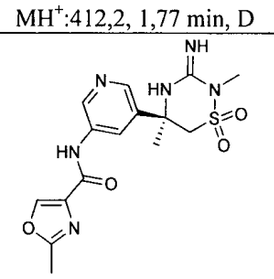
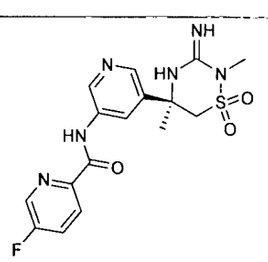
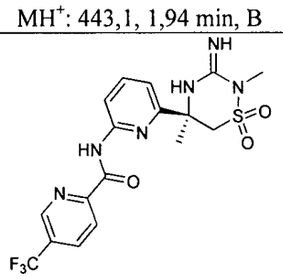
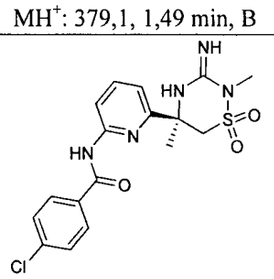
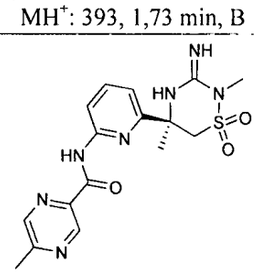
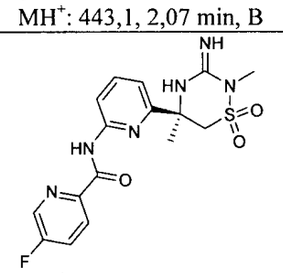
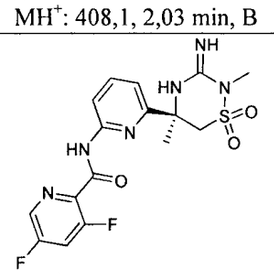
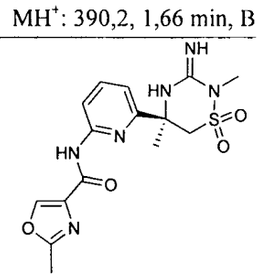
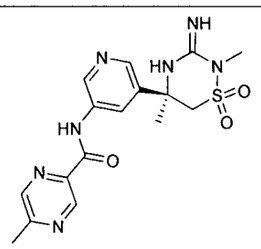
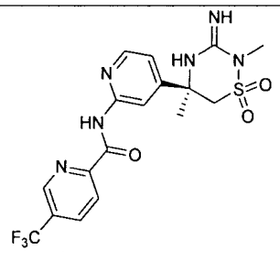
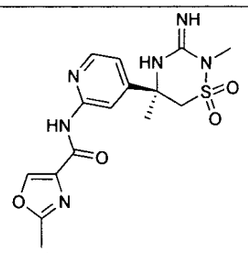
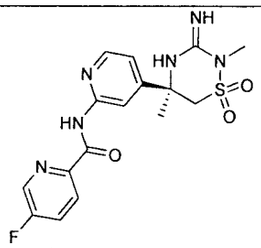
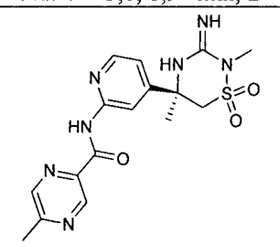
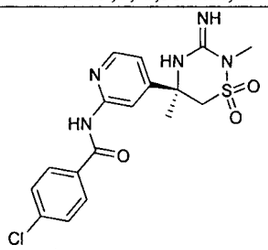
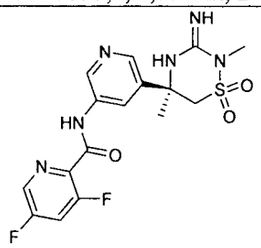
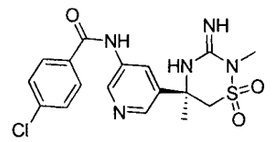
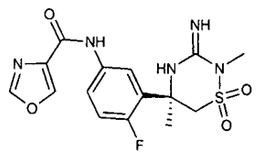
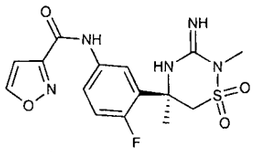
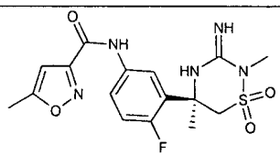
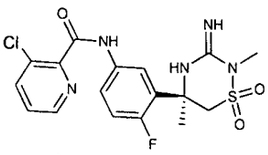
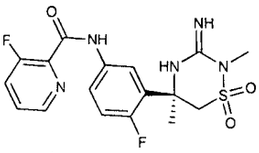
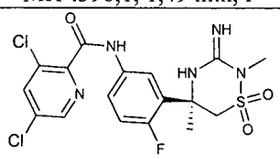
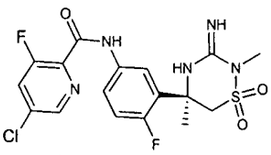
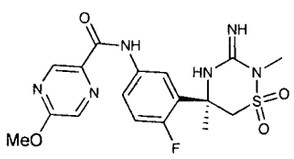
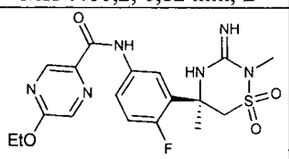
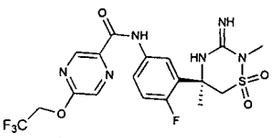
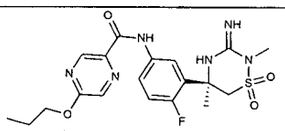
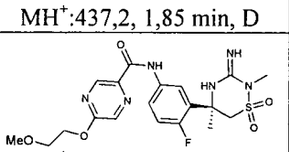
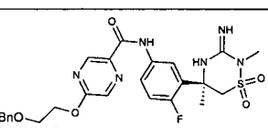
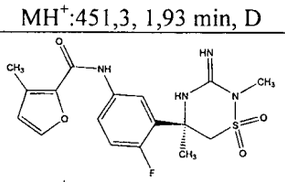
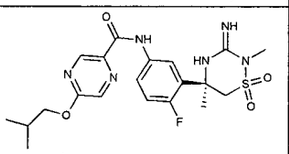
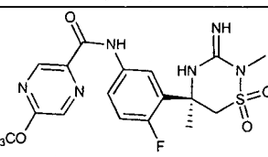
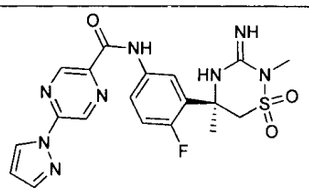
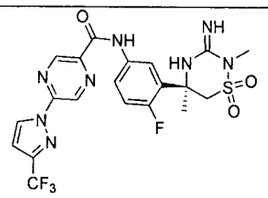
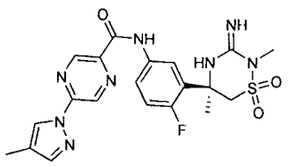
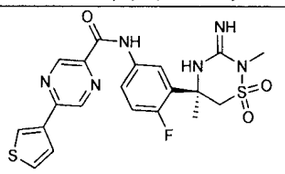
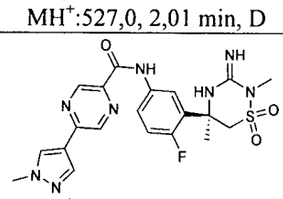
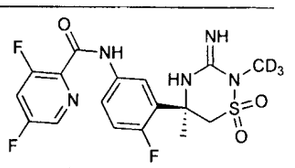
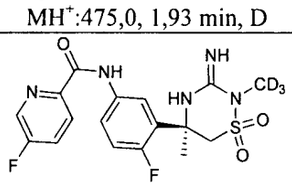
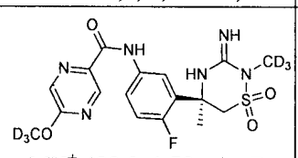
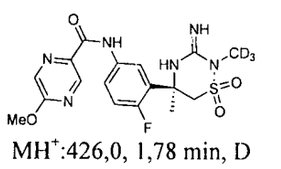
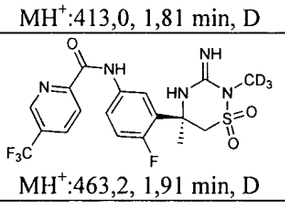
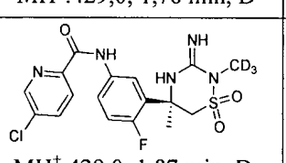
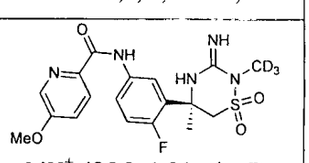
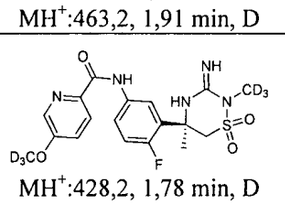
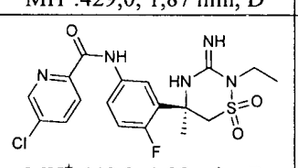
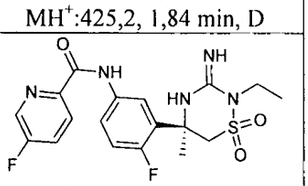
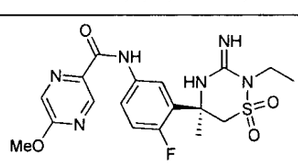
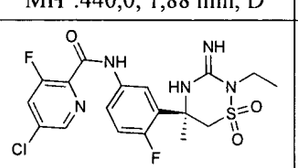
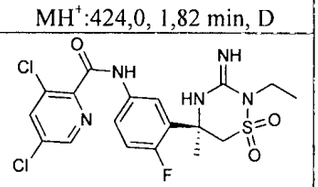
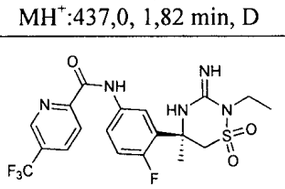
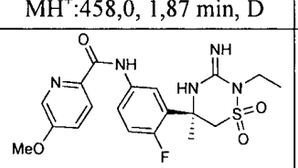
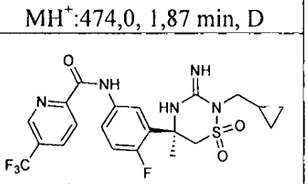
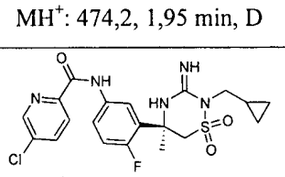
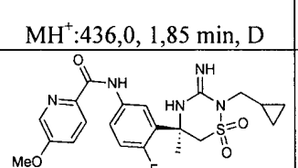
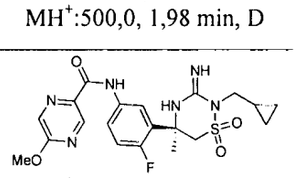
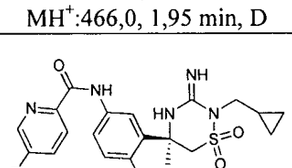
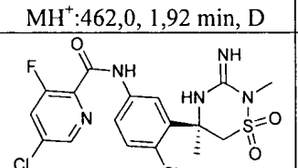
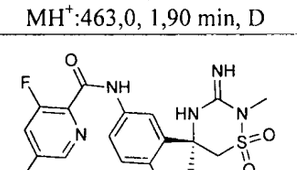
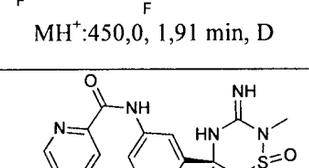
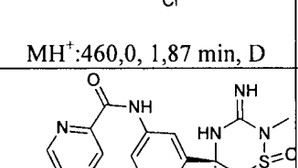
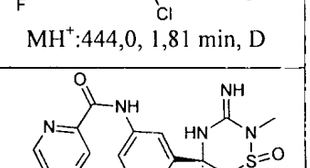
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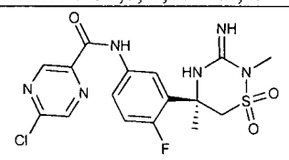
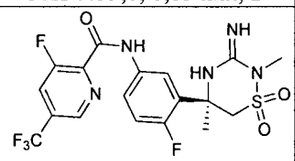
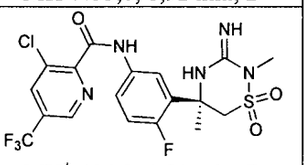
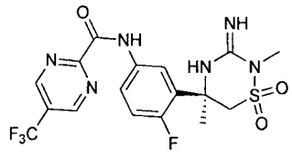
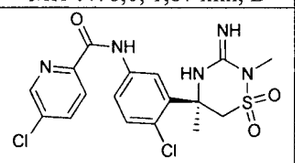
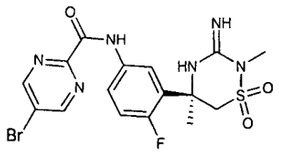
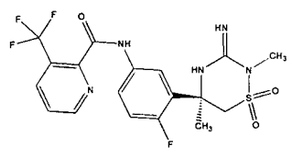
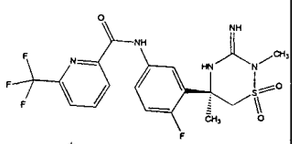
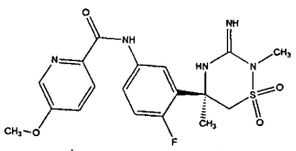
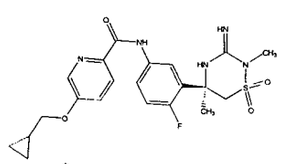
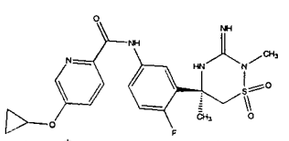
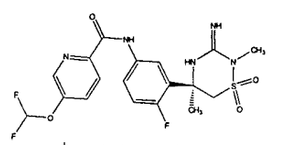
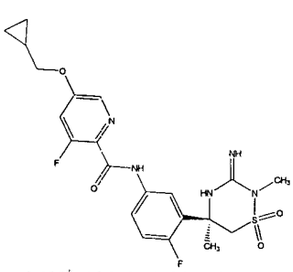
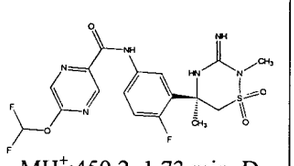
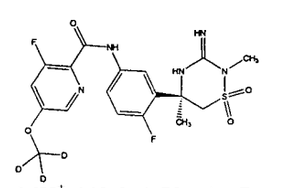
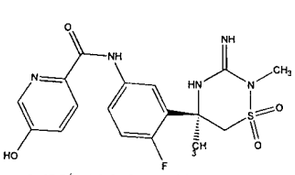
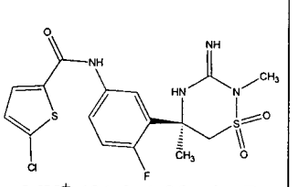
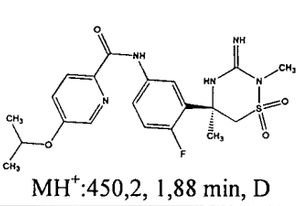
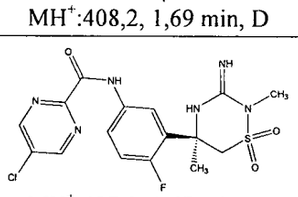
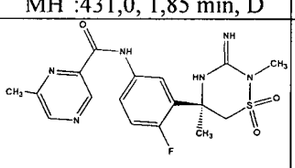
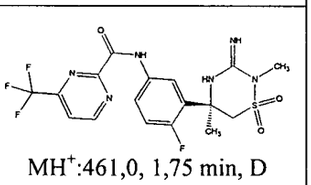
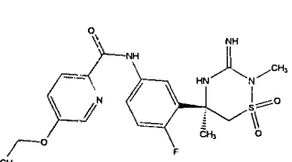
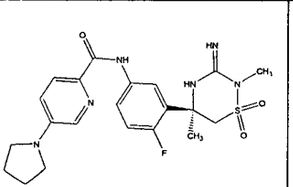
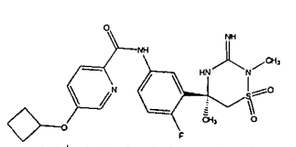
Tabla V: Los siguientes ejemplos se prepararon utilizado un procedimiento similar al descrito en el Esquema 11b utilizando las arilaminas y ácidos carboxílicos apropiados.

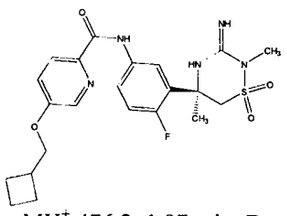
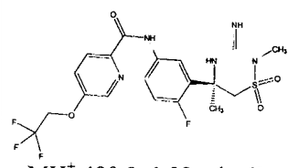
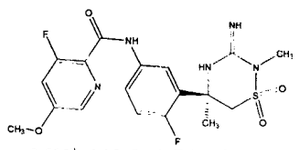
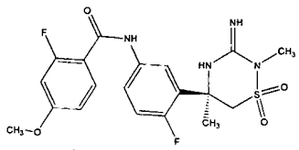
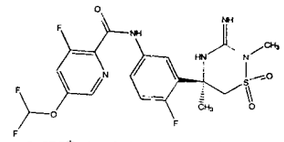
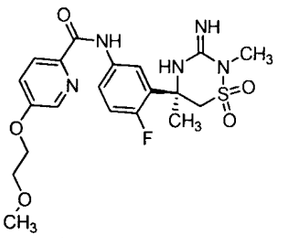
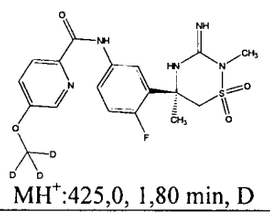
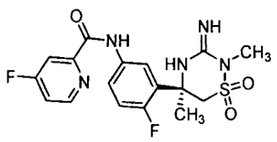
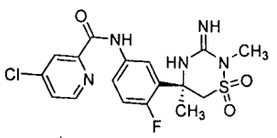
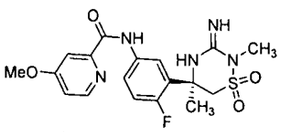
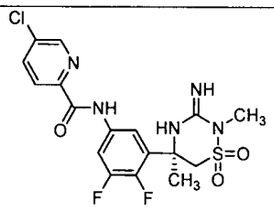
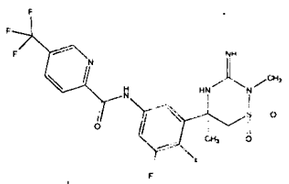
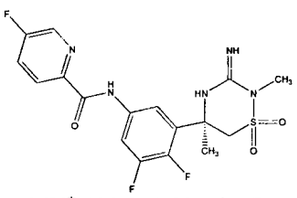
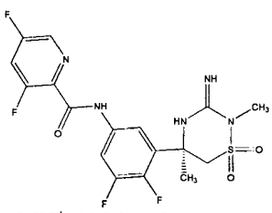
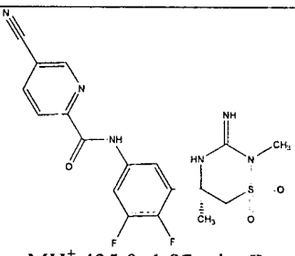
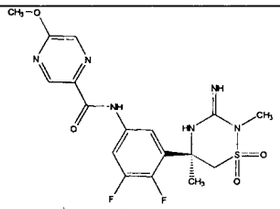
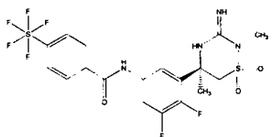
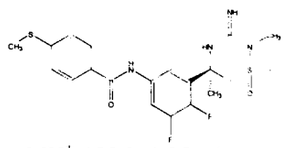
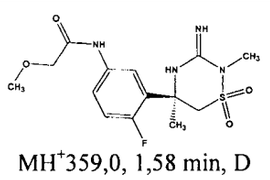
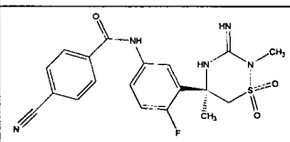
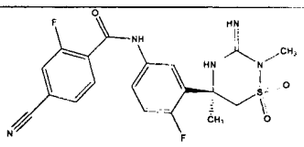
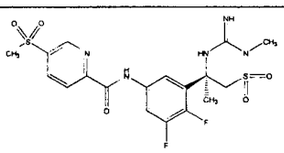
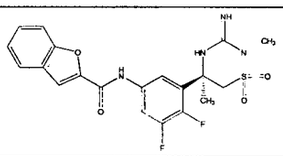
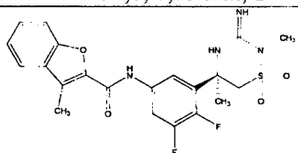
Ejemplos (Datos de LCMS enlistados con cada compuesto: MH^+ observado, tiempo de retención de HPLC y método de LCMS)					
21	 MH^+: 442, 1,89 min, D	**22**	 MH^+: 392, 1,76 min, D	**23**	 MH^+: 378, 1,64 min, D
24	 MH^+: 396,0, 1,69 min, D	**25**	 MH^+: 410,0, 1,79 min, D	**26**	 MH^+: 460,0, 1,90 min, D
27	 MH^+: 407, 1,86 min, D	**28**	 MH^+: 392, 1,76 min, D	**29**	 MH^+: 470,0, 1,87 min, D
30	 MH^+: 428, 1,76 min, D	**31**	 MH^+:448,2, 2,02 min, D	**32**	 MH^+: 426, 1,88 min, D
33	 MH^+: 409,2, 1,68 min, D	**34**	 MH^+: 426,2, 3,25 min, A	**35**	 MH^+: 406,2, 1,8 min, D
36	 MH^+: 407,2, 1,71 min, D	**37**	 MH^+: 444, 1,86 min, D	**38**	 MH^+: 410,2, 1,78 min, D

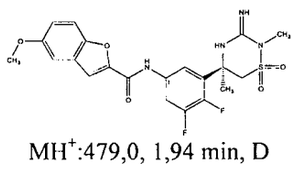
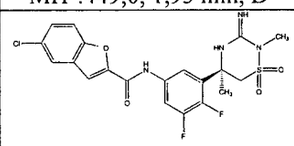
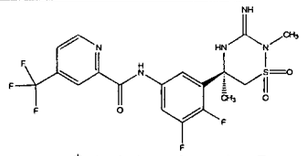
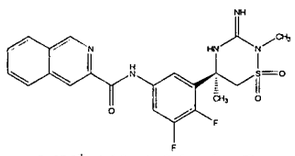
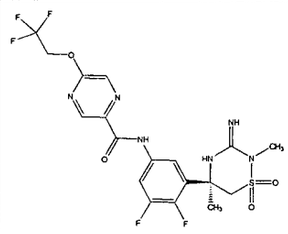
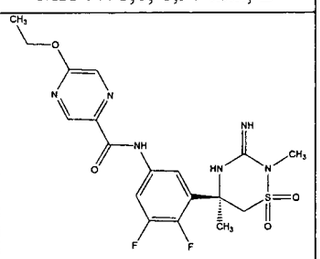
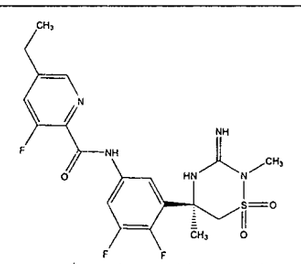
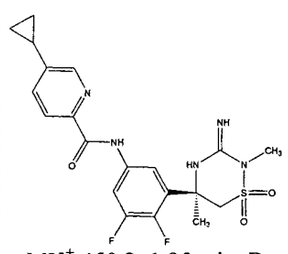
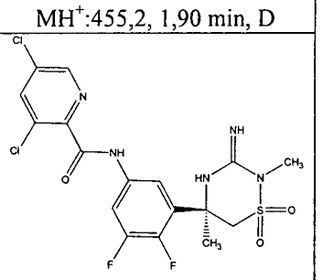
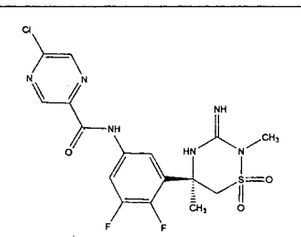
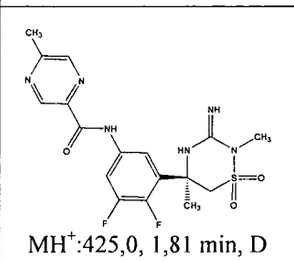
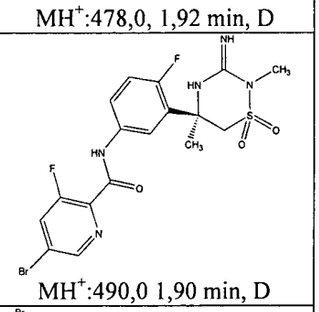
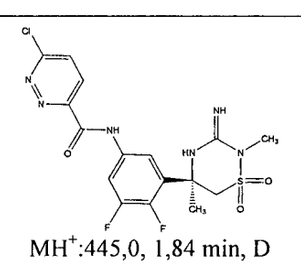
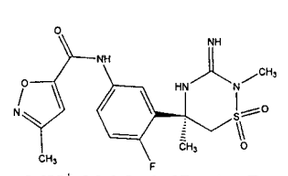
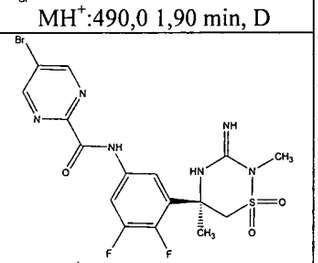
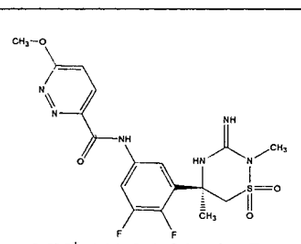
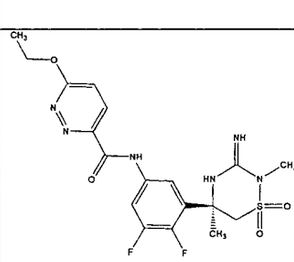
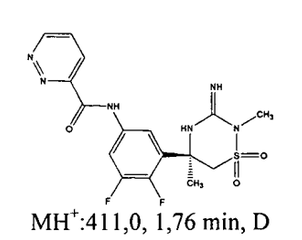
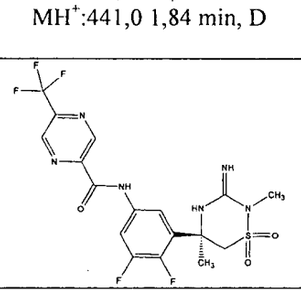
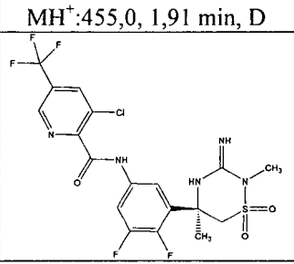
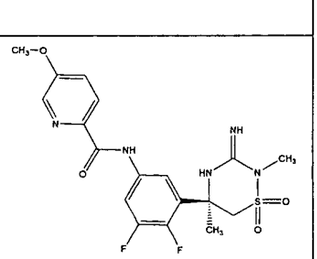
39	 MH$^+$: 476,0, 1,91 min, D	**40**	 MH$^+$: 426,0, 1,83 min, D	**40a**	 MH$^+$: 425,1, 1,91 min, B
40b	 MH$^+$: 478, 2,25 min, B	**40c**	 MH$^+$: 443,9, 2,18 min, B	**40d**	 MH$^+$: 410,2, 2,02 min, B
40e	 MH$^+$: 428, 2,06 min, B	**40f**	 MH$^+$: 414,1, 1,86 min, B	**40g**	 MH$^+$: 446,0, 2,01 min, B
40h	 MH$^+$:466,2, 1,84 min, D	**40i**	 MH$^+$:412,2, 1,77 min, D	**40j**	 MH$^+$:409,3, 1,55 min, D
40k	 MH$^+$: 443,1, 1,94 min, B	**40l**	 MH$^+$: 379,1, 1,49 min, B	**40m**	 MH$^+$: 393, 1,73 min, B
40n	 MH$^+$: 443,1, 2,07 min, B	**40o**	 MH$^+$: 408,1, 2,03 min, B	**40p**	 MH$^+$: 390,2, 1,66 min, B
40q	 MH$^+$: 393,1, 1,86 min, B	**40r**	 MH$^+$: 411,1, 1,79 min, B	**40s**	 MH$^+$: 379,2, 1,64 min, B

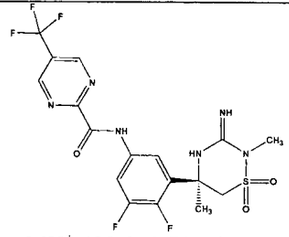
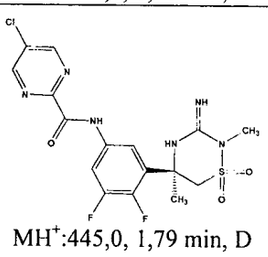
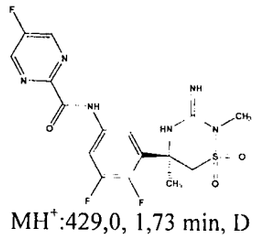
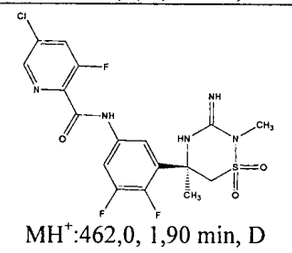
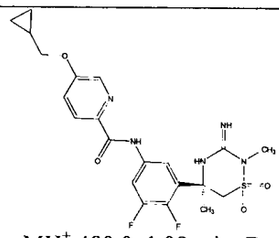
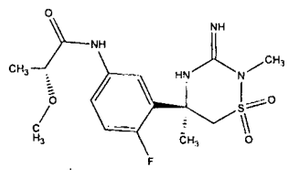
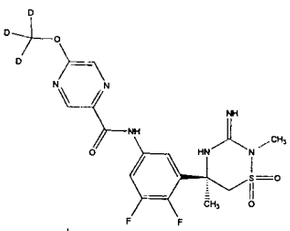
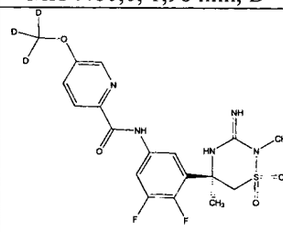
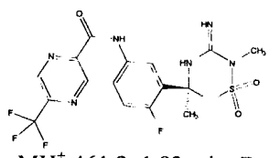
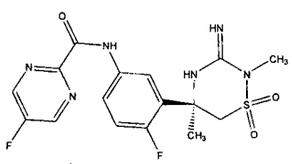
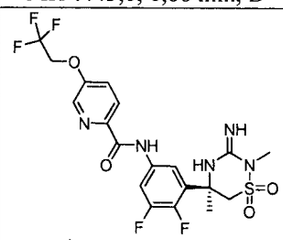
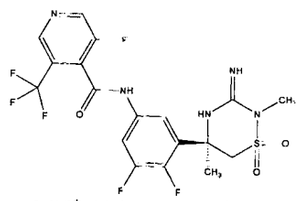
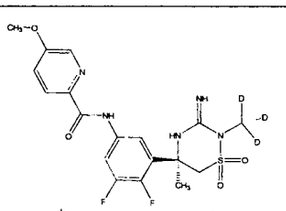
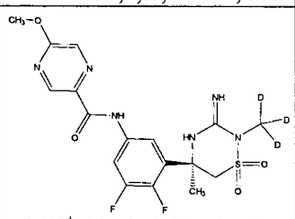
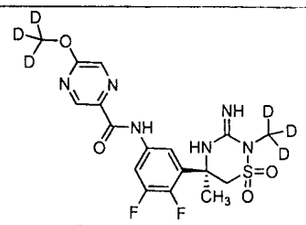
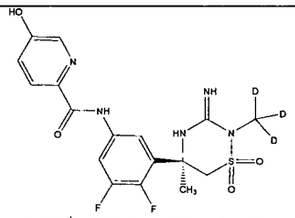
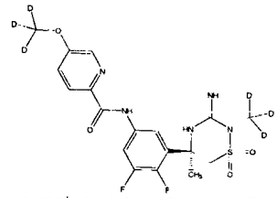
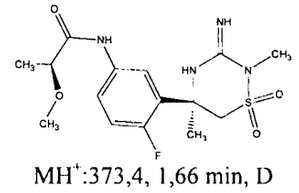
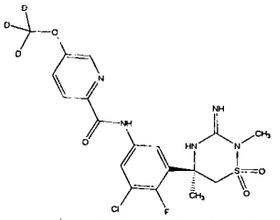
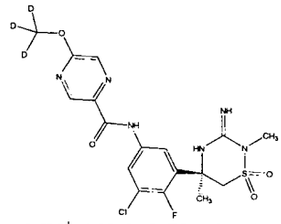
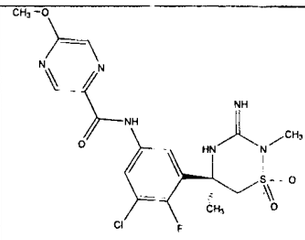
40t	 MH$^+$: 390,1, 1,46 min, B	**40u**	 MH$^+$: 443,0, 1,94 min, B	**40v**	 MH$^+$: 379,1, 1,55 min, B
40w	 MH$^+$: 393,1, 1,77 min, D	**40x**	 MH$^+$: 390,2, 1,53 min, B	**40y**	 MH$^+$: 408,0, 1,85 min, B
40z	 MH$^+$: 411,0, 1,69 min, B	**40aa**	 MH$^+$: 408,1, 1,76 min, B	**40ab**	 MH$^+$:382,2, 1,61 min, D
40ac	 MH$^+$:382,2, 1,65 min, D	**40ad**	 MH$^+$:396,1, 1,49 min, F	**40ae**	 MH$^+$:426,2, 1,73 min, D
40af	 MH$^+$:410,2, 1,71 min, D	**40ag**	 MH$^+$:460,2, 1,82 min, D	**40ah**	 MH$^+$:444,2, 1,78 min, D
40ai	 MH$^+$:423,2, 1,76 min, D	**40aj**	 MH$^+$:437,2, 1,85 min, D	**40ak**	 MH$^+$:491,2, 1,91 min, D
40al	 MH$^+$:451,3, 1,93 min, D	**40am**	 MH$^+$:467,2, 1,79 min, D	**40an**	 MH$^+$:543,1, 2,01 min, D
40ao	 MH$^+$:395,2, 1,81 min, D	**40ap**	 MH$^+$:465,2, 1,99 min, D	**40aq**	 MH$^+$:426,0, 1,75 min, D

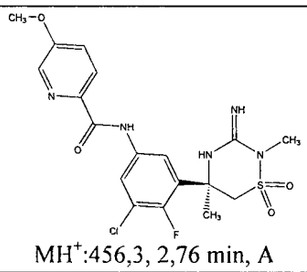
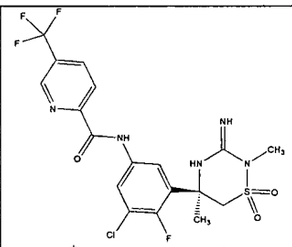
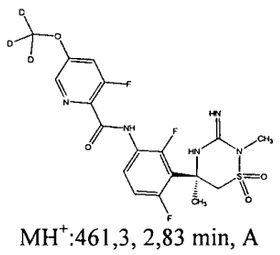
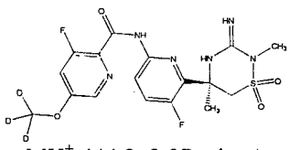
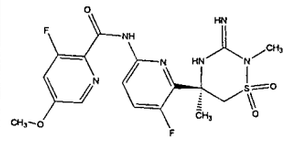
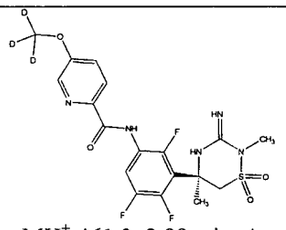
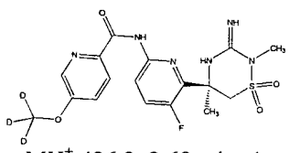
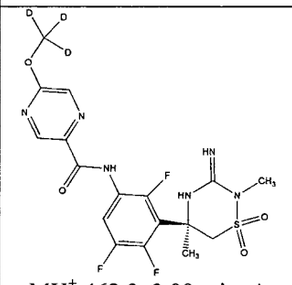
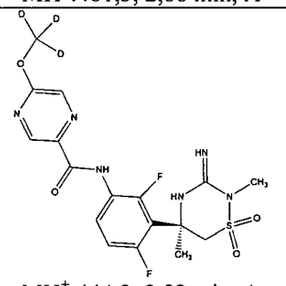
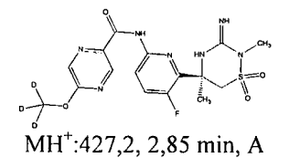
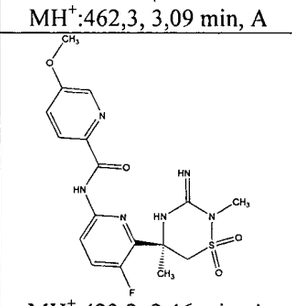
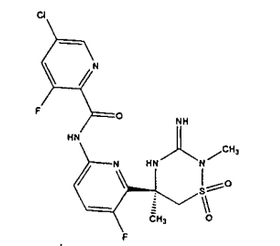
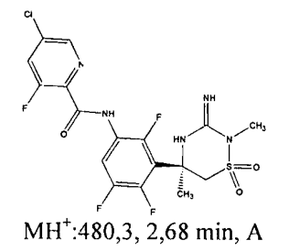
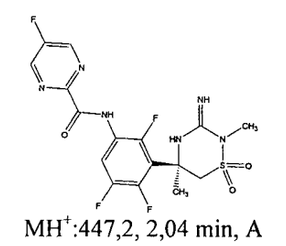
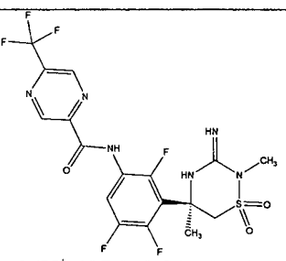
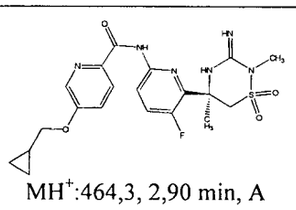
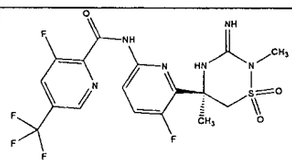
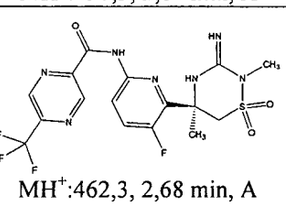
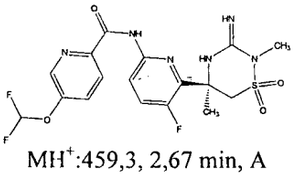
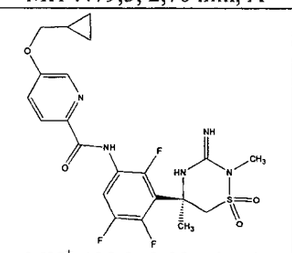
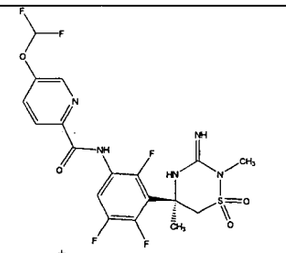
40ar	 MH$^+$:459,0, 1,86 min, D	**40as**	 MH$^+$:527,0, 2,01 min, D	**40at**	 MH$^+$:473,0, 1,93 min, D
40au	 MH$^+$:475,0, 1,93 min, D	**40av**	 MH$^+$:473,0, 1,78 min, D	**40aw**	 MH$^+$:431,2, 1,75 min, D
40ax	 MH$^+$:413,0, 1,81 min, D	**40ay**	 MH$^+$:429,0, 1,78 min, D	**40az**	 MH$^+$:426,0, 1,78 min, D
40ba	 MH$^+$:463,2, 1,91 min, D	**40bb**	 MH$^+$:429,0, 1,87 min, D	**40bc**	 MH$^+$:425,2, 1,84 min, D
40bd	 MH$^+$:428,2, 1,78 min, D	**40be**	 MH$^+$:440,0, 1,88 min, D	**40bf**	 MH$^+$:424,0, 1,82 min, D
40bg	 MH$^+$:437,0, 1,82 min, D	**40bh**	 MH$^+$:458,0, 1,87 min, D	**40bi**	 MH$^+$:474,0, 1,87 min, D
40bj	 MH$^+$: 474,2, 1,95 min, D	**40bk**	 MH$^+$:436,0, 1,85 min, D	**40bl**	 MH$^+$:500,0, 1,98 min, D
40b	 MH$^+$:466,0, 1,95 min, D	**40bn**	 MH$^+$:462,0, 1,92 min, D	**40bo**	 MH$^+$:463,0, 1,90 min, D
40bp	 MH$^+$:450,0, 1,91 min, D	**40bq**	 MH$^+$:460,0, 1,87 min, D	**40br**	 MH$^+$:444,0, 1,81 min, D
40bs		**40bt**		**40bu**	

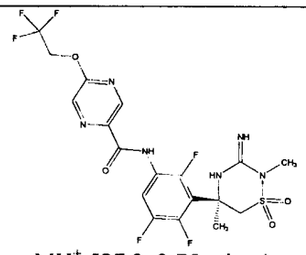
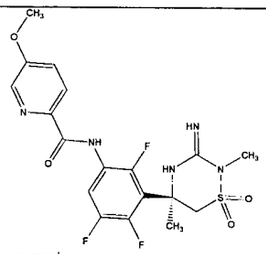
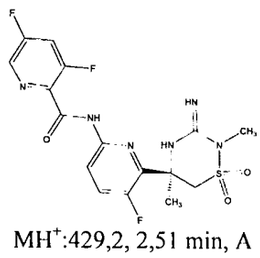
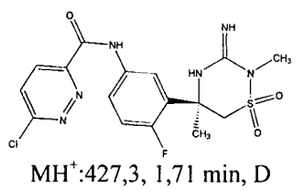
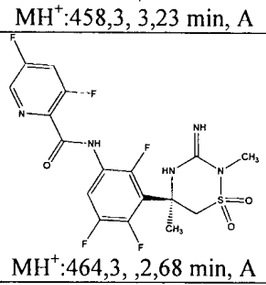
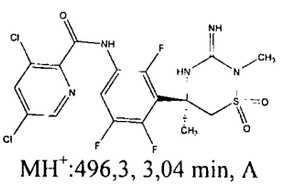
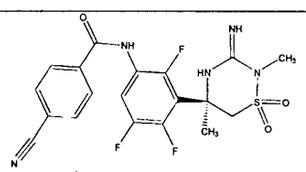
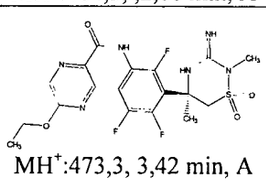
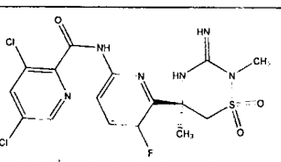
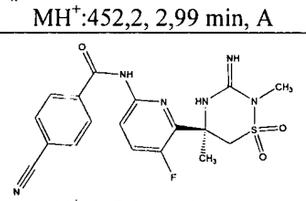
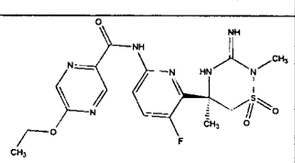
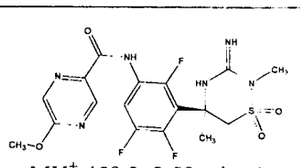
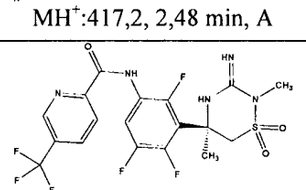
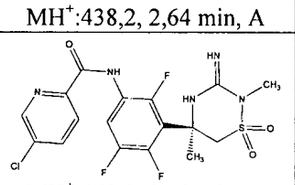
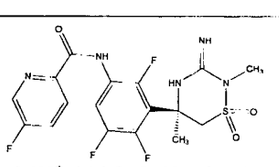
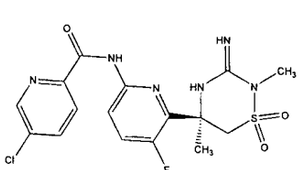
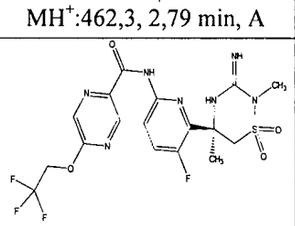
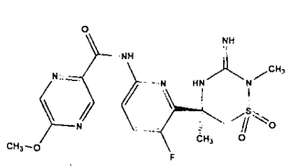
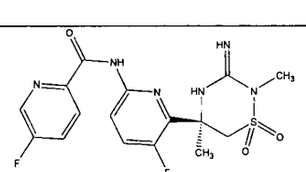
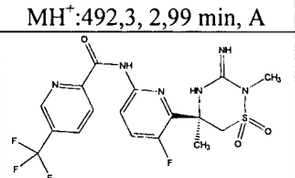
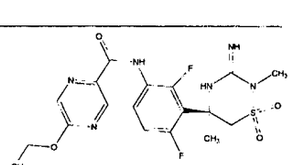
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40bv	 MH+:427,0, 1,79 min, D	**40bw**	 MH+:478,0, 1,87 min, D	**40bx**	 MH+:494,2, 1,81 min, D
40by	 MH+:461,2, 1,73 min, D	**40bz**	 MH+:442,0, 1,86 min, D	**40ca**	 MH+:473,0, 1,71 min, D
40cb	 MH+:460,2, 1,78 min, D	**40cc**	 MH+:460,2, 1,87 min, D	**40cd**	 MH+:422,2, 1,79 min, D
40ce	 MH+:484,2, 1,90 min, D	**40cf**	 MH+:448,0, 1,88 min, D	**40cg**	 MH+:458,0, 1,59 min, F
40ch	 MH+:480,0, 1,92 min, D	**40ci**	 MH+:459,2, 1,73 min, D	**40cj**	 MH+:443,0, 1,79 min, D
40ck	 MH+:408,2, 1,69 min, D	**40cl**	 MH+:431,0, 1,85 min, D	**40cm**	 MH+:450,2, 1,88 min, D
40cn	 MH+:427,0, 1,67 min, D	**40co**	 MH+:407,0, 1,72 min, D	**40cp**	 MH+:461,0, 1,75 min, D
40cq	 MH+:436,2, 1,84 min, D	**40cr**	 MH+:461,4, 1,83 min, D	**40cs**	 MH+:462,0, 1,92 min, D

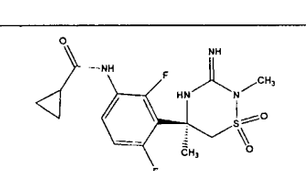
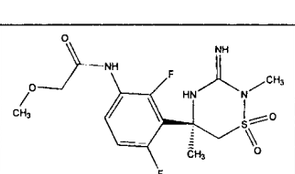
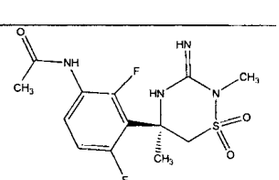
40ct	 MH$^+$:476,2, 1,97 min, D	**40cu**	 MH$^+$:490,0, 1,92 min, D	**40cv**	 MH$^+$:440,0, 1,76 min, D
40cw	 MH$^+$:439,0, 1,79 min, D	**40cx**	 MH$^+$:476,0, 1,72 min, D	**40cy**	 MH$^+$:466,0, 1,82 min, D
40cz	 MH$^+$:425,0, 1,80 min, D	**40da**	 MH$^+$:410, 1,79 min, D	**40db**	 MH$^+$:426,0, 1,83 min, D
40dc	 MH$^+$:422,0, 1,71 min, D	**40dd**	 MH$^+$:444,0, 1,94 min, D	**40de**	 MH$^+$:478,0, 2,04 min, D
40df	 MH$^+$:428,0, 1,89 min, D	**40dg**	 MH$^+$:446,0, 1,85 min, D	**40dh**	 MH$^+$:435,0, 1,87 min, D
40di	 MH$^+$:441,0, 1,85 min, D	**40dj**	 MH$^+$:534,8, 2,04 min, D	**40dk**	 MH$^+$:455,0, 1,95 min, D
40dl	 MH$^+$359,0, 1,58 min, D	**40dm**	 MH$^+$:416,0, 1,75 min, D	**40dn**	 MH$^+$:434,0, 1,75 min, D
40do		**40dp**		**40dq**	

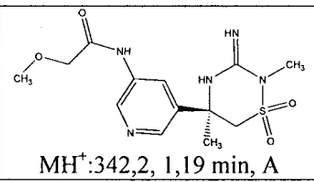
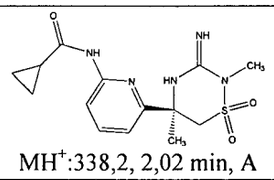
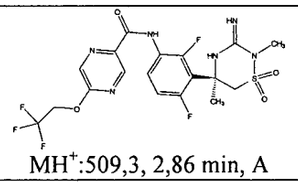
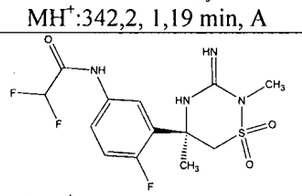
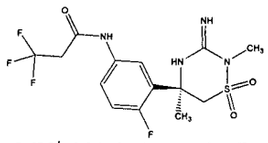
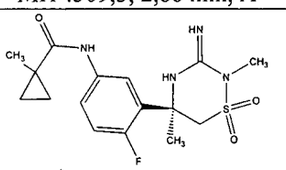
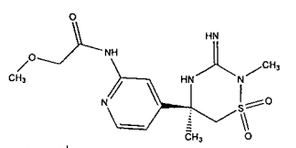
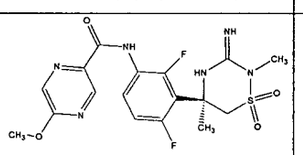
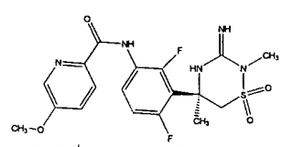
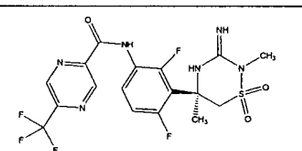
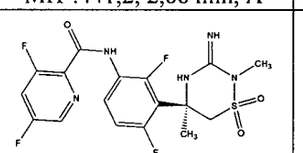
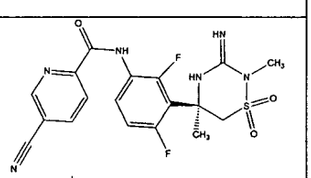
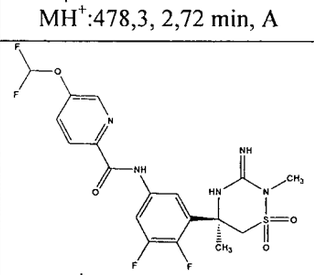
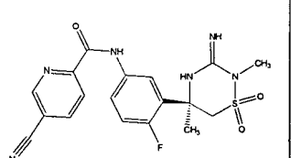
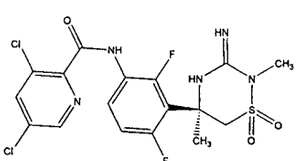
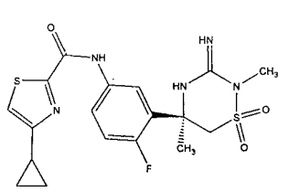
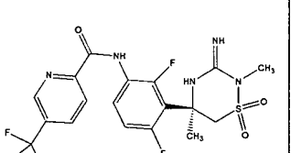
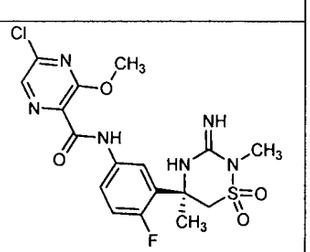
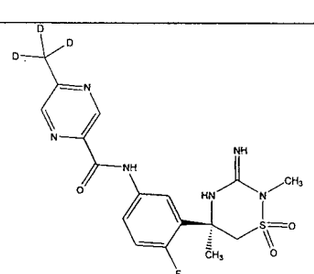
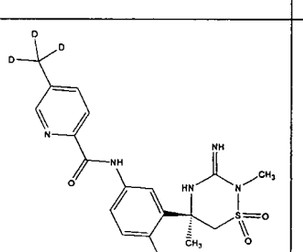
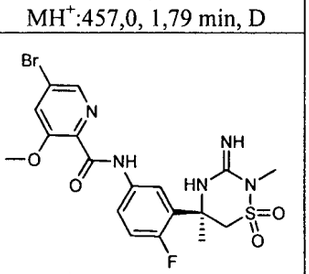
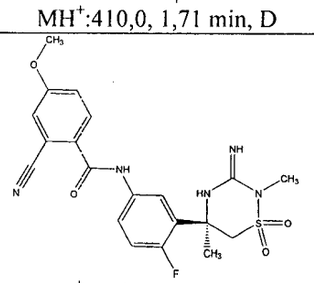
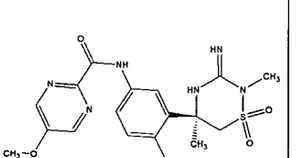
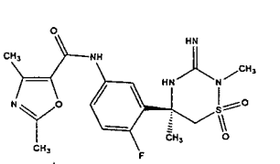
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40dr	 MH^+:479,0, 1,94 min, D	**40ds**	 MH^+:483,0, 2,01 min, D	**40dt**	 MH^+:478,0, 1,97 min, D
40du	 MH^+:460, 1,96 min, D	**40dv**	 MH^+:509,0, 2,11 min, D	**40dw**	 MH^+:455,2, 1,90 min, D
40dx	 MH^+:456,2, 1,92 min, D	**40dy**	 MH^+:450,2, 1,95 min, D	**40dz**	 MH^+:478,0, 1,92 min, D
40ea	 MH^+:445,0, 1,87 min, D	**40eb**	 MH^+:425,0, 1,81 min, D	**40ec**	 MH^+:490,0 1,90 min, D
40ed	 MH^+:445,0, 1,84 min, D	**40ee**	 MH^+:396,2, 1,67 min, D	**40ef**	 MH^+:488,8, 1,80 min, D
40eg	 MH^+:441,0 1,84 min, D	**40eh**	 MH^+:455,0, 1,91 min, D	**40ei**	 MH^+:411,0, 1,76 min, D
40ej		**40ek**		**40el**	

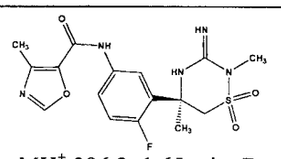
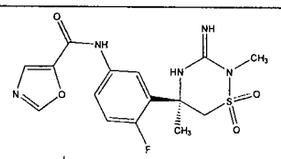
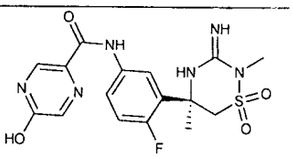
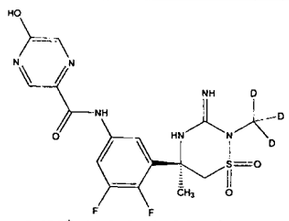
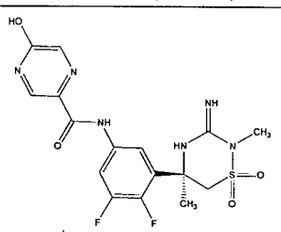
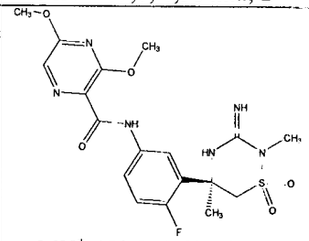
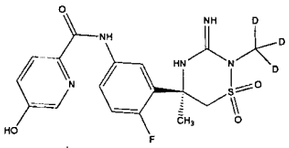
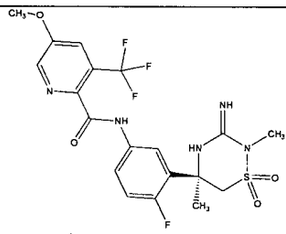
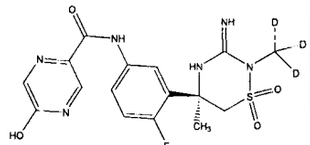
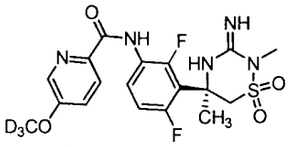
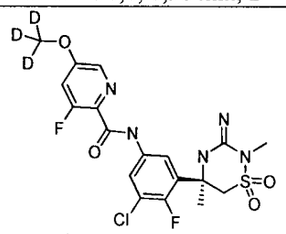
	MH+:479,0, 1,95 min, D		MH+:422,0, 1,71 min, D		MH+:440,0, 1,88 min, D
40em	 MH+:422,0, 1,71 min, D	**40en**	 MH+:445,0, 1,79 min, D	**40eo**	 MH+:429,0, 1,73 min, D
40ep	 MH+:462,0, 1,90 min, D	**40eq**	 MH+:480,0, 1,98 min, D	**40er**	 MH+:373,2, 1,64 min, D
40es	 MH+:444,2, 1,84 min, D	**40et**	 MH+:443,0, 1,88 min, D	**40eu**	 MH+:461,2, 1,83 min, D
40ev	 MH+:411,2, 1,61 min, D	**40ew**	 MH+:508,0, 1,99 min, D	**40ex**	 MH+:496,0, 1,88 min, D
40ez	 MH+:443,0, 1,85 min, D	**40fa**	 MH+:444,0, 1,84 min, D	**40fb**	 MH+:447,0, 1,83 min, D
40fc	 MH+:429,0, 1,75 min, D	**40fd**	 MH+:446,0, 1,84 min, D	**40fe**	 MH+:373,4, 1,66 min, D
40ff	 MH+:459,3, 1,78 min, A	**40fg**	 MH+:460,3, 2,72 min, A	**40fh**	 MH+:457,3, 2,71 min, A

40fi	 MH$^+$:456,3, 2,76 min, A	**40fj**	 MH$^+$:494,3, 3,08 min, A	**40fk**	 MH$^+$:461,3, 2,83 min, A
40fl	 MH$^+$:444,2, 2,87 min, A	**40fm**	 MH$^+$:441,2, 2,80 min, A	**40fn**	 MH$^+$:461,3, 2,88 min, A
40fo	 MH$^+$:426,2, 2,68 min, A	**40fp**	 MH$^+$:462,3, 3,09 min, A	**40fq**	 MH$^+$:444,2, 2,82 min, A
40fr	 MH$^+$:427,2, 2,85 min, A	**40fs**	 MH$^+$:423,2, 2,46 min, A	**40ft**	 MH$^+$:445,2, 3,04 min, A
40fu	 MH$^+$:480,3, 2,68 min, A	**40fv**	 MH$^+$:447,2, 2,04 min, A	**40fw**	 MH$^+$:497,3, 2,84 min, A
40fx	 MH$^+$:464,3, 2,90 min, A	**40fy**	 MH$^+$:479,3, 2,70 min, A	**40fz**	 MH$^+$:462,3, 2,68 min, A
40ga	 MH$^+$:459,3, 2,67 min, A	**40gb**	 MH$^+$:498,3, 3,83 min, A	**40gc**	 MH$^+$:494,3, 3,46 min, A

40gd	 MH$^+$:527,3, 3,75 min, A	**40ge**	 MH$^+$:458,3, 3,23 min, A	**40gf**	 MH$^+$:429,2, 2,51 min, A
40gg	 MH$^+$:427,3, 1,71 min, D	**40gh**	 MH$^+$:464,3, ,2,68 min, A	**40gi**	 MH$^+$:496,3, 3,04 min, A
40gj	 MH$^+$:452,2, 2,99 min, A	**40gk**	 MH$^+$:473,3, 3,42 min, A	**40gl**	 MH$^+$:461,3, 3,21 min, A
40gm	 MH$^+$:417,2, 2,48 min, A	**40gn**	 MH$^+$:438,2, 2,64 min, A	**40go**	 MH$^+$:459,3, 2,58 min, A
40gp	 MH$^+$: 496,3, 2,96 min, A	**40gq**	 MH$^+$:462,3, 2,79 min, A	**40gr**	 MH$^+$:446,2, 2,60 min, A
40gs	 MH$^+$:427,2, 2,74 min, A	**40gt**	 MH$^+$:492,3, 2,99 min, A	**40gu**	 MH$^+$:424,2, 2,92 min, A
40gv	 MH$^+$:411,2 2,89 min, A	**40gw**	 MH$^+$:461,3, 3,40 min, A	**40gx**	 MH$^+$:455,3, 2,61 min, A

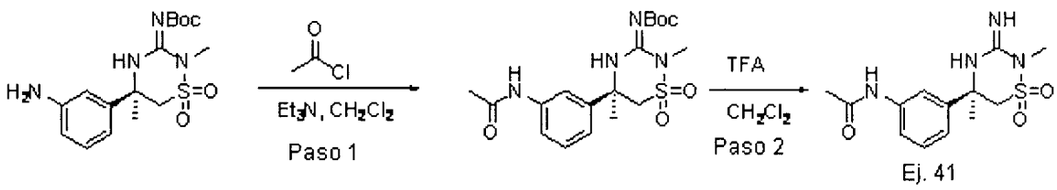
40gy	 MH$^+$:373,2, 2,24 min, A	**40gz**	 MH$^+$:377,2, 1,96 min, A	**40ha**	 MH$^+$:347,2, 1,76 min, A

40hb	 MH$^+$:342,2, 1,19 min, A	**40hc**	 MH$^+$:338,2, 2,02 min, A	**40hd**	 MH$^+$:509,3, 2,86 min, A
40he	 MH$^+$:365,0, 1,62 min, D	**40hf**	 MH$^+$:397,0, 1,71 min, D	**40hg**	 MH$^+$:369,0, 1,71 min, D
40hh	 MH$^+$:342,2, 1,62 min, A	**40hi**	 MH$^+$:441,2, 2,88 min, A	**40hj**	 MH$^+$:440, 2,07 min, D
40hk	 MH$^+$:478,3, 2,72 min, A	**40hl**	 MH$^+$:446,2, 2,33 min, A	**40hm**	 MH$^+$:435,2, 2,39 min, A
40hn	 MH$^+$:476,0, 1,92 min, D	**40ho**	 MH$^+$:417,2, 1,73 min, D	**40hp**	 MH$^+$:478,3, 2,68 min, A
40hq	 MH$^+$:438,0, 1,89 min, D	**40hr**	 MH$^+$:478,3, 1,99 min, A	**40hs**	 MH$^+$:457,0, 1,79 min, D
40ht	 MH$^+$:410,0, 1,71 min, D	**40hu**	 MH$^+$:409,2, 1,79 min, D	**40hv**	 MH$^+$:500,0, 1,81 min, D
40hw	 MH$^+$:446,0, 1,79 min, D	**40hx**	 MH$^+$:423,0, 1,68 min, D	**40hy**	 MH$^+$:410,2, 1,69 min, D

40hz	 MH$^+$:396,2, 1,65 min, D	**40ia**	 MH$^+$:382,2, 1,58 min, D	**40ib**[a]	 MH$^+$:409,0, 1,58 min, D
40ic[a]	 MH$^+$:430,0, 1,66 min, D	**40id**[a]	 MH$^+$:427,0, 1,68 min, D	**40ie**	 MH$^+$:453,2, 1,60 min, D
40if	 MH$^+$:411,0, 1,83 min, D	**40ig**	 MH$^+$:490,0, 1,96 min, D	**40ih**[a]	 MH$^+$:412,0, 1,72 min, D
40ii	 MH$^+$:443,2, 2,57 min, A	**40ij**	 MH$^+$:477,3, 2,95 min, A		

[a] Las amidas de hidroxipirazina se formaron empleando el ácido de ciclopropilmetiléter pirazina (Entrada 5, Tabla IVb) en lugar de ácido 1,3–oxazol–4–carboxílico en el paso 1 del Esquema 11b.

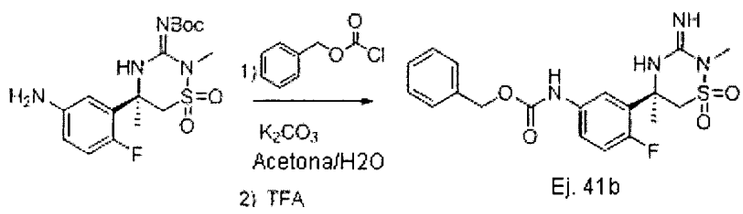
Esquema 12:



Paso 1: A una solución de la anilina de la Tabla IV entrada 1 (80 mg) y Et_3N (50 µL) en CH_2Cl_2 (2 mL) se le agregó cloruro de acetilo (1,2 eq.). La solución resultante se agitó a TA durante 2 horas. Se agregó agua y la capa acuosa se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y concentró. El residuo en bruto se purificó mediante cromatografía flash (SiO_2: 0 a 60% EtoAc en hex).

Paso 2: El Ejemplo 41 se preparó como la sal TFA del producto del paso 1 utilizando un método similar a aquel descrito en el Esquema 11b paso 2. Datos de LCMS: (método D): t_R = 0,91 min, *m/e* = 311 (M+H).

Esquema 12b:

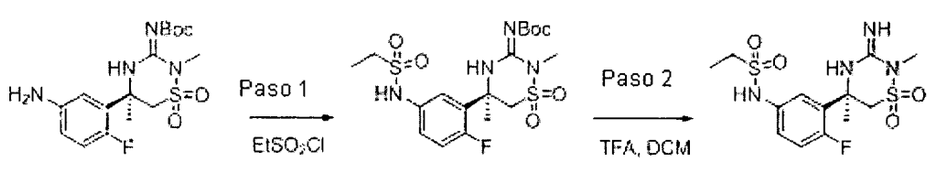


Ej. 41b

A una mezcla de la anilina del Esquema 10 (50 mg, 0,13 mmol) y carbonato de potasio (18 mg, 0,13 mmol) en 1:1 acetona: agua (4 mL) se agregó cloroformiato de bencilo (0,028 mL, 0,19 mmol). La mezcla se agitó a TA durante 30 min. Se agregó agua y la mezcla se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 70:30 hexanos:EtOAc) para proporcionar el carbamato.

Ejemplo 41b se preparó como su sal TFA a partir del carbamato antes mencionado empleando un método similar a aquel descrito en el Esquema 11b paso 2. Datos de LCMS: (método D): t_R = 1,88 min, *m/e* = 421,0 (M+H).

Esquema 12c:

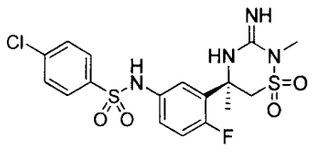
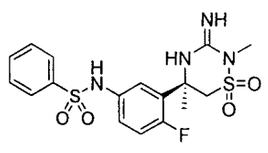


Ej. 41c

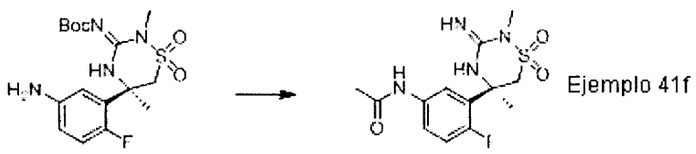
Paso 1: A una mezcla de la anilina (200 mg, 0,517 mmol, Esquema 10) y DIEA (0,36 mL, 2,07 mmol) en CH_2Cl_2 (2 mL) a TA se le agregó gota a gota cloruro de etilsulfonilo (0,074 mL, 0,775 mmol). Después de 18 h, la reacción se templó con HCl 1 M y la capa acuosa se extrajo con DCM. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y concentraron bajo presión reducida.

Paso 2: El **Ejemplo 41c** se preparó a partir del material antes mencionado utilizando un método similar al descrito en el Esquema 11b paso 2. Luego de la desprotección, el residuo resultante se purificó mediante cromatografía en fase inversa (C18: elución de gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar el **Ejemplo 41c** como su sal TFA. LCMS (condiciones D): t_R = 1,64 min, *m/e* = 379,0 (M+H).

Tabla Va: Los siguientes ejemplos se prepararon utilizando un método similar a aquel descrito en el Esquema 12c.

Ejemplos (Datos de LCMS mostrados con cada compuesto: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
41d	 MH^+:460,8, 1,86 min, D	**41e**	 MH^+:427,0, 1,78 min, D

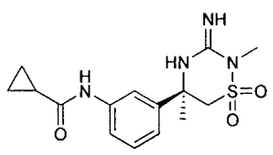
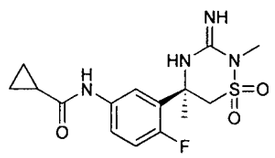
Esquema 12d:



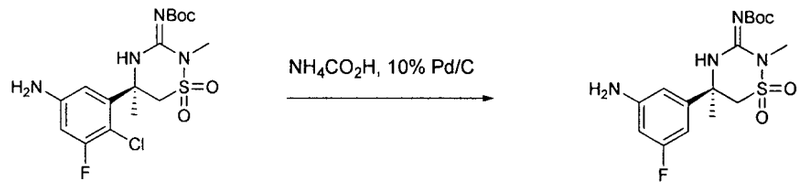
A la anilina (Esquema 10, 70 mg, 0,18 mmol) en 2 mL de DCM se le agregó anhídrido acético (19 µL, 0,2 mmol) y trietilamina (29 µL, 0,2 mmol). La reacción se agitó durante 3 horas a temperatura ambiente, luego se vertió en agua. La mezcla se extrajo con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo*. El residuo se purificó por medio de

cromatografía en gel de sílice (0–50% EtOAc/hexanos durante 30 minutes) para proporcionar un producto de metilamida. Este material se agitó en 2 mL de TFA al 20%/DCM durante 1 hr y luego se concentró *in vacuo* para proporcionar el **Ejemplo 41f** como una sal trifluoracetato (0,041g, 69%). Datos de LCMS: (método A): t_R = 2,96 min, *m/e* = 379,2 (M+H).

Tabla VI: Los siguientes ejemplos se prepararon utilizando un método similar a aquel descrito en Esquema 12 utilizando los cloruros ácidos apropiados y las arilaminas.

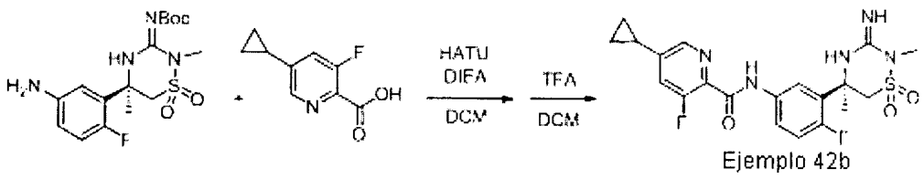
Ejemplos (Datos de LCMS mostrados con cada compuesto: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
42	 MH^+:337, 1,57 min, D	**42a**	 MH^+:335,0, 1,66 min, D

Esquema 12e:



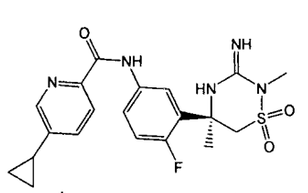
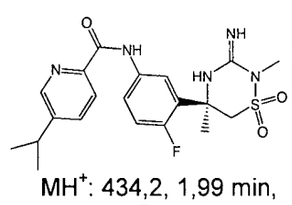
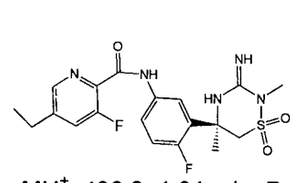
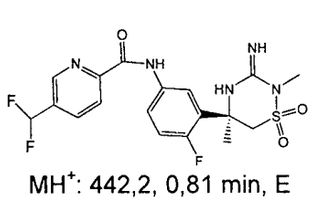
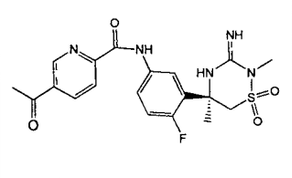
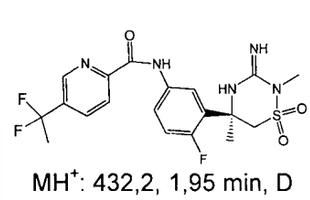
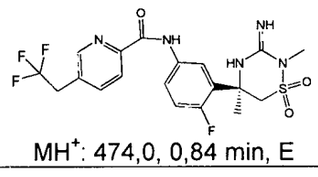
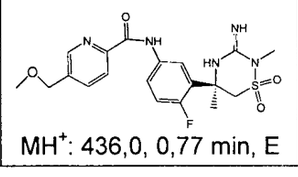
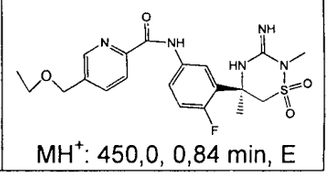
Una mezcla de 2–cloro–3–fluoranilina (252 mg, 0,60 mmol), formiato de amonio (5,0 g, 79 mmol) en 25 mL de isopropanol se calentó a 70°C durante la noche. Después de filtración y concentración, el residuo se purificó por medio de cromatografía en gel de sílice (elución con 0–30% EtOAc/Hex) para proporcionar el producto 3–fluor anilina (150 mg).

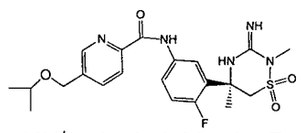
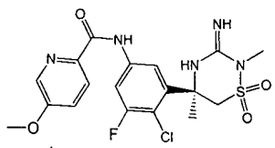
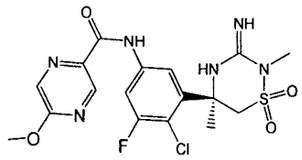
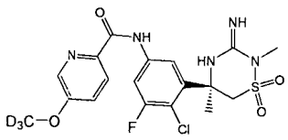
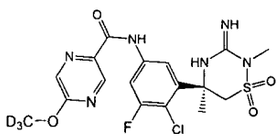
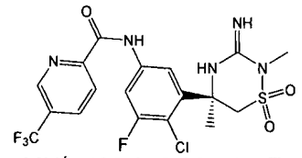
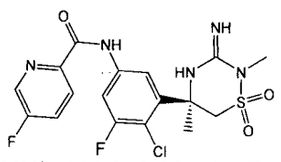
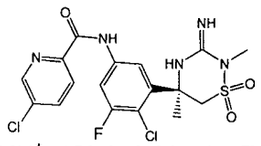
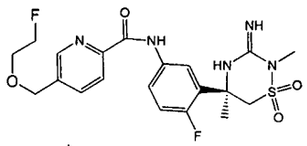
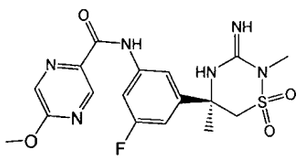
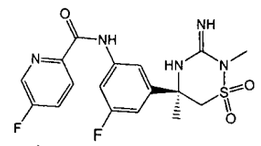
Esquema 12f:



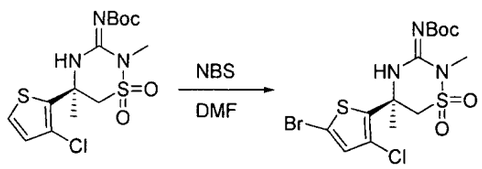
Una mezcla de anilina (96 mg, 0,25 mmol, Esquema 10), el ácido (Esquema 11x, 81 mg, 0,45 mmol), HATU (230 mg, 0,60 mmol), y DIEA (0,36 mL, 2,0 mmol) en 5 mL de DCM se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con DCM, se lavó con ácido cítrico al 5%, $NaHCO_3$ sat. y salmuera. Después del secado ($MgSO_4$) y concentración, el residuo fue sometido a cromatografía en gel de sílice (elución con 0–25% EtOAc/Hex). El producto resultante se disolvió en 6 mL de 25% de TFA/DCM y se agitó a temperatura ambiente durante 1 h. La concentración y secado *in vacuo* proporcionó el **Ejemplo 42b** (143 mg) como una sal TFA. LCMS (condiciones D): t_R = 1,91 min, *m/e* = 450,2 (M+H).

Tabla VIb: Los siguientes ejemplos se prepararon a partir de la correspondiente anilina y ácido carboxílico empleando un procedimiento similar a aquel descrito en el Esquema 12f.

Ejemplos (Datos de LCMS mostrados con cada compuesto: MH^+ observado, tiempo de retención de HPLC y método de LCMS)					
42c	 MH^+: 432,2, 1,95 min, D	**42 d**	 MH^+: 434,2, 1,99 min, D	**42 e**	 MH^+: 438,2, 1,91 min, D
42f	 MH^+: 442,2, 0,81 min, E	**42 g**	 MH^+: 434,2, 0,76 min, E	**42 h**	 MH^+: 432,2, 1,95 min, D
42i	 MH^+: 474,0, 0,84 min, E	**42 j**	 MH^+: 436,0, 0,77 min, E	**42 k**	 MH^+: 450,0, 0,84 min, E

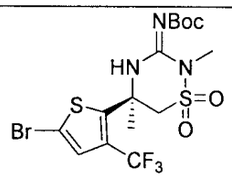
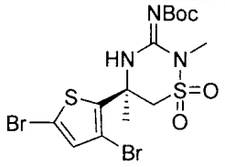
42l	 MH+: 464,0, 0,88 min, E	**42 m**	 MH+: 456,0, 1,87 min, D	**42 n**	 MH+: 457,0, 0,84 min, E
42o	 MH+: 459,0, 0,84 min, E	**42 p**	 MH+: 460,0, 0,84 min, E	**42 q**	 MH+: 493,9, 0,88 min, E
42r	 MH+: 444,0, 0,82 min, E	**42 s**	 MH+: 459,9, 0,88 min, E	**42 t**	 MH+: 468,0, 0,79 min, E
42u	 MH+: 432,0, 0,78 min, E	**42 v**	 MH+: 410,0, 0,79 min, E		

Esquema 13:

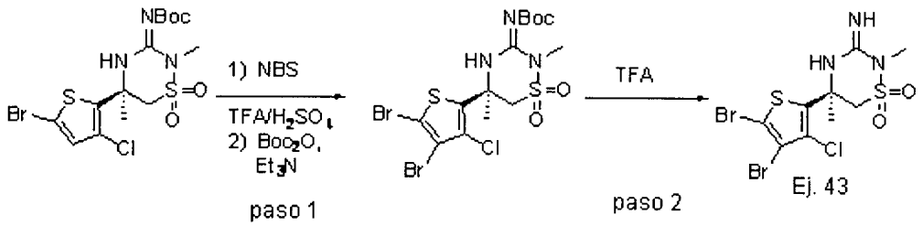


A una solución del tiofeno de la Tabla IIb Entrada 3 (2,2 g, 5,6 mmol) en DMF en una hoja de aluminio envuelta alrededor de un frasco de fondo redondo bajo una atmósfera de N_2 se agregó NBS (2,7 g, 15 mmol). La solución resultante se calentó hasta 50°C con agitación durante 8 horas. La solución se enfrió hasta TA. A la solución se le agregó una solución acuosa de $NaHCO_3$ y $Na_2S_2O_5$. La capa acuosa se extrajo con EtOAc. La capa orgánica se lavó con $NaHCO_{3\,(ac.)}$ sat. (2x). La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró. El producto en bruto se purificó mediante cromatografía flash (SiO_2: elución de gradiente 100:0 a 83:17 hexanos:EtOAc) para proporcionar el bromotiofeno (1,7 g, 63% de rendimiento).

Tabla VII: Los siguientes compuestos se prepararon empleando un procedimiento similar a aquel descrito en el Esquema 13 utilizando el material de partida apropiado.

Entrada	2–bromotiofeno	Entrada	2–bromotiofeno
1		2	

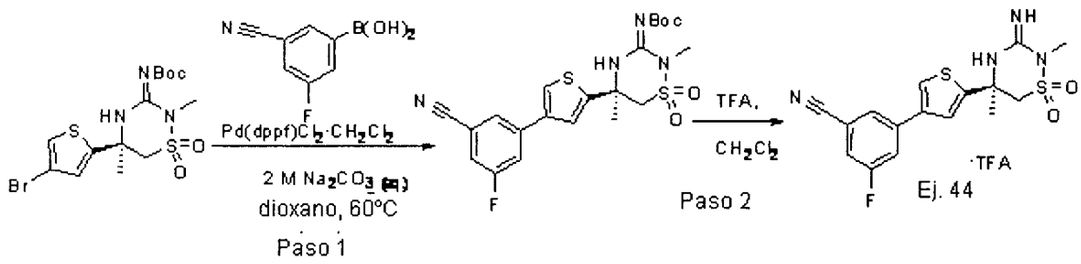
Esquema 14:



Paso 1: A una solución del tiofeno del Esquema 13 (100 mg, 0,21 mmol) en TFA (cerca de 2 mL) se agregó NBS (94 mg, 0,53 mmol) y H_2SO_4 (4 gotas). La solución se dejó agitar a TA durante 30 min. Después de ese tiempo, se agregó NBS adicional (80 mg) y la solución se agitó durante 30 min. adicionales. Luego, la mezcla se templó con $NaHCO_{3\,(ac.)}$ sat. y $Na_2S_2O_{5\,(s)}$. La capa acuosa se extrajo con EtOAc. La capa orgánica se lavó con $NaHCO_{3\,(ac.)}$ sat. (2x), se secó sobre Na_2SO_4, se filtró y concentró. El producto en bruto se suspendió en CH_2Cl_2. A esta mezcla se agregó di–*terc*–butildicarbonato (96 mg, 0,21 mmol) y Et_3N (25 mg, 0,23 mmol). La mezcla resultante se agitó a TA durante la noche. Luego, la solución se concentró y el residuo en bruto se purificó mediante TLC prep (SiO_2: 3:1 hexanos:EtOAc) para proporcionar el dibromotiofeno (49 mg).

Paso 2: El Ejemplo 43 se preparó utilizando un método similar a aquel descrito en el Esquema 11b Paso 2. LCMS (condiciones A): t_R = 3,07 min, *m/e* = 452,2 (M+H).

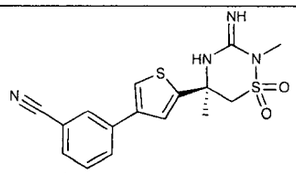
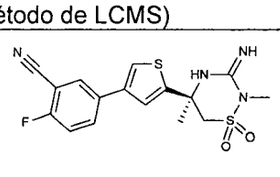
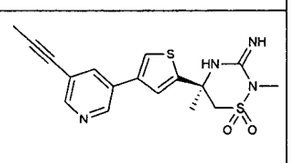
Esquema 15:

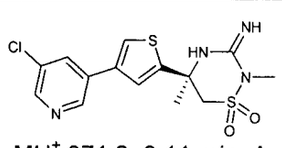
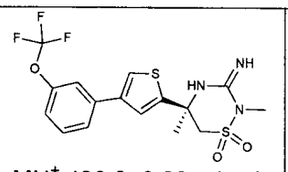
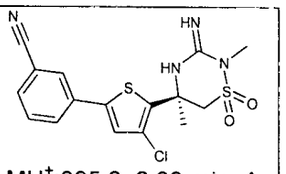
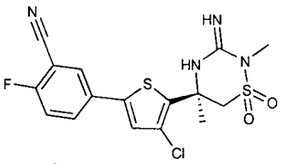
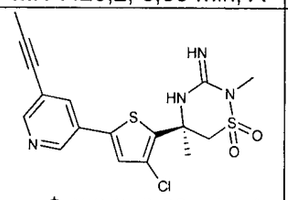
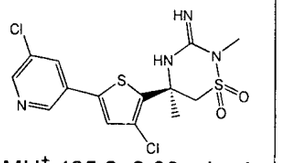
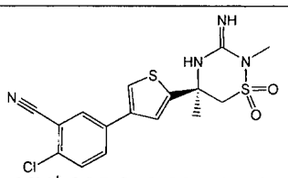
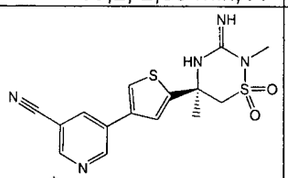
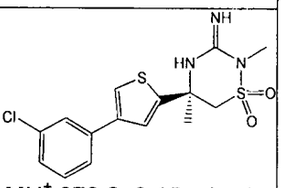
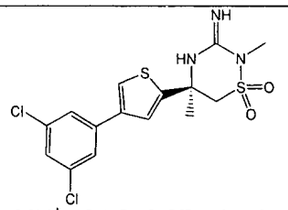
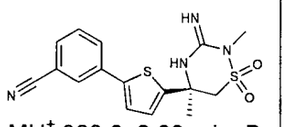
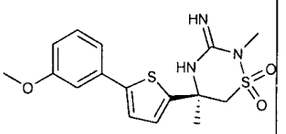
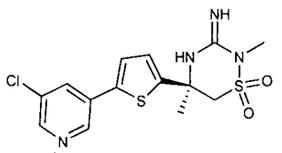
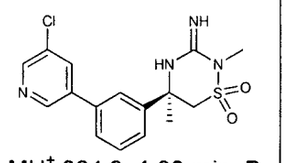
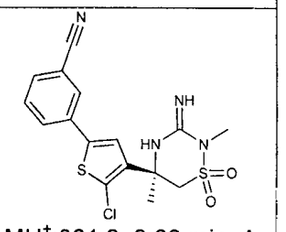
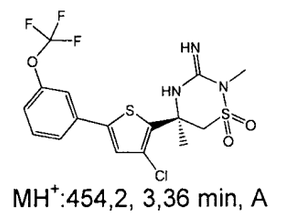
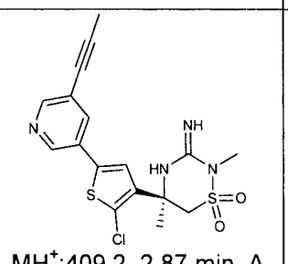
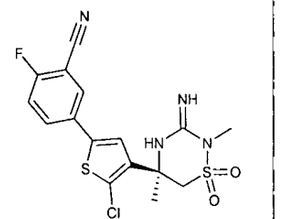
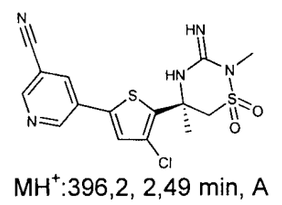
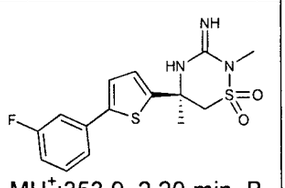
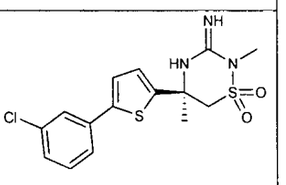
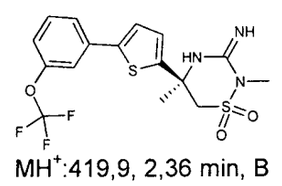
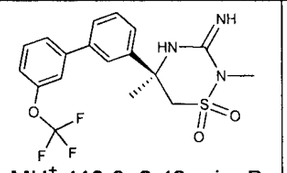
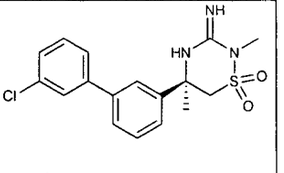


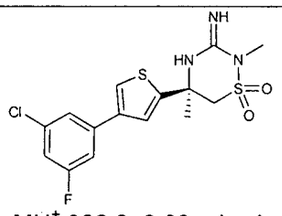
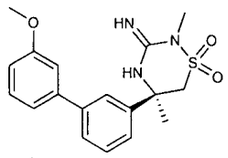
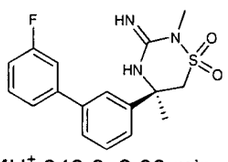
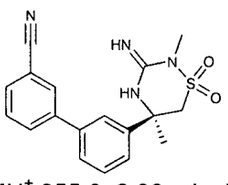
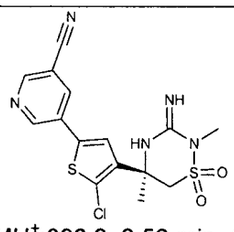
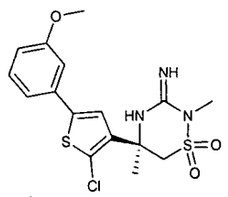
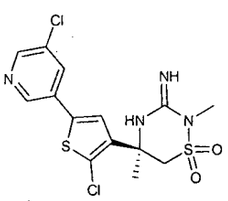
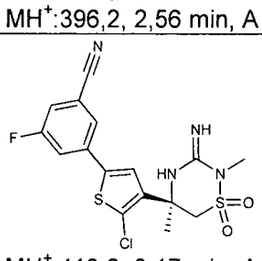
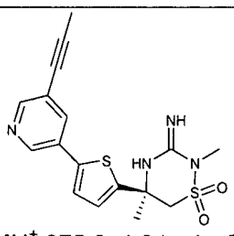
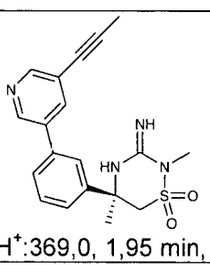
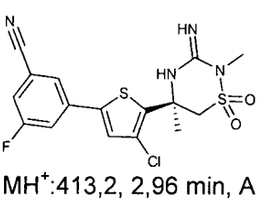
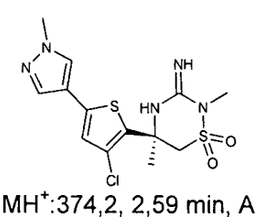
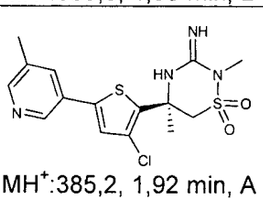
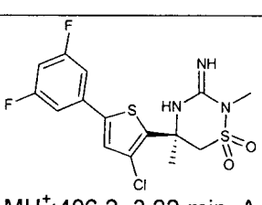
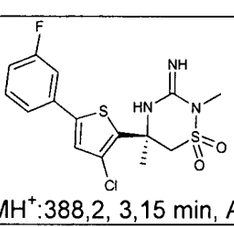
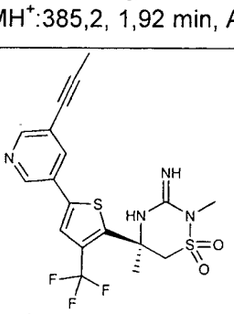
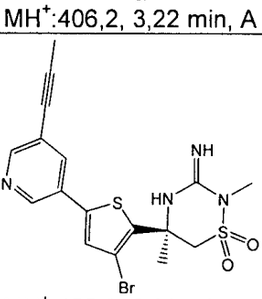
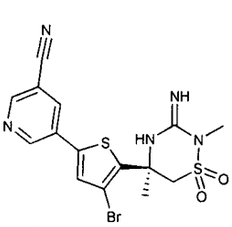
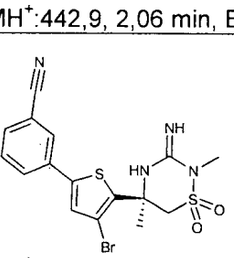
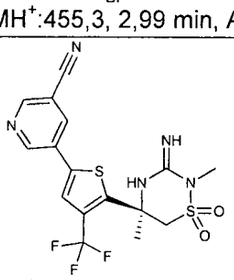
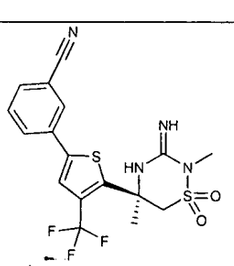
Paso 1: A un frasco de microondas que contenía el bromuro de tiofeno (Esquema 3) (149 mg, 0,34 mmol) se le agregó ácido 3–ciano–5–fluorfenil borónico (146 mg, 0,88 mmol), $Na_2CO_{3\,(ac.)}$ 2 M (0,31 mL) y dioxano (2,5 mL). La mezcla se desgasificó burbujeando N_2 a través de la misma durante 5 min. A esta mezcla se le agregó complejo de [1,1'–bis(difenilfosfino)ferroceno]dicloropaladio(II) con CH_2Cl_2 (60mg, 0,074 mmol). El frasco se tapó y la atmósfera se purgó con nitrógeno. La mezcla se calentó hasta 60°C con agitación durante 2 horas. La mezcla se enfrió hasta TA y se diluyó con EtOAc. Luego, la mezcla se filtró a través de Celite. La capa orgánica se lavó con salmuera. La capa acuosa se retroextrajo con EtOAc (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante TLC preparativa (SiO_2: 3:1 hexanos:EtOAc) para proporcionar el compuesto de biarilo (105 mg).

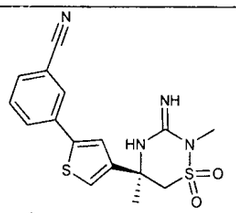
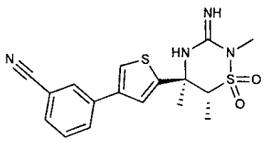
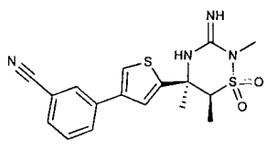
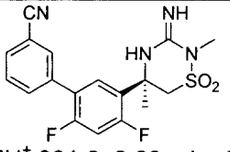
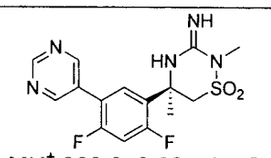
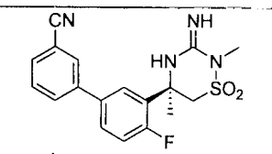
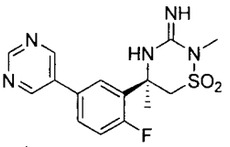
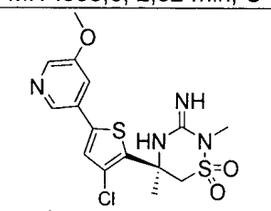
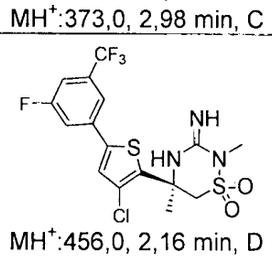
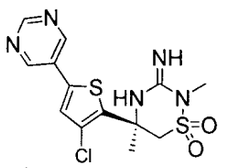
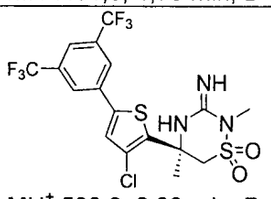
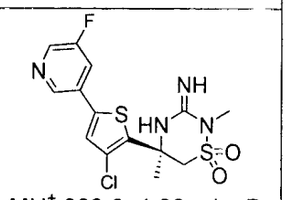
Paso 2: A una solución del compuesto de biarilo del paso 1 en CH_2Cl_2 (1,0 mL) se le agregó TFA (1,0 mL). La solución resultante se agitó a TA durante 1,5 horas. El solvente se eliminó *in vacuo* para proporcionar el **Ejemplo 44** en forma de una sal trifluoracetato. Datos de LCMS: (método A): t_R = 2,96 min, *m/e* = 379,2 (M+H).

Tabla VIII: Los siguientes ejemplos se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 15 utilizando el bromuro de arilo y ácido/ éster borónico apropiados.

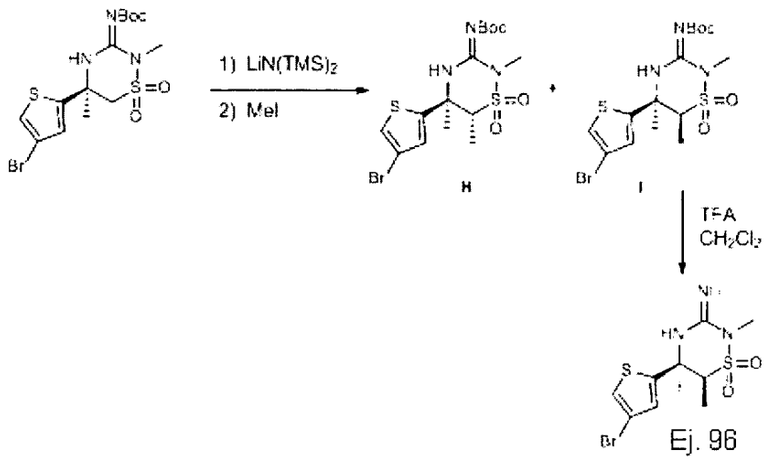
Ejemplos datos de LCMS mostrados con cada compuesto: MH^+ observado, Tiempo de retención de HPLC y método de LCMS)					
45		**46**		**47**	
MH^+:361,2, 2,66 min, A		MH^+:379,2, 3,43 min, A		MH^+:375,2, 2,90 min, A	

48	 MH^+:371,2, 3,11 min, A	**49**	 MH^+:420,2, 3,33 min, A	**50**	 MH^+:395,2, 2,99 min, A
51	 MH^+:413,2, 3,11 min, A	**52**	 MH^+:409,2, 2,83 min, A	**53**	 MH^+:405,2, 2,80 min, A
54	 MH^+:395,2, 3,00 min, A	**55**	 MH^+:362,2, 2,37 min, A	**56**	 MH^+:370,2, 3,15 min, A
57	 MH^+:404,2, 3,27 min, A	**58**	 MH^+:360,8, 2,09 min, B	**59**	 MH^+:365,9, 2,19 min, B
60	 MH^+:370,9, 1,95 min, B	**61**	 MH^+:364,9, 1,98 min, B	**62**	 MH^+:361,2, 2,66 min, A
63	 MH^+:454,2, 3,36 min, A	**64**	 MH^+:409,2, 2,87 min, A	**65**	 MH^+:413,2, 3,16 min, A
66	 MH^+:396,2, 2,49 min, A	**67**	 MH^+:353,9, 2,20 min, B	**68**	 MH^+:369,9, 2,27 min, B
69	 MH^+:419,9, 2,36 min, B	**70**	 MH^+:413,9, 2,42 min, B	**71**	 MH^+:363,9, 2,28 min, B

72	 MH$^+$:386,2, 3,09 min, A	**73**	 MH$^+$:359,2, 2,17 min, B	**74**	 MH$^+$:348,0, 2,38 min, B
75	 MH$^+$:355,0, 2,30 min, B	**76**	 MH$^+$:396,2, 2,56 min, A	**77**	 MH$^+$:400,2, 3,10 min, A
78	 MH$^+$:406,2, 2,88 min, A	**79**	 MH$^+$:413,2, 3,17 min, A	**80**	 MH$^+$:375,0, 1,94 min, B
81	 MH$^+$:369,0, 1,95 min, B	**82**	 MH$^+$:413,2, 2,96 min, A	**83**	 MH$^+$:374,2, 2,59 min, A
84	 MH$^+$:385,2, 1,92 min, A	**85**	 MH$^+$:406,2, 3,22 min, A	**86**	 MH$^+$:388,2, 3,15 min, A
87	 MH$^+$:442,9, 2,06 min, B	**88**	 MH$^+$:455,3, 2,99 min, A	**89**	 MH$^+$:440,2, 2,77 min, A
90	 MH$^+$:441,2, 3,10 min, A	**91**	 MH$^+$:361,2, 2,66 min, B	**92**	 MH$^+$:428,9, 2,34 min, B

93	 MH$^+$:361,2, 2,80 min, A	**94**	 MH$^+$:375,2, 2,84 min, A	**95**	 MH$^+$:375,2, 2,94 min, A
95a	 MH$^+$:391,0, 3,09 min, C	**95b**	 MH$^+$:368,0, 2,32 min, C	**95c**	 MH$^+$:373,0, 2,98 min, C
95d	 MH$^+$:350,0, 2,15 min, C	**95e**	 MH$^+$:401,0, 1,78 min, D	**95f**	 MH$^+$:456,0, 2,16 min, D
95g	 MH$^+$:372,0, 1,77 min, D	**95h**	 MH$^+$:506,0, 2,23 min, D	**95i**	 MH$^+$:389,0, 1,90 min, D

Esquema 16:

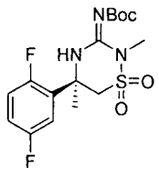
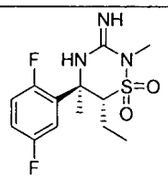
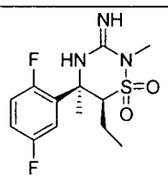
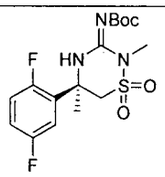
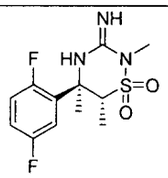
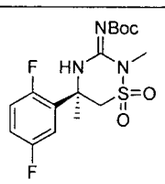
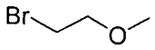
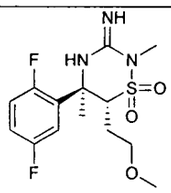


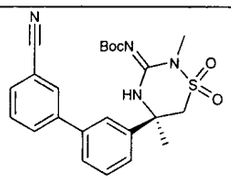
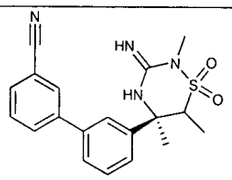
Paso 1: A una solución del tiofeno (Esquema 3) (238 mg, 0,54 mmol) en THF anhidro (2,5 mL) a –78°C se agregó una solución de LHMDS (1,0 M en THF, 1,63 mL). La solución resultante se agitó a –78°C durante 1 hora. A esta solución se le agregó yoduro de metilo (0,086 mL, 1,36 mmol). La solución resultante se agitó a –78°C durante 1,25 horas adicionales. Luego de ese tiempo, se agregó agua y la mezcla se dejó calentar hasta TA. Luego, la capa acuosa se extrajo con

EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó por medio de cromatografía flash (SiO_2: elución de gradiente 100:0 a 80:20 hexanos:EtOAc) para proporcionar el isómero trans H de más rápida elución (20 mg, 8,1 %) y el isómero cis I de más lenta elución (168 mg, 68%).

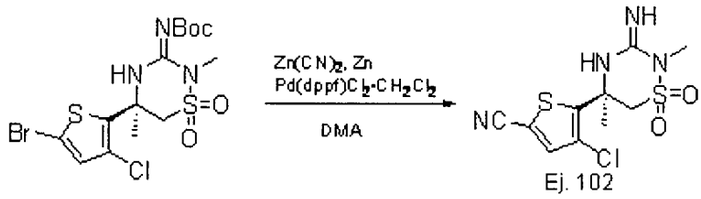
Paso 2: A una solución de **I** (16 mg, 0,035 mmol) en CH_2Cl_2 (1 mL) se le agregó TFA (1 mL). La solución resultante se agitó a TA durante 1,5 horas. La solución se concentró para proporcionar el **Ejemplo 96** (15 mg) como la sal trifluoracetato. Datos de LCMS: (método A): t_R = 2,79 min, *m/e* = 354,2 (M+H).

Tabla IX: Los siguientes ejemplos se prepararon utilizando un método similar a aquel descrito en el Esquema 16 excepto que se empleó NaHMDS en lugar de LHMDS en el paso 1.

Núcleo	Haluro de alquilo	Ejemplos		LCMS MH^+ Obser.	Tiempo de Ret (min)	método lcms
		**97**		318,1	2,02	B
		98		318,0	2,44	B
	MeI	**99**		304,0	1,77	B
		**100**		348,1	2,12	B

	MeI	**101**		369,0	2,16	B

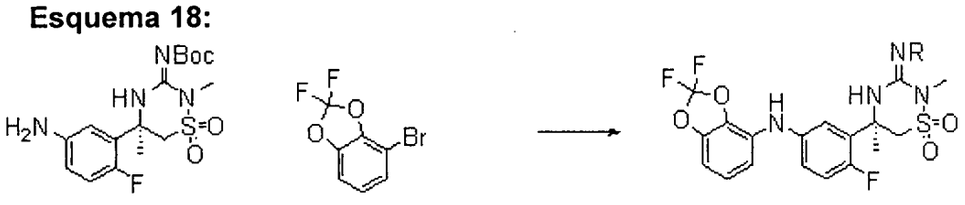
Esquema 17:



Ej. 102

Un frasco de microondas cerrado herméticamente que contenía una suspensión del tiofeno del Esquema 13 (74 mg, 0,16 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (19 mg, 0,023 mmol) , zinc (8,2 mg, 0,12 mmol), cianuro de zinc (11 mg, 0,094 mmol) en N,N–dimetilacetamida (2,0 mL) se desgasificó burbujeando N_2 a través de la mezcla durante 5 min. A continuación, la mezcla se calentó hasta 85°C con agitación durante 2 horas. La mezcla se enfrió hasta TA y se diluyó con Et_2O. La capa orgánica se lavó con agua (2x), se secó sobre Na_2SO_4, se filtró y concentró. El residuo en bruto se purificó mediante TLC preparativa (SiO_2: 95:5 CH_2Cl_2:MeOH) para proporcionar **Ejemplo 102** (15 mg). datos de LCMS: (método A): t_R = 2,22 min, *m/e* = 319,2 (M+H).

Esquema 18:



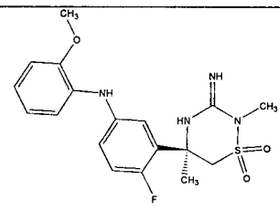
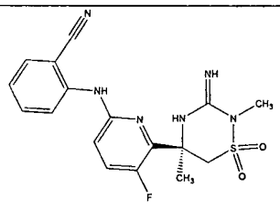
J

K R = Boc
Ej. 103 R = H

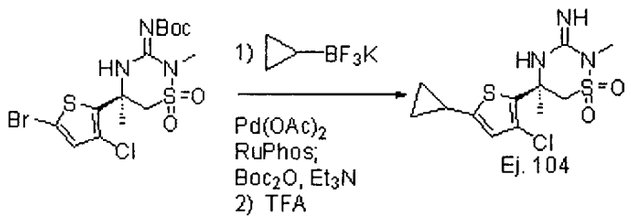
Un recipiente de microondas de 20 mL se secó a la llama y se enfrió bajo vacío, luego se retrocargó con N_2, seguido por dos ciclos de vacío / retrocarga de N_2. La anilina (Esquema 10) (55 mg, 142 µmol), Pd_2dba_3–$CHCl_3$ (17 mg, 19 µmol), di–*terc*–butilfosfinil–2–bifenilo (15 mg, 50 µmol), terc-butóxido sódico (31 mg, 322

μmol) y 4–bromo–2,2–difluorbenzo[d][1,3]dioxol **J** (48 mg, 202 μmol) se suspendieron en tolueno anhidro (2 mL), el frasco de microondas se cerró herméticamente y se colocó en un baño de aceite a 65°C precalentado. Después de agitación durante 18 h, la mezcla de reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ acuoso saturado (1x), se secó sobre $MgSO_4$, se filtró y concentró bajo presión reducida para dar un aceite amarillo, el cual se sometió a cromatografía en gel de sílice empleando 0→20% de EtOAc/hexanos como eluyente para proporcionar el compuesto intermedio **K** como una película (39 mg). Este compuesto intermedio se desprotegió con TFA (2 mL) en CH_2Cl_2 (3 mL) a TA, luego se diluyó con tolueno (5 mL), se concentró bajo presión reducida, y se sometió a RP–HPLC (C18, 30 ml/min, 10%–100% MeCN/H_2O) con TFA al 0.1%) para proporcionar el **Ejemplo 103** con un rendimiento del 32% (24,9 mg, sal TFA). LCMS (condiciones C): t_R = 3,44 min, *m/e* = 443,2 (M+H).

Tabla IXa: Los siguientes Ejemplos se prepararon empleando los métodos descritos en el Esquema 18, con la siguiente modificación: La reacción de acoplamiento se llevó a cabo a 80°C:

Ejemplos (Datos de LCMS: MH^+ observado, Tiempo de retención de HPLC y método de LCMS)			
103a	 MH^+:393, 2,01 min, D	**103b**	 MH^+:389, 1,88 min, D

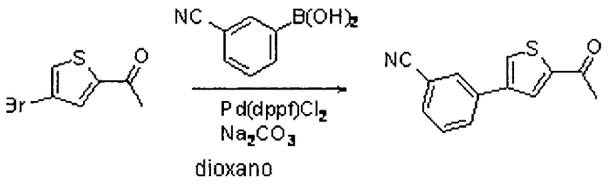
Esquema 19:



Paso 1: A un frasco de microondas que contenía 3 mL de tolueno/agua (3:1) se le agregó bromotiofeno del Esquema 13 (50 mg, 0,11 mmol), $Pd(OAc)_2$ (5 mg, 0,02 mmol), RuPhos (21 mg, 0,04 mmol), trifluorborato de ciclopropilo potásico (17 mg, 0,12 mmol) y Cs_2CO_3 (108 mg, 0,33 mmol). El frasco se cerró herméticamente y el frasco se purgó con N_2. Luego, la mezcla se calentó a 70°C durante 12 horas. Se agregó más $Pd(OAc)_2$ (5 mg, 0,02 mmol), RuPhos (21 mg, 0,04 mmol), ciclopropil trifluorborato potásico (17 mg, 0,12 mmol) y la mezcla se calentó bajo una atmósfera de N_2 hasta 70°C durante 12 horas adicionales. La mezcla se enfrió hasta TA, se filtró a través de célite y se extrajo con CH_2Cl_2. La capa acuosa se secó sobre Na_2SO_4, se filtró y concentró. La mezcla en bruto se disolvió luego en CH_2Cl_2. A esta solución se le agregó Boc_2O (24 mg, 0,11 mmol) y Et_3N (13 mg, 0,13 mmol). La solución resultante se agitó durante la noche a TA. La solución se concentró y el producto en bruto se purificó mediante TLC preparativa (SiO_2; 70:30 hexanos:EtOAc).

Paso 2: El Ejemplo 104 se preparó a partir del material antes mencionado utilizando un método similar al descrito en el Esquema 11b paso 2. Datos de LCMS: (método A): t_R = 2,85 min, *m/e* = 334,2 (M+H).

Esquema 20:



La biarilcetona se formó utilizando un método similar a aquel descrito en el Esquema 15 paso 1.

Tabla X: Los siguientes ejemplos se formaron empleando métodos similares a los descritos en el Esquema 1a comenzando a partir de la cetona en el Esquema 20 y la sulfonamida apropiada de la Tabla I.

Ejemplos (datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)

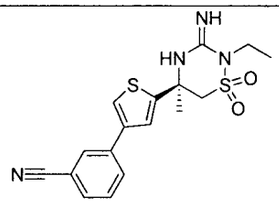
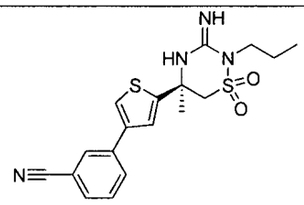
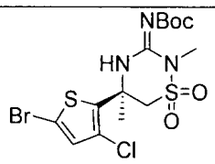
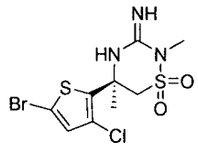
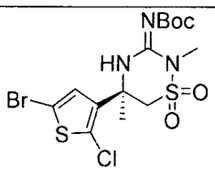
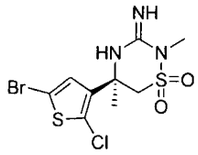
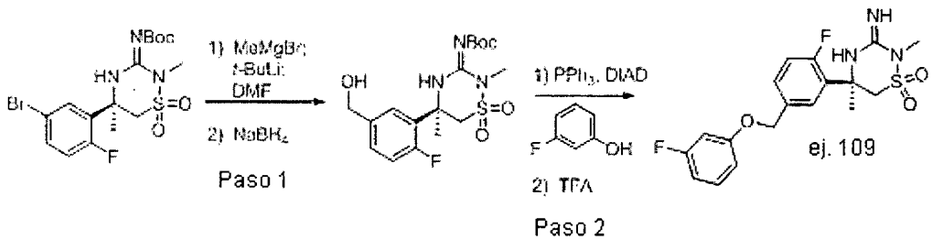
105	 MH$^+$:374.9, 2.13 min, B	**106**	 MH$^+$:388.9, 2.22 min, B

Tabla XI: Los siguientes ejemplos se prepararon utilizando un método similar a aquel descrito en el Esquema 11b paso 2.

Carbamato	Ejemplos		LCMS MH$^+$ Obser.	Tiempo ret. LCMS (min)	método LCMS
	**107**		374,2	2,81	A
	**108**		374,2	2,69	A

Esquema 21:



Paso 1: A una solución del bromuro (Tabla IIb, entrada 14) (500 mg, 1,11 mmol) en THF (7 mL) a –20°C se le agregó una solución de MeMgBr (3 M en Et_2O, 0,48 mL, 1,4 mmol). La solución se agitó durante 30 min a –20°C. Luego, la solución se enfrió hasta –78°C. A la solución se le agregó *t*–BuLi (1,7 M en pentano, 1,6 mL, 2,8 mmol). La solución se agitó durante 2 h a –78°C. A la solución se le agregó DMF (0,13 mL, 1,7 mmol). La solución se dejó calentar lentamente hasta TA durante 2,5 horas. Luego, a la solución se le agregó NH_4Cl sat. (ac.) (20 mL) y la mezcla se extrajo con EtOAc (3x). Las capas orgánicas

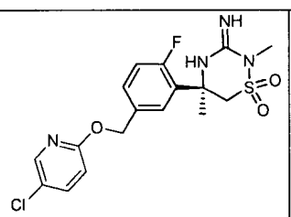
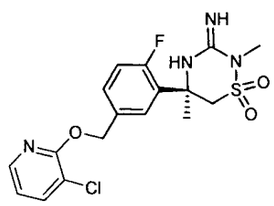
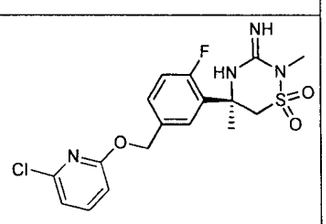
combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó por medio de cromatografía flash (SiO_2: 3:1 heptano:EtOAc) para proporcionar el aldehído (237 mg, 54%).

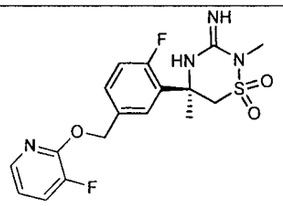
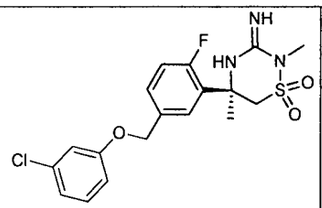
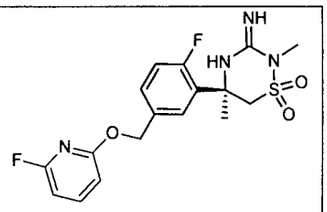
A una solución del aldehído (1,04 g, 2,60 mmol) en MeOH (10 mL) a 0°C se le agregó en porciones durante 3 min $NaBH_4$ (197 mg, 5,21 mmol). La mezcla resultante se agitó durante 20 min. Luego, a la solución se le agregó NH_4Cl sat. (ac.) (30 mL) y la mezcla se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó por medio de cromatografía flash (SiO_2: 1:1 heptano:EtOAc) para proporcionar el alcohol (949 mg, 91%).

Paso 2: A una solución del alcohol del paso 1 (105 mg, 0,26 mmol) y trifenilfosfina (102 mg, 0,39 mmol) en THF (3 mL) se le agregó 3–fluorfenol (0,030 mL, 0,33 mmol). A esta solución se le agregó por goteo DIAD (0,075 mL, 0,39 mmol) y la solución resultante se agitó durante 2 horas. La reacción se cargó sobre una columna flash de SiO_2 y se purificó (elución de gradiente 100:0 a 0:100 heptano:EtOAc) para proporcionar el éter (73 mg, 56%).

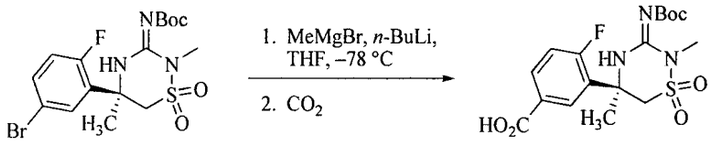
Ej. 109 se preparó a partir del material antes mencionado utilizando un método similar al descrito en el Esquema 11b paso 2. LCMS (condiciones B): t_R = 2,10 min, *m/e* = 396,0 (M+H).

Tabla XII: Los siguientes ejemplos se prepararon a partir del alcohol bencílico descrito en el Esquema 21 paso 1 utilizando un método similar a aquel descrito en el Esquema 21 paso 2 utilizando el alcohol de arilo apropiado.

Ejemplos (Datos de LCMS mostrados con cada compuesto: MH^+ observado, Tiempo de retención de HPLC y método de LCMS)					
110		**111**		**112**	
MH^+:412,0, 2,17 min, B		MH^+:413,0, 2,02 min, B		MH^+:397,0, 1,99 min, B	

113		114		115	
	MH^+:396,0, 2,06 min, B		MH^+:397,1, 1,96 min, B		MH^+:412,9, 2,08 min, B

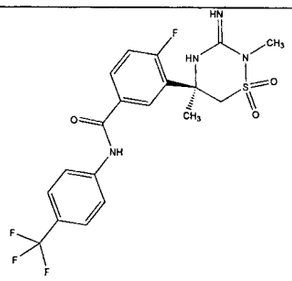
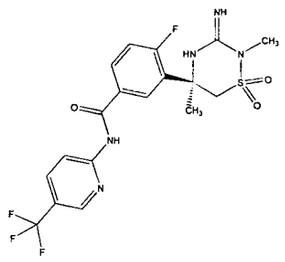
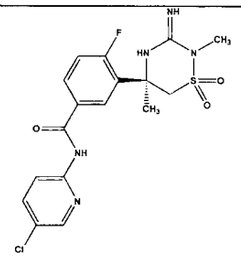
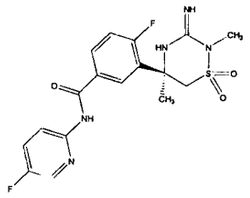
Esquema 22:



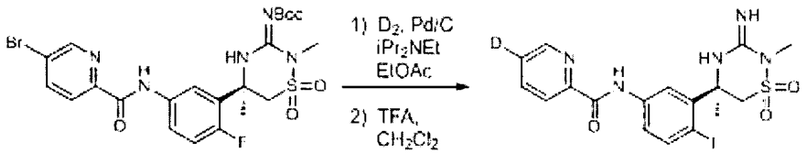
A una solución agitada del bromuro (Tabla IIb, entrada 14, 2,55 g, 5,66 mmol) en THF anhidro (45 mL) se agregó una solución de MeMgBr (3 M en Et_2O, 2,4 mL, 7,20 mmol) a –78°C bajo nitrógeno. Luego de completarse la adición, la mezcla de reacción se agitó durante 20 min. Luego de ese tiempo, una solución de *n*–BuLi (2,5 M en hexanos, 5,1 mL, 12,8 mmol) se agregó por goteo durante 5 min. La mezcla de reacción luego se agitó durante 50 min a –78°C y se extrajo el baño de enfriamiento. Se burbujeó gas de CO_2 en la mezcla de reacción durante 50 min. Después de ese tiempo, la reacción se templó con NH_4Cl acuoso saturado (50 mL) y ácido clorhídrico 1 N (ac.) (100 mL). La mezcla resultante se extrajo con EtOAc (3 × 100 mL). Los extractos combinados se lavaron con salmuera (100 mL), se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo presión reducida. El residuo se purificó mediante cromatografía en columna (sílice, metanol al 10% /cloruro de metileno) para proporcionar el ácido carboxílico (1,49 g, 53%).

Tabla XIII: Los siguientes ejemplos se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 11b utilizando el ácido del Esquema 22 y la arilamina apropiada. Las relaciones molares empleadas para el ácido, amina y BOPCl fueron 1:1,3:1,5 respectivamente.

Ejemplos
(Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)

116	 MH$^+$:459,0, 2,35 min, B	**117**	 MH$^+$:460,1, 2,02 min, B
118	 MH$^+$:426,1, 1,86 min, B	**119**	 MH$^+$:410,1, 1,74 min, B

Esquema 23:

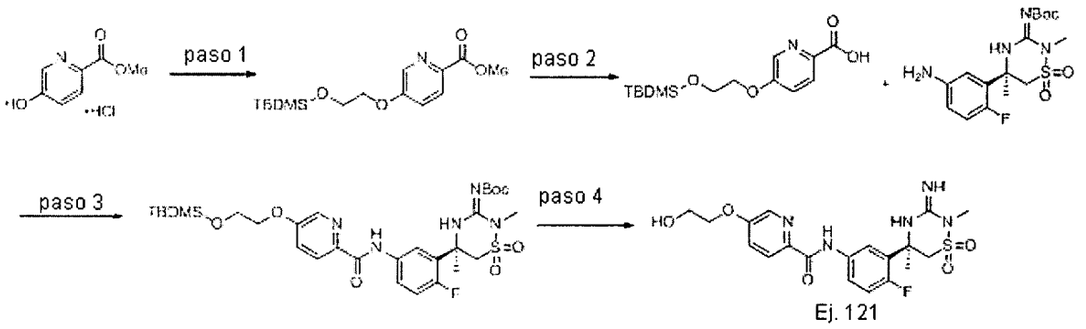


Ej. 120

A un frasco de fondo redondo herméticamente cerrado que contenía una solución del bromuro (Tabla V: intermediario Boc para el Ej. 29) (48 mg, 0,084 mmol) en EtOAc (4 mL) bajo una atmósfera de N_2 se le agregó iPr_2NEt (22 µL, 0,13 mmol) y Pd/C al 10%, tipo Degussa (9,0 mg, 0,0042 mmol). El frasco se evacuó y se retrocargó con D_2 (3x). La mezcla se agitó bajo una atmósfera de D_2 durante 4,5 horas. La mezcla se purgó con N_2, se filtró y concentró. El residuo se repartió entre EtOAc y $NaHCO_3$ 1/2 sat. (ac.). La capa acuosa se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y concentraron para proporcionar el deuterato (38 mg, 92%) en forma de un sólido blanco.

El Ejemplo 120 se preparó como su sal TFA a partir del material antes mencionado utilizando un procedimiento similar a aquel descrito en el Esquema 11b paso 2. Datos de LCMS: (método D): t_R = 1,76 min, *m/e* = 393,0 (M+H).

Esquema 24:



Paso 1: Al clorhidrato de 5–hidroxipicolinato de metilo preparado en el esquema 11h (0,40 g, 2,1 mmol) en DMF (1 mL) se le agregó carbonato potásico (0,88 g, 6,3 mmol) y (2–bromoetoxi)–*terc*–butildimetilsilano (0,68 mL, 3,2 mmol). La reacción se calentó hasta 70°C y se agitó durante 18 h. Se agregó otro equivalente de (2–bromoetoxi)–*terc*–butildimetilsilano y la reacción se agitó durante 1,5 h adicionales a 90 ° C. La reacción se enfrió hasta temperatura ambiente y se agregó agua. La mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–30% EtOAc/hex) en el transcurso de 30 minutes para proporcionar el producto (0,31 g, 47%).

Paso 2: A compuesto preparado en el paso 1 (0,31 g, 1,0 mmol) en THF (1,5 mL) se le agregó LiOH 2N (1,5 mL, 3 mmol). La reacción se agitó a temperatura ambiente durante 4 h. El pH de la reacción se ajustó hasta pH~4 utilizando ácido cítrico acuoso saturado. La mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo* para proporcionar el ácido carboxílico (0,18 g, 60%).

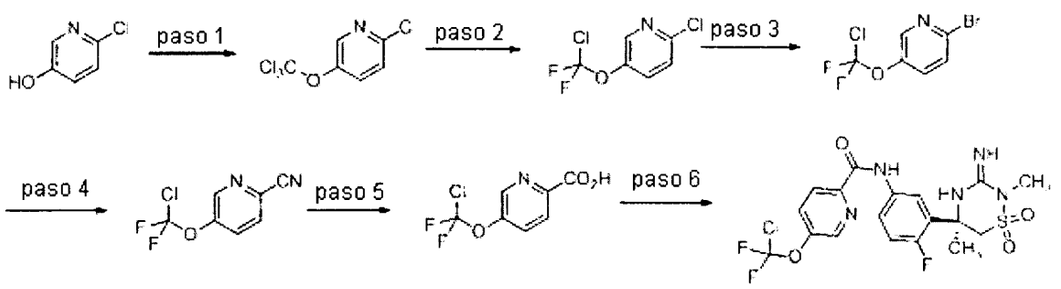
Paso 3: A la anilina preparada en el esquema 10 (0,15 g, 0,39 mmol) en piridina (1,5 mL) se le agregó el ácido carboxílico preparado en el paso 2 (0,17

g, 0,58 mmol) seguido por BOP Cl (0,23 g, 0,89 mmol). La reacción se agitó a temperatura ambiente durante 4,5 h. Luego, la reacción se concentró *in vacuo* y el residuo se absorbió en EtOAc y se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró, y concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–30% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el producto de amida (0,14 g, 54%).

Paso 4: Al producto del paso 3 (0,20 g, 0,30 mmol) en THF (1 mL) se le agregó TBAF (1,0 M en THF, 0,33 mL, 0,33 mmol). La reacción se agitó a temperatura ambiente durante 24 h. Se agregó EtOAc a la mezcla de reacción y la mezcla se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–70% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el alcohol (0,14 g, 85%).

A ese producto (0,14 g, 0,25 mmol) en DCM (2 mL) se le agregó TFA (2 mL). La reacción se agitó a temperatura ambiente durante 1 h y se concentró *in vacuo*. Luego, la reacción se agitó durante 1 h con metanol (1 mL) y NH_3 7N /MeOH (0,5 mL). Luego, la reacción se concentró *in vacuo* y se absorbió en EtOAc. La mezcla se lavó con $NaHCO_3$ saturado, agua y salmuera, se secó ($MgSO_4$), se filtró y concentró *in vacuo* para proporcionar el **Ejemplo 121** (0,10 g, 88%). Datos de LCMS: (método D): t_R = 1,68 min, *m/e* = 452,0 (M+H).

Esquema 25



Ej. 122

Paso 1: A 2–cloro–5–hidroxipiridina (10 g, 80 mmol) en $NaOH_{(ac.)}$ 1.5 M (67 mL) a 0°C se le agregó tiofosgeno (6,0 mL, 79 mmol) en cloroformo (46 mL)

por goteo. Luego de la adición, la reacción se agitó durante 2 h. La mezcla luego se extrajo con $CHCl_3$. Las capas combinadas de $CHCl_3$ se lavaron con HCl (ac) 1N y agua, se secaron ($MgSO_4$), y filtraron. En esta solución se burbujeó gas de Cl_2 hasta que la reacción se calentó (~1 minuto). La reacción se agitó a temperatura ambiente durante 2h y luego se burbujeó gas de Cl_2 a través de la mezcla nuevamente. Luego, la reacción se agitó durante 18 h. Se burbujeó luego gas de nitrógeno a través de la mezcla de reacción para eliminar el gas de Cl_2 residual. Luego, la reacción se concentró *in vacuo*. El residuo se purificó mediante cromatografía en fase inversa [C18 (800g) 5% (2 volúmenes de columna (CV), 5–100% (10 CV), 100 (2 CV); ácido fórmico al 0,1% /agua//ácido fórmico al 0,1% /acetonitrilo] para proporcionar el triclorometiléter (4,0 g, 21%).

Paso 2: A trifluoruro de antimonio (4,1 g, 22,7 mmol) y pentacloruro de antimonio (0,22 mL, 1,7 mmol) a 120°C se le agregó triclormetiléter preparado en el paso 1 (2,8 g, 11,3 mmol). La mezcla se calentó hasta 150°C, se agitó durante 1 h y luego se enfrió hasta temperatura ambiente. Se agregaron DCM y $NaHCO_3$ (ac) saturado y la capa acuosa se extrajo con DCM. La combinación se lavó con 20% $KF_{(ac)}$, agua y salmuera, se secó ($MgSO_4$), se filtró y concentró *in vacuo* para proporcionar producto (2,0 g, 83%).

Paso 3: Al clorodifluormetiléter preparado en el paso 2 (2,0 g, 9,3 mmol) en propanonitrilo (11 mL) se le agregó bromotrimetilsilano (2,8 mL, 21 mmol). La reacción se calentó hasta 100°C y se agitó durante 6,5 h. La reacción se enfrió hasta temperatura ambiente y se agregó $NaHCO_3$ saturado. La mezcla se extrajo con EtOAc. Los orgánicos combinados se lavaron con agua y salmuera, se secaron ($MgSO_4$), se filtraron, y concentraron *in vacuo* para proporcionar un producto (2,1 g) el cual se utilizó en el siguiente paso sin más purificación.

Paso 4: A la bromopiridina preparada en el paso 3 (0,33 g, 1,3 mmol) en DMF (2,7 mL) en un frasco de reacción de microondas se burbujeó gas de N_2 durante 5 minutos. Se agregó $Zn(CN)_2$ (0,22 g, 1,9 mmol) y se burbujeó nitrógeno

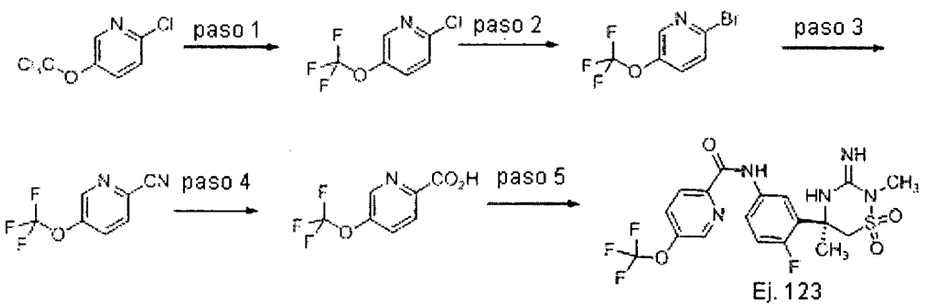
a través de la mezcla de reacción durante 5 minutos. Se agregó $Pd(PPh_3)_4$ (0,078 g, 0,07 mmol) y se burbujeó nitrógeno a través de la reacción durante 5 minutos. El recipiente de reacción se tapó y se calentó hasta 100°C, luego se agitó durante 2,5 h y se enfrió hasta temperatura ambiente. Se agregaron agua y EtOAc y luego la combinación se filtró a través de una almohadilla de Celite lavando con EtOAc. A continuación, el filtrado se extrajo con EtOAc. Luego, las capas orgánicas se combinaron y lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo,* luego se purificaron por medio de cromatografía en gel de sílice (0–8% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el producto (0,21 g, 81%).

Paso 5: Al nitrilo preparado en el paso 4 (0,21 g, 1,0 mmol) en etanol (2 mL) se le agregó $LiOH_{(ac)}$ 2N (2,7 mL). La reacción se calentó hasta 100°C y se agitó durante 2 h. La reacción se enfrió hasta temperatura ambiente y se eliminó el etanol *in vacuo.* El pH de la capa acuosa se ajustó hasta pH~4 utilizando ácido cítrico acuoso saturado. Se agregó cloruro de sodio sólido y la mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo* para proporcionar un sólido blanco (0,14 g, 62%).

Paso 6: A la anilina preparada en el esquema 10 (0,20 g, 0,52 mmol) en THF (0,84 mL) a 0°C se le agregó el ácido carboxílico preparado en el paso 5 (0,14 g, 0,63 mmol), *N,N*–diisopropiletilamina (0,27 mL, 1,6 mmol), y 50% anhídrido cíclico del ácido 1–propanofosfónico en acetato de etilo (0,42 mL, 0,71 mmol), respectivamente. La mezcla de reacción luego se agitó durante 1h a 0°C y luego otra hora a temperatura ambiente. Se agregó agua a la reacción y la mezcla se agitó vigorosamente durante 20 minutos. Luego, la mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo.* El residuo se purificó por medio de cromatografía en gel de sílice (0–30% EtOAc/hex durante 30 minutos) para proporcionar la amida (0,26 g, 84%). A la amida (0,26 g, 0,44 mmol) en DCM (1 mL) a temperatura ambiente se le agregó TFA (0,68 mL, 8,8 mmol). La reacción

se agitó durante 18 h y luego se concentró *in vacuo*. El residuo se absorbió en DCM y se agitó con $NaHCO_3$ saturado (ac). La mezcla se extrajo con DCM. Las capas de DCM combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo* para proporcionar el **Ejemplo 122**. Datos de LCMS: (método D): t_R = 2,06 min, *m/e* = 492 (M+H).

Esquema 26



Paso 1: Al trifluoruro de antimonio (4,05 g, 23 mmol) y pentacloruro de antimonio (0,22 mL, 1,7 mmol) a 120°C se le agregó el triclorometiléter preparado en el paso 1 del esquema 25 (2,80 g, 11 mmol). La reacción se calentó hasta 165°C bajo nitrógeno y se agitó durante 14 h y luego se calentó hasta 175°C y se agitó durante 4h adicionales. La reacción se enfrió hasta temperatura ambiente. La masa sólida resultante se agitó vigorosamente con $NaHCO_3$ saturado (ac.) [¡emanación de gas!] y EtOAc. La mezcla se filtró a través de un tapón de Celite lavando con EtOAc. El líquido filtrado se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–10% EtOAc/hex en el transcurso de 30 minutos) (0,90 g, 40%).

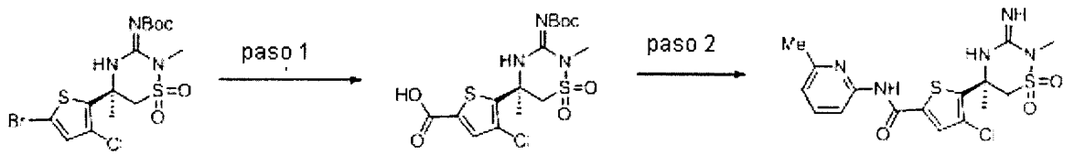
Paso 2: El trifluormetiléter preparado en el paso 1 fue convertido en la bromopiridina de acuerdo con el procedimiento en el paso 3 del esquema 25.

Paso 3: La bromopiridina preparada en el paso 2 fue convertida en la cianopiridina de acuerdo con el procedimiento en el paso 4 del esquema 25.

Paso 4: La cianopiridina preparada en el paso 3 fue convertida en el ácido piridilcarboxílico de acuerdo con el procedimiento en el paso 5 del esquema 25.

Paso 5: El ácido piridilcarboxílico preparado en el paso 4 fue convertido en el **Ej. 123** de acuerdo con los procedimientos en el paso 6 del esquema 25. LCMS (condiciones D): t_R = 2,04 min, *m/e* = 476,0 (M+H).

Esquema 27



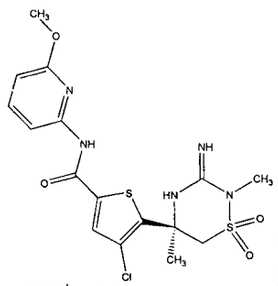
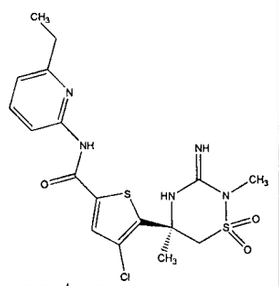
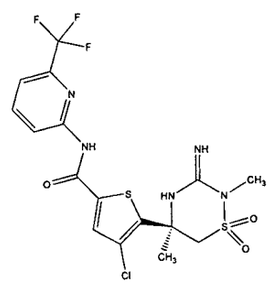
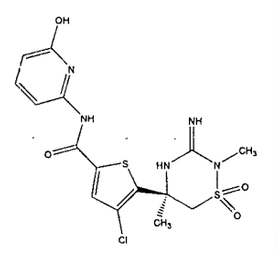
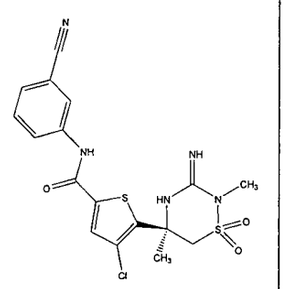
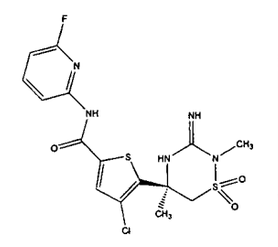
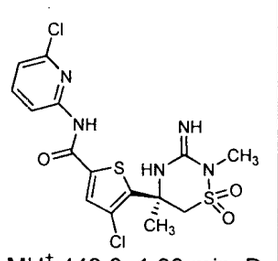
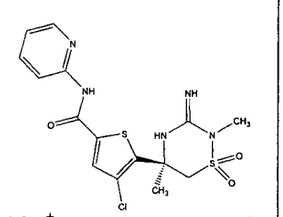
Esquema 13 Ej. 124

Paso 1: Al bromotiofeno preparado en el esquema 13 (1,34 g, 2,83 mmol) en THF (9,2 mL) a 0°C se le agregó cloruro de metilmagnesio (3,0 M en THF, 1,18 mL, 3,54 mmol). La reacción se agitó durante 30 minutos a 0°C y luego se enfrió hasta –78°C. Se agregó *n*–butillitio (2,5 M en hexanos, 2,55 mL, 6,38 mmol) durante el lapso de 10 minutos. La reacción se agitó durante 1 hora a –78° y luego se introdujeron burbujas de gas de CO_2 a través de la reacción. Se retiró el baño frío y la reacción se dejó calentar hasta temperatura ambiente continuando con el burbujeo de gas de CO_2 a través de la mezcla. a la mezcla se le agregó HCl $_{(ac.)}$ 1N y la mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–80% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el ácido carboxílico (0,97 g, 78%).

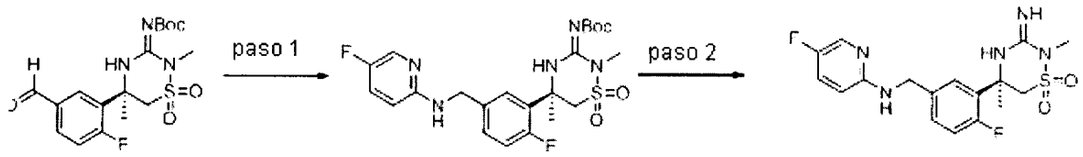
Paso 2: Al ácido carboxílico preparado en el paso 1 (0,027 g, 0,06 mmol) en piridina (0,25 mL) se le agregó 2–amino–6–metilpiridina (0,013 g, 0,12 mmol) y cloruro de bis(2–oxo–3–oxazolidinil)fosfínico (0,024 g, 0,09 mmol). La reacción se agitó durante 18 h a temperatura ambiente y luego se concentró *in vacuo*. Se agregó agua y la mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), filtraron y

concentraron *in vacuo.* El residuo se purificó mediante TLC en gel de sílice preparativa (1000 µm SiO_2, 30% EtOAc/hexano) para proporcionar el producto (13 mg, 40%). A la amida (0,065 g, 0,14 mmol) en DCM (0,4 mL) se le agregó TFA (0,2 mL). La reacción se agitó durante 20 h a TA y luego se concentró in vacuo para proporcionar el **Ej. 124** como la sal TFA. Datos de LCMS: (método D): t_R = 1,59 min, *m/e* = 428,0 (M+H).

Tabla XIV: Los siguientes ejemplos se prepararon utilizando procedimientos similares a aquellos descritos en el Esquema 27 utilizando las arilaminas apropiadas.

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)		
125  MH^+:466,0, 1,82 min, D	**126**  MH^+:482,0, 2,21 min, D	**127**  MH^+:442,0, 1,70 min, D
128  MH^+:430,0, 1,74 min, D	**129**  MH^+:438,0, 1,84 min, D	**130**  MH^+:432,0, 1,83 min, D
130a  MH^+:448,0, 1,89 min, D	**130b**  MH^+:414,0, 1,65 min, D	

Esquema 28

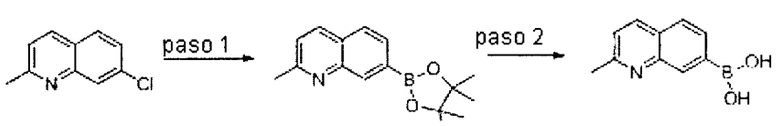


Ej. 131

Paso 1: Al aldehído (compuesto intermedio del esquema 21 paso 1 antes del tratamiento con $NaBH_4$) (0,10 g, 0,2 mmol) en metanol (1,5 mL) y piridina (0,5 mL) se le agregó tamices mol. 4 Å (100 mg), 2–amino–5–fluorpiridina (0,056 g, 0,5 mmol), y ácido acético (0,02 mL, 0,35 mmol). La reacción se calentó hasta 50°C y se agitó durante 18 h. Después de enfriamiento hasta temperatura ambiente, se agregó bicarbonato sódico saturado (0,5 mL) y la mezcla se agitó durante 10 minutos. Luego, la mezcla se filtró y el filtrado se concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–35% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el producto (0,077 g, 78%).

Paso 2: Al material preparado en el paso 1 (0,077 g, 0,16 mmol) en DCM (0,4 mL) se le agregó TFA (0,24 mL, 3,1 mmol). La reacción se agitó a temperatura ambiente durante 2 h y luego se concentró *in vacuo*. El residuo se absorbió en DCM y se lavó con $NaHCO_3$ saturado (ac) agua, y salmuera. La capa de DCM se secó ($MgSO_4$), se filtró y concentró *in vacuo*. Luego, el residuo se absorbió en DCM y se agregó un exceso de HCl 2N /éter. La mezcla se concentró para proporcionar el **Ej. 131** (57 mg) como la sal HCl. Datos de LCMS: (método D): t_R = 1,56 min, *m/e* = 396,2 (M+H).

Esquema 29:

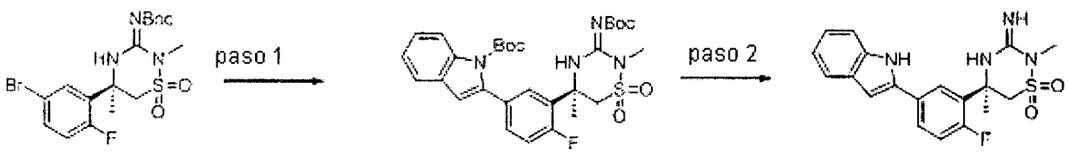


Paso 1: A 7–cloroquinaldina (1,2 g, 6,5 mmol) en THF (80 mL) se le agregó bis(pinacolato)diboro (1,9 g, 7,6 mmol), clorhidrato de 1,3–bis(2,6–diisopropilfenil)imidazol–2–ilideno (0,17 g, 0,4 mmol), y acetato de potasio (1,6 g, 16 mmol). Se burbujeó nitrógeno a través de la reacción durante 10 minutos. Se agregó acetato de paladio (0,044 g, 0,20 mmol) y la reacción se calentó a reflujo y

se agitó durante 6 horas. La reacción se filtró a través de un tapón de gel de sílice lavando con EtOAc. El líquido filtrado se concentró *in vacuo*. El líquido filtrado se purificó por medio de cromatografía en gel de sílice (0–30% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el éster borónico (0,97 g, 55%).

Paso 2: Al éster borónico preparado en el paso 1 (0,78 g, 2,9 mmol) en THF (6 mL) se le agregó agua (24 mL) y metaperyodato sódico (0,93 g, 4,4 mmol). La reacción se agitó durante 1 h y luego se agregaron $HCl_{(ac)}$ 3M (19 mL). La mezcla se agitó durante 45 minutos y luego se extrajo con EtOAc. Luego, la capa acuosa se basificó con $NaHCO_{3(ac)}$ saturado y se extrajo con EtOAc. La capa orgánica se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y concentró *in vacuo* para proporcionar el ácido borónico (0,34 g, 63%).

Esquema 30:



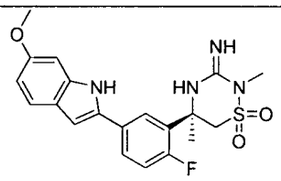
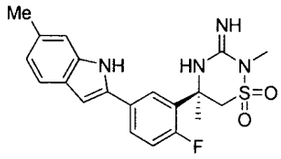
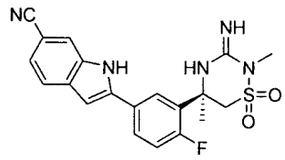
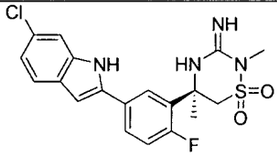
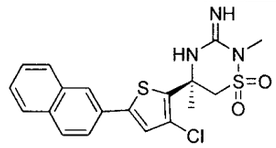
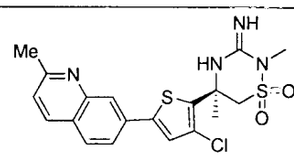
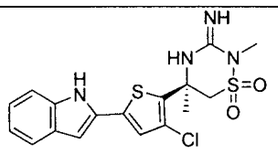
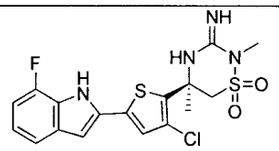
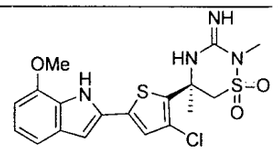
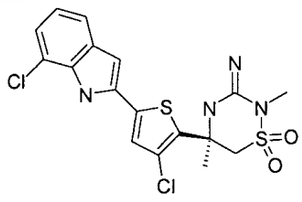
Ej. 132

Paso 1: Al bromuro (Tabla IIb, entrada 14) (0,15 g, 0,33 mmol) en un frasco de reacción de microondas se le agregó *t*–butanol (1,5 mL), ácido 1–(*t*–butoxicarbonil)–indol–2–borónico (0,16 g, 0,60 mmol) y carbonato de potasio acuoso (2M, 0,25 mL, 0,50 mmol). Se burbujeó nitrógeno a través de la mezcla de reacción durante 10 minutos. Se agregó $PdCl_2$(dppf) (0,054 g, 0,066 mmol) y se burbujeó nitrógeno a través de la reacción durante 5 minutos. El recipiente de la reacción se tapó, se calentó hasta 65°C, y se agitó durante 3 h. La reacción se enfrió hasta temperatura ambiente y se agregó EtOAc. La mezcla se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–20% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el producto de biarilo (0,12 g, 60%).

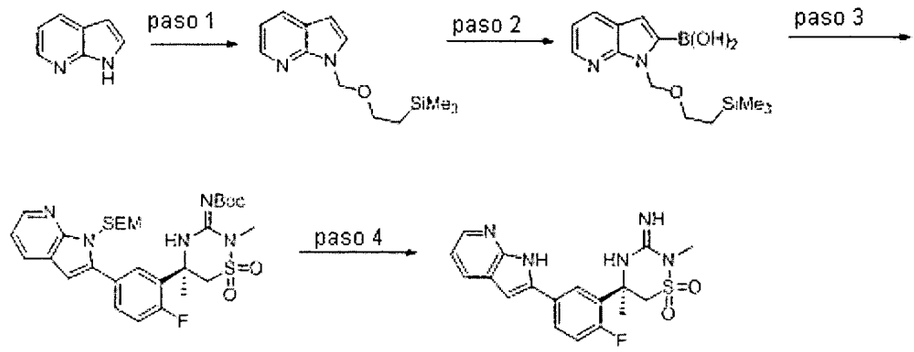
Paso 2: Al producto preparado en el paso 1 (0,12 g, 0,20 mmol) en DCM (2 mL) se le agregó TFA (2 mL). La reacción se agitó a temperatura ambiente durante 1 h y luego se concentró *in vacuo* para proporcionar el **Ej. 132**

como una sal TFA (0,078 g, 78%). Datos de LCMS: (método D): t_R = 1,96 min, *m/e* = 387,0 (M+H). El residuo se purificó adicionalmente según lo necesario mediante cromatografía en fase inversa [C18 5% (2 volúmenes de columna (CV, según el inglés), 5–100% (10 CV), 100 (2 CV); ácido fórmico al 0,1% /agua//ácido fórmico al 0,1% /acetonitrilo].

Tabla XV: Los siguientes ejemplos se prepararon utilizando procedimientos similares a aquellos descritos en el Esquema 30 utilizando los bromuros de arilo y ácidos borónicos apropiados.

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)					
133	 MH^+:417,0, 1,93 min, D	**134**	 MH^+:401,0, 2,01 min, D	**135**	 MH^+:412,0, 1,93 min, D
136	 MH^+:421,0, 2,03 min, D	**137**	 MH^+:420,0, 2,07 min, D	**138**	 MH^+:435,0, 1,68 min, D
139	 MH^+:409,0, 1,95 min, D	**140**	 MH^+:428,0, 1,99 min, D	**141**	 MH^+:439,0, 1,96 min, D
141a	 MH^+:443,0, 2,13 min, D	**	**	**	**

Esquema 31:



Ej. 142

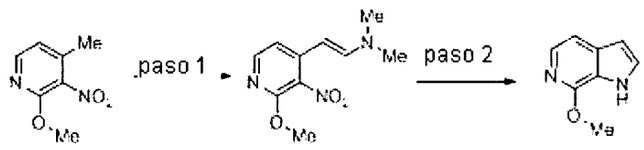
Paso 1: A 7–azaindol (1,5 g, 12,7 mmol) en DMF (30 mL) a 0°C se le agregó NaH (60% dispersión en aceite mineral, 0,56 g, 14 mmol). La reacción se agitó durante 15 minutos a temperatura ambiente y luego se enfrió hasta –40°C (baño de enfriamiento de EtOAc/CO_2). Luego se agregó (2–(clorometoxi)etil) trimetilsilano (2,5 mL, 14 mmol) y la reacción se dejó calentar hasta temperatura ambiente. La reacción se agitó a temperatura ambiente durante 18 h. Se agregó EtOAc y la mezcla se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–10% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el indol SEM–protegido (2,9 g, 91%).

Paso 2: Al indol SEM–protegido preparado en el paso 1 (0,99 g, 4,0 mmol) en THF (10 mL) a –40°C se le agregó *n*–BuLi (2,5 M en hexanos, 1,9 mL, 4,8 mmol). La mezcla se agitó a –40°C durante 1 h y luego se agregó triisopropilborato (1,2 mL, 5,2 mmol). La mezcla se dejó calentar hasta temperatura ambiente agitando al mismo tiempo durante 18 h. A la mezcla de reacción se le agregó HCl (ac) 1N. La mezcla se agitó a temperatura ambiente durante 30 minutos. Luego, la mezcla se ajustó hasta pH~5 empleando $NaHCO_3$ saturado (ac). La mezcla se extrajo con éter. Los extractos etéreos combinados se lavaron con agua y salmuera, se secaron (Na_2SO_4), filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–50% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el ácido indolborónico (0,20 g, 17%).

Paso 3: Al bromuro (Tabla IIb, entrada 14) (0,21 g, 0,46 mmol) en *t*–butanol (3 mL) se agregó en un frasco de reacción de microondas el ácido borónico preparado en el paso 2 (0,20 g, 0,68 mmol) y $K_2CO_{3\ (ac)}$ 2M (0,34 mL, 0,68 mmol). Se burbujeó nitrógeno a través de la reacción durante 10 minutos. Se agregó $PdCl_2$(dppf) (0,075 g, 0,092 mmol) y la reacción se cerró herméticamente y se calentó hasta 65°C. Después de 3 h, la reacción se enfrió hasta temperatura ambiente y se agregó EtOAc. La mezcla se lavó con agua y salmuera ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–20% EtOAc/hex en el transcurso de 30 minutos) para proporcionar el producto de acoplamiento (0,21 g, 74%).

Paso 4: Al producto de acoplamiento preparado en el paso 3 (0,086 g, 0,14 mmol) se le agregó HCl 4M en etanol (6 mL). La reacción se calentó hasta 60°C y se agitó durante 20 h. La reacción se concentró *in vacuo* y luego se purificó mediante cromatografía en fase inversa (C18: elución de gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:ácido fórmico) para proporcionar el **Ej. 142** (0,030 g). Datos de LCMS: (método D): t_R = 1,67 min, *m/e* = 388,0 (M+H).

Esquema 32:

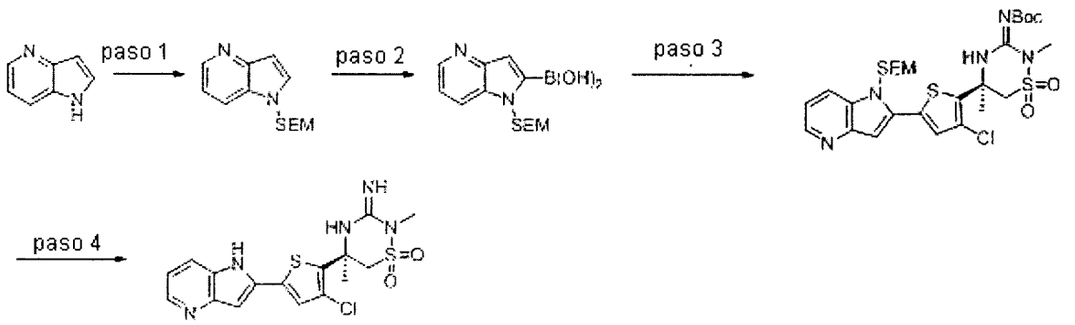


Paso 1: A la nitropiridina (5,1 g, 30 mml) en DMF (5 mL) se le agregó 1,1–metoxi–*N,N*–dimetilmetanamina (15 mL, 110 mmol). La reacción se calentó hasta 130°C y se agitó durante 16 h. La reacción se enfrió hasta temperatura ambiente y luego se agregó a un vaso de laboratorio de hielo. El sólido resultante se aisló mediante filtración para proporcionar el producto (5,9 g, 88%).

Paso 2: A la enamina preparada en el paso 1 (5,9 g, 26 mmol) en etanol (275 mL) se le agregó paladio sobre carbón al 10%, tipo Degussa (1,5 g). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno (102 kpa (15 psi)) durante 15 minutos. La reacción se filtró a través de un lecho de célite

lavando con DCM. El líquido filtrado se concentró *in vacuo* para proporcionar el indol (4,3 g, 61%).

Esquema 33:



Ej. 143

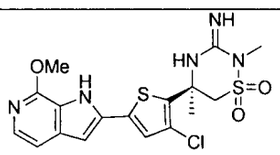
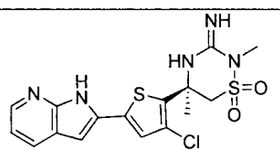
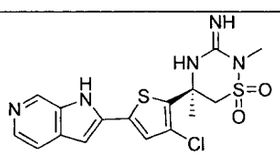
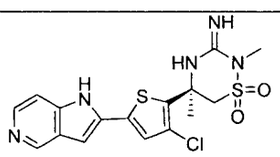
Paso 1: El 4–azaindol fue protegido con el grupo SEM de acuerdo con el procedimiento descrito en el paso 1 del Esquema 31.

Paso 2: El indol SEM protegido preparado en el paso 1 fue convertido en el ácido 2–borónico de acuerdo con el procedimiento descrito en el paso 2 del Esquema 31.

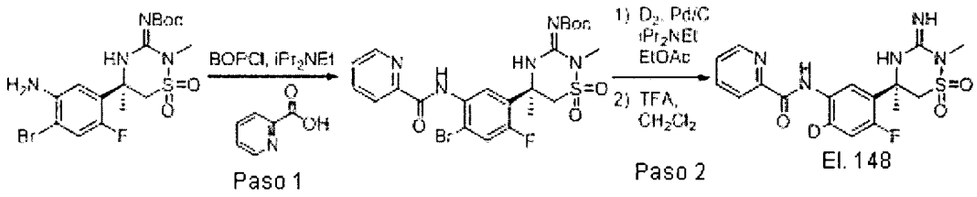
Paso 3: Al ácido indol 2-borónico SEM-protegido preparado en el paso 2 (0,40 g, 1,37 mmol) en un frasco de reacción de microondas en *t*–butanol (3 mL) se le agregó carbonato de potasio (2M, 0,6 mL, 1,1 mmol) y el bromotiofeno preparado en el esquema 13 (0,36 g, 0,76 mmol). Se burbujeó nitrógeno a través de la mezcla de reacción durante 10 minutos después de lo cual se agregó $PdCl_2$(dppf) (0,12 g, 0,15 mmol). El recipiente de reacción se tapó y se calentó hasta 65°C. La reacción se agitó durante 16 h y luego se enfrió hasta temperatura ambiente. Se agregó EtOAc y la mezcla se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y concentró *in vacuo*. El residuo se absorbió en DCM (2 mL) y se agregó $(Boc)_2O$ (166 mg). La reacción se agitó a temperatura ambiente durante 18 h. La reacción se concentró *in vacuo* para proporcionar un residuo el cual se purificó por medio de cromatografía en gel de sílice (0–40% EtOAc/hex) para proporcionar una mezcla de producto deseado y producto bis–boc (360 mg). La mezcla se empleó directamente en el paso siguiente.

Paso 4: El biarilo preparado en el paso 3 (0,28 g, 0,43 mmol) se calentó en HCl 4N en etanol (12 mL) hasta 65°C durante 12 h. La reacción se concentró *in vacuo* para proporcionar el material deseado y el compuesto intermedio indol *N*–hidroximetilo. La mezcla se absorbió en acetona (2 mL) y etanol (1 mL) y se agregó carbonato de potasio (0,15 g, 1,1 mmol). La mezcla se agitó a temperatura ambiente durante 1 h y luego se agregó a NH_4Cl saturado$_{(ac)}$. La mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó mediante TLC en gel de sílice preparativa (10% MeOH/DCM) para proporcionar el **Ej. 143** (0,10 g, 57%). Datos de LCMS: (método D): t_R = 1,67 min, *m/e* = 410,0 (M+H). (Alternativamente, el residuo pudo ser purificado mediante cromatografía en fase inversa [C18 5% (2 volúmenes de columna (CV, según el inglés), 5–100% (10 CV), 100 (2 CV); ácido fórmico al 0,1% /agua//ácido fórmico al 0,1% /acetonitrilo]).

Tabla XVI: Utilizando las condiciones descritas en el Esquema 33, los siguientes ejemplos se prepararon a partir de los bromuros de arilo y ácidos arilborónicos apropiados.

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
144	 MH^+:440,0, 1,65 min, D	**145**	 MH^+:410,0, 1,78 min, D
146	 MH^+:410,0, 1,70 min, D	**147**	 MH^+:410,0, 1,67 min, D

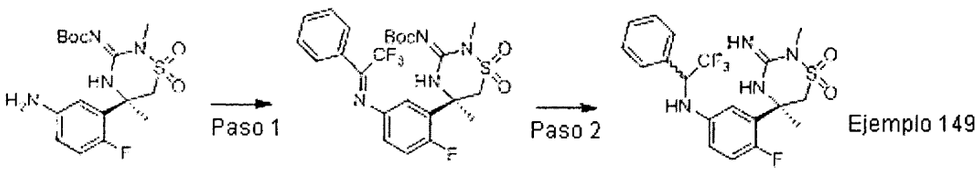
Esquema 34:



Paso 1: A una suspensión de la anilina del Esquema 10a (95 mg, 0,20 mmol), ácido picolínico (30 mg, 0,25 mmol) y BOPCl (78 mg, 0,31 mmol) en CH_2Cl_2 (4 mL) a 0°C se le agregó iPr_2NEt (89 µL, 0,51 mmol). La mezcla resultante se calentó hasta TA y se agitó durante 16 horas. La mezcla se repartió entre CH_2Cl_2 y agua. La capa acuosa se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y concentraron. El producto en bruto se purificó mediante TLC preparativa (SiO_2: 1:1 hexanos:EtOAc) para proporcionar la amida (47 mg, 40%) como un sólido blanco.

Paso 2: El **Ej. 148** se preparó como su sal TFA del material antes mencionado utilizando un procedimiento similar a aquel descrito en el Esquema 23. Datos de LCMS: (método D): t_R = 1,75 min, *m/e* = 393,0 (M+H).

Esquema 35:



Paso 1: A una mezcla a TA de anilina (Esquema 10, 0,1 g, 0,26 mmol), 2 mL DCM, diisopropiletilamina (45 µL, 0,26 mmol), y trifluoracetofenona (0,045 g, 0,26 mmol) se le agregó lentamente por goteo tetracloruro de titanio (1,0 M en DCM, 0,26 mL, 0,26 mmol). La reacción se agitó durante 2 horas. Luego se vertió bicarbonato sódico acuoso saturado en la reacción, formando un precipitado blanco, el cual luego se filtró a través de célite. La célite se lavó con DCM y el líquido filtrado se extrajo con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–30% EtOAc/hexanos en el transcurso de 20 minutos) para proporcionar el compuesto imina (0,051 g, 36%).

Paso 2: A la imina preparada en el paso 1 (0,051 g, 0,09 mmol) agitando en 2 mL de MeOH se le agregó borohidruro sódico (0,007 g, 0,18 mmol). La reacción se agitó a temperatura ambiente durante 1 hora, luego se concentró hasta sequedad *in vacuo*. La reacción se purificó mediante RP HPLC preparativa (10–100% acetonitrilo con ácido fórmico al 0,1% /agua con ácido fórmico al 0,1% en el transcurso de 22 minutos) para proporcionar el producto de amina. Este material se trató con 2 mL 20% TFA/DCM durante 1 hora, y luego se concentró *in vacuo* para proporcionar el **Ejemplo 149** (1:1 mezcla de diastereómeros) como una sal trifluoracetato (39 mg, 75%). Datos de LCMS: (método D): t_R = 1,97 min, *m/e* = 445,0 (M+H).

Tabla XVII: Los siguientes ejemplos fueron preparados de acuerdo con los métodos descritos en el Esquema 35:

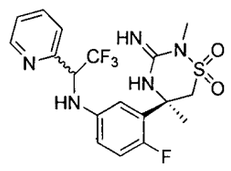
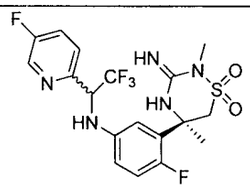
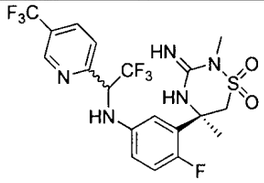
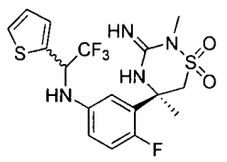
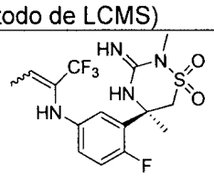
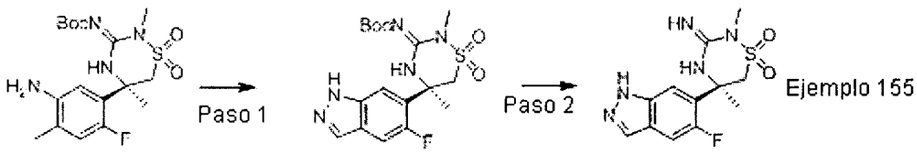
Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
150	 MH^+:446.0, 1.87 min, D	**151**	 MH^+:464.0, 1.93 min, D
152	 MH^+:514.0, 1.99 min, D	**153**	 MH^+:451.0, 1.93 min, D

Tabla XVIII: El siguiente Ejemplo se preparó como una mezcla de diastereómeros empleando la siguiente secuencia: (1) Esquema 35, Paso 1, (2) Esquema 11b, Paso 2:

Ejemplo (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)	
154	

	MH^+:395,0, 1,89 min, D

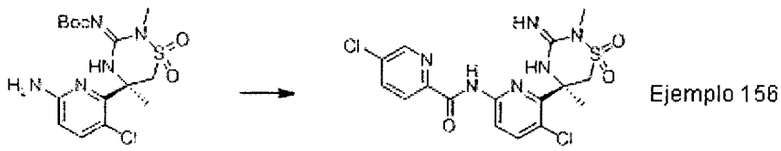
Esquema 36:



Paso 1: A la anilina (Tabla IV, entrada 5 0,2 g, 0,5 mmol) agitando a temperatura ambiente en ácido acético glacial (5 mL) se le agregó por goteo una solución de nitrito sódico (0,035 g, 0,5 mmol) en agua (0,25 mL). La reacción se agitó a temperatura ambiente durante 6 horas, luego se concentró hasta sequedad *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–100% EtOAc/hexanos en el transcurso de 30 minutos) para proporcionar el compuesto de indazol como un sólido (0,060 g, 29%).

Paso 2: El material del paso 1 (0,005g, 0,012 mmol) se trató de acuerdo con el Esquema 11b, paso 2 para proporcionar el **Ejemplo 155** como la sal TFA (0,005 g, 97%). Datos de LCMS: (método D): t_R = 1,63 min, *m/e* = 312,0 (M+H).

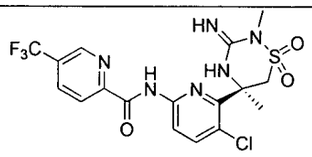
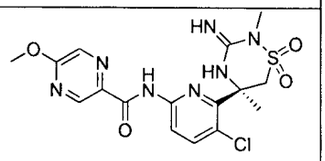
Esquema 37:



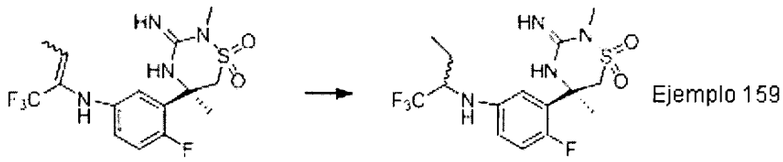
Al compuesto de aminopiridina (Tabla IIIb, 0,068 g, 0,17 mmol) agitando en 1,68 mL 4:1 DMF:diisopropiletilamina a temperatura ambiente se le agregó cloruro de 5–cloropicolinoílo (Esquema 11p) y 1 cristal de DMAP. La reacción se calentó hasta 50°C y se agitó durante 48 horas. La reacción se enfrió hasta temperatura ambiente y se concentró *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–60% EtOAc/hexanos en el transcurso de 20

minutos, luego 60–100% EtOAc/hexanos 20–30 minutos) para proporcionar un producto de amida (0,014 g, 15%). Este material se trató de acuerdo con el Esquema 11b, paso 2 para proporcionar el **Ejemplo 156** (0,014 g, 97%) como una sal trifluoracetato. Datos de LCMS: (método D): t_R = 1,91 min, *m/e* = 443,0 (M+H).

Tabla XIX: Los siguientes ejemplos se prepararon de acuerdo con los métodos descritos en el Esquema 37 utilizando cloruros ácidos de la Tabla IVj:

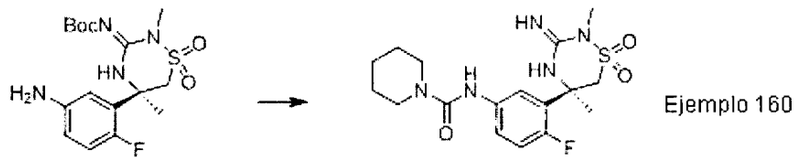
Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
157	 MH^+:477.0, 1.93 min, D	**158**	 MH^+:440.0, 1.84 min, D

Esquema 38:



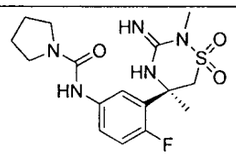
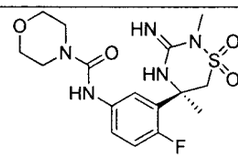
Al **Ejemplo 154** (0,020 g, 0,04 mmol) agitando en 2 mL de EtOH se le agregó paladio sobre carbono al 10% (0,010 g). Esta solución fue sometida a una atmósfera de hidrógeno (balón) y se agitó durante 16 horas. La reacción se filtró a través de célite y se lavó con MeOH. El líquido filtrado se concentró hasta sequedad *in vacuo* y se purificó mediante RP HPLC preparativa (10–100% acetonitrilo con ácido fórmico al 0,1%/agua con ácido fórmico 0,1% en el transcurso de 22 minutos) para proporcionar el **Ejemplo 159** como una mezcla de diastereómeros como una sal de formiato (0,013 g, 65%). Datos de LCMS: (método D): t_R = 1,92 min, *m/e* = 397,0 (M+H).

Esquema 39:

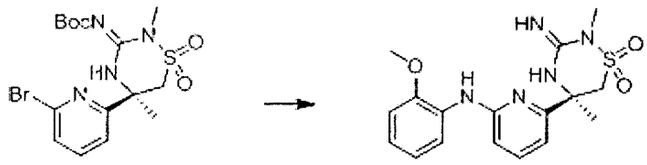


Paso 1: A la anilina (Esquema 10, 0,1 g, 0,26 mmol) agitando en 3 mL de DCM se agregó trietilamina (54 µL, 0,39 mmol) y cloruro de 1–piperidinacarbonilo (34 µL, 0,27 mmol), y la mezcla se dejó agitar durante 3 días a temperatura ambiente. La reacción se vertió en agua y se extrajo con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–80% EtOAc/hexanos en el transcurso de 20 minutos) para proporcionar un producto de urea (0,093 g, 72%). Luego, este compuesto se trató de acuerdo con el Esquema 11b, Paso 2 para proporcionar el **Ejemplo 160** (0,094 g, 98%) como una sal trifluoracetato. Datos de LCMS: (método D): t_R = 1,75 min, *m/e* = 398,2 (M+H).

Tabla XX: Los siguientes ejemplos se prepararon de acuerdo con los métodos descritos en el Esquema 39 utilizando el cloruro de carbonilo apropiado:

Ejemplo (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
161	 MH^+:384.2, 1.61 min, D	**161a**	 MH^+:400.0, 1.47 min, D

Esquema 40:

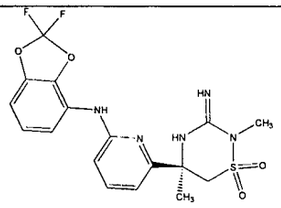
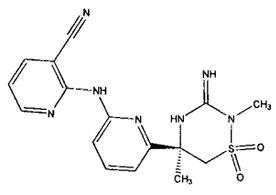
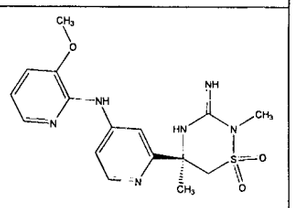
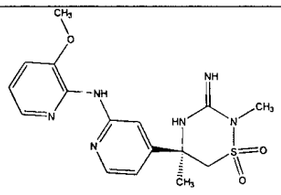
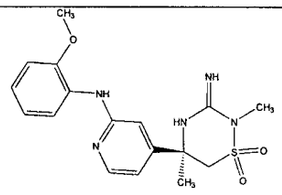


Ej. 162

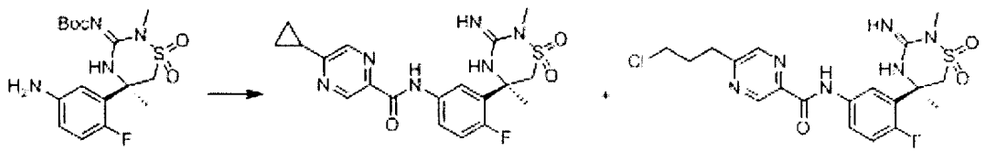
El compuesto de bromopiridina (Esquema 7a , paso 6) 0,07 g, 0,16 mmol) junto con *O*–anisidina (22 µL, 0,19 mmol), tris(dibencilidenacetona)dipaladio (0,003 g, 0,003 mmol), 2,2'–bis(difenilfosfino)–1,1'–binaftilo racémico (0,004 g, 0,006 mmol), y t-butóxido de sodio (0,022 g, 0,22 mmol) se agitaron en un frasco de microondas cerrado herméticamente, secado a la llama lavado a chorro con nitrógeno en 2 mL de tolueno anhidro a 80°C durante 3,5 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se vertió en agua, y se extrajo con

DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), filtraron y concentraron *in vacuo*. El residuo se purificó por medio de cromatografía en gel de sílice (0–60% EtOAc/hexanos en el transcurso de 20 minutos) para proporcionar el producto de biarilamina (0,007 g, 9%). Este material se trató de acuerdo con el Esquema 11b, Paso 2 para proporcionar el **Ejemplo 162** en forma de una sal trifluoracetato (0,007 g, 97%). Datos de LCMS: (método D): t_R = 1,80 min, *m/e* = 376,2 (M+H).

Tabla XXI: Los siguientes ejemplos se prepararon de acuerdo con los métodos en el Esquema 40:

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)					
163	 MH^+:426.0, 2.05 min, D	**164**	 MH^+:372.0, 1.83 min, D	**165**	 MH^+:377.0, 1.65 min, D
166	 MH^+:377.0, 1.18 min, D	**167**	 MH^+:376.0, 1.38 min, D		**

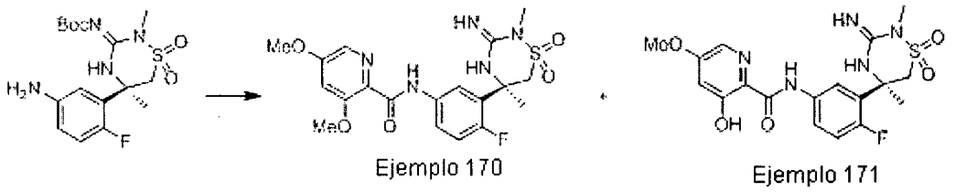
Esquema 41:



Ejemplo 168 Ejemplo 169

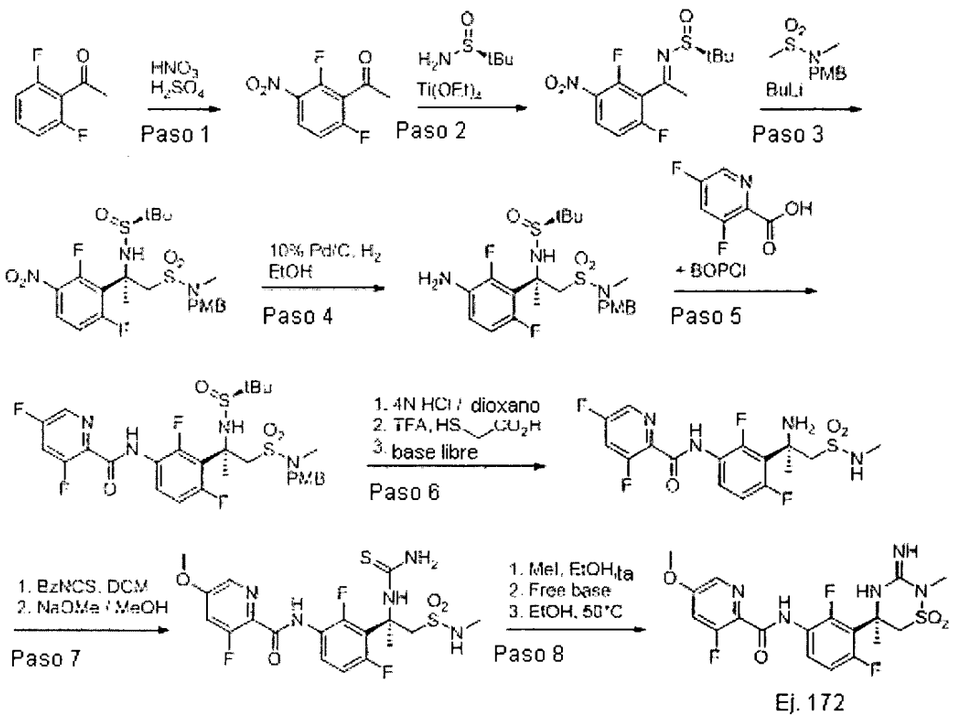
La anilina mostrada (Esquema 10) se trató de acuerdo con el Esquema 11b utilizando ácido 5–ciclopropilpirazina–2–carboxílico (Tabla IVg, entrada 4) para proporcionar, después de separación, ambos **Ejemplo 169** [Datos de LCMS: (método D): t_R = 1,80 min, *m/e* = 433,0 (M+H)] y el **Ejemplo 168** [Datos de LCMS: (método D): t_R = 1,83 min, *m/e* = 469,0 (M+H)] ambos como sales TFA.

Esquema 42:



La anilina mostrada (Esquema 10) se trató de acuerdo con el Esquema 11b utilizando el ácido 3,5–dimetoxipiridin–2–carboxílico (Esquema 11q) para proporcionar, después de separación, ambos **Ejemplo 170** [Datos de LCMS: (método D): t_R = 1,73 min, *m/e* = 452,0 (M+H)] y el **Ejemplo 171** [Datos de LCMS: (método D): t_R = 1,85 min, *m/e* = 438,0 (M+H)] ambos como sales TFA.

Esquema 43:



Paso 1: A una mezcla de –40°C de H_2SO_4 concentrado (100 mL) y HNO_3 humeante (100 mL) se agregó 1–(2,6–difluorfenil)etanona (20 g, 128 mmol) por goteo. La mezcla resultante se agitó a –40°C durante 2h y luego se vertió lentamente sobre hielo. Esa mezcla se diluyó con DCM y las fases se separaron. La capa acuosa se neutralizó con $NaHCO_3$ sat. ac. y luego se extrajo con DCM. Todas las porciones orgánicas se combinaron, se secaron sobre $MgSO_4$, filtraron y

concentraron para proporcionar 1–(2,6–difluor–3–nitrofenil)etanona (26,3 g, 131 mmol, > teórico) la cual se empleó sin más purificación.

Paso 2: La nitrofenil cetona del paso previo se trató de acuerdo con el Esquema 1a, Paso 1 [sustituyendo (S)–2–metil–2–propansulfinamida por (R)–2–metil–2–propansulfinamida] para proporcionar un producto de ketimina (17,1 g, 44% en base a 1–(2,6–difluorfenil)etanona del Paso 1).

Paso 3: La ketimina del paso 2 (17,1 g, 56,2 mmol) se trató de acuerdo con el Esquema 1a, Paso 3 para proporcionar el producto de adicón sin deseado (6 g, 20%) así como también una mezcla de diastereómeros sin y anti (6 g, 3:1, 20%).

Paso 4: A una solución del producto de adición sin del Paso 3 (2,71 g, 5,1 mmol) en 25 mL de etanol se agregó 10% Pd/C (298 mg). La mezcla se colocó bajo atmósfera de balón de H_2 durante la noche. Después de filtración a través de Celite, el líquido filtrado se concentró. El residuo en bruto se purificó mediante columna de sílice flash (60%–100% EtOAc/hexanos) para proporcionar el producto de anilina (1,75 g, 68% de rendimiento).

Paso 5: Una mezcla de la anilina del Paso 4 (453 mg, 0,9 mmol), ácido 3,5–difluorpicolínico (215 mg, 1,4 mmol), y BOPCl (527 mg, 2,07 mmol) en 4 mL de piridina se agitó durante la noche. Después de templado con HCl (ac) 1N, la mezcla se extrajo con acetato de etilo. Las porciones orgánicas se combinaron, se secaron sobre $MgSO_4$ y concentraron. El residuo en bruto se purificó mediante columna de sílice flash (40% EtOAc/hexano) para proporcionar un producto de amida (431 mg, 74% de rendimiento).

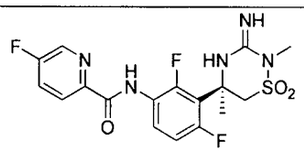
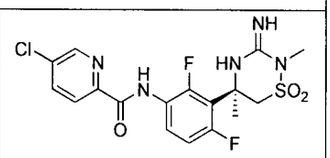
Paso 6: A una solución del material antes mencionado (431 mg, 0,67 mmol) en 3 mL de DCM y 1 mL de metanol se le agregó HCl 4N en dioxano (1 mL, 4,0 mmol). Luego de que la mezcla se agitó durante 1 h, se concentró. Esta muestra se trató con una mezcla de TFA (4 mL) y ácido tioglicólico (0,46 mL, 6,7 mmol). Después de agitar la mezcla durante 4 h, la misma se concentró. El residuo en bruto se neutralizó mediante la adición cuidadosa de solución de bicarbonato sódico saturado. La mezcla resultante se extrajo con acetato de etilo, las porciones orgánicas se combinaron, se secaron sobre sulfato de magnesio y

se concentraron a un producto de amina el cual se utilizó en el siguiente paso sin más purificación.

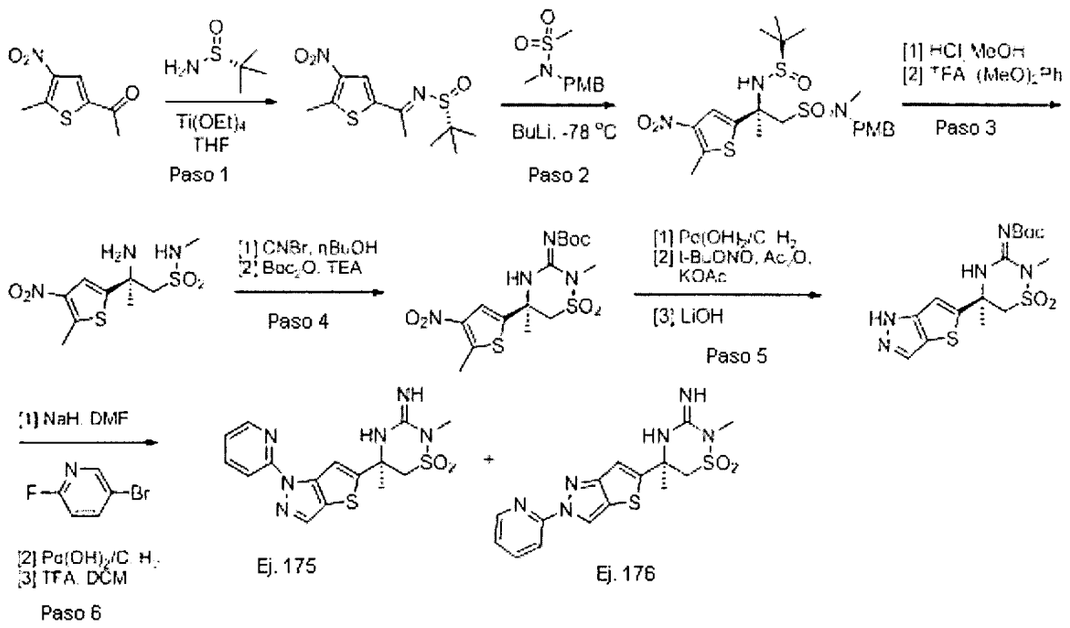
Paso 7: Al material del paso 6 (que se presume que es 0,67 mmol) en 5 mL de DCM se agregó isotiocianato de benzoílo (0,12 mL, 0,87 mmol). La mezcla se agitó durante la noche a TA. Después de su concentración, el residuo se disolvió en 5 mL de metanol, y se agregó metóxido de sodio (25% en metanol, 0,37 mL). La mezcla se agitó durante 2 h a TA. Se templó con 2 gotas de ácido acético. Después de concentrar la mezcla, el material en bruto se diluyó con carbonato sódico saturado, y se extrajo con DCM. Las porciones orgánicas combinadas se secaron sobre sulfato de magnesio y concentraron para proporcionar un producto de isotiourea el cual se utilizó en el siguiente paso sin purificación.

Paso 8: A una solución del material del paso 7 (que se supone que es 0,67 mmol) en 5 mL de etanol se le agregó yoduro de metilo (0,05 mL, 0,8 mmol). La mezcla se agitó durante la noche a temperatura ambiente y luego se diluyó con bicarbonato sódico saturado. Después de que la mezcla se extrajera con acetato de etilo, las capas orgánicas se combinaron, se secaron sobre sulfato magnésico, y se concentraron. El residuo en bruto se disolvió en 5 mL de etanol, y la mezcla se calentó a 50°C durante 2 h. Luego, la mezcla se diluyó con bicarbonato sódico saturado, y se extrajo con acetato de etilo. Las porciones orgánicas se combinaron, se secaron sobre sulfato magnésico, y se concentraron. El residuo en bruto se purificó mediante HPLC de fase inversa (C18 compresión radial, 10% a 100% MeCN/agua con TFA al 0.1%) para proporcionar el **Ejemplo 172** en forma de una sal TFA (40,3 mg, 14% del producto del Paso 5). LCMS (condiciones A): t_R = 2,43 min, *m/e* = 458,3 (M+H).

Tabla XXII: Los siguientes ejemplos se prepararon a partir de 1–(2,6–difluorfenil)etanona utilizando métodos similares a aquellos descritos en el Esquema 43, sustituyendo el ácido apropiado en el Paso 5:

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
173	 MH^+:428.2, 2.46 min, A	**174**	 MH^+:442.2, 3.17 min, A

Esquema 44:



Pasos 1–4:1–(5–Metil–4–nitrotiofen–2–il)etanona, obtenida mediante nitración de 1–(5–metiltiofen–2–il)etanona de acuerdo con el procedimiento de la bibliografía técnica (E. Campaigne, J. L. Diedrich, *J. Am. Chem. Soc.* **1951**, *73*, 5240–5243), se convirtió en el producto del paso 4 utilizando procedimientos similares en la siguiente secuencia: (i) Esquema 1a, pasos 1–4, (ii) Esquema 3b.

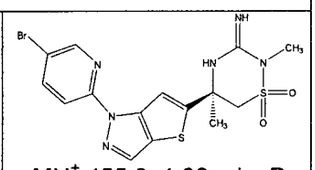
Paso 5: A una solución del producto del paso 4 (570 mg, 1,37 mmol) en MeOH (25 mL) se le agregó 10% $Pd(OH)_2/C$ (250 mg), y la reacción se agitó en un agitador Parr bajo una atmósfera de H_2 (340 kPa (50 psi)) durante 18 h. La

reacción se filtró sobre una almohadilla de celite, el residuo del filtro se enjuagó con MeOH y las capas orgánicas combinadas se concentraron bajo presión reducida para proporcionar un residuo (423 mg, 80%). A una solución de este residuo (423 mg, 1,08 mmol) en tolueno (3 mL) se le agregó KOAc (85 mg, 0,86 mmol), anhídrido acético (0,205 mL, 2,16 mmol) y *terc*–butilnitrito (0,145 mL, 1,2 mmol). La reacción se agitó a 90 °C durante 4,5 h, luego se enfrió hasta TA y se diluyó con EtOAc. Después de filtración a través de célite, el líquido filtrado se concentró bajo presión reducida para proporcionar un residuo el cual fue sometido a cromatografía en gel de sílice (elución de gradiente 100:0 a 70:30 hexanos:EtOAc). La mezcla resultante de materiales acetilados y desacetilados (298 mg) se disolvió en THF (5 mL) y se trató con LiOH 1 M acuoso (2 mL) durante 30 min a TA. La reacción se diluyó con EtOAc, las capas se separaron y la capa acuosa se extrajo con EtOAc (1 x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, y concentraron bajo vacío para proporcionar el producto del paso 5 (282 mg, 65%).

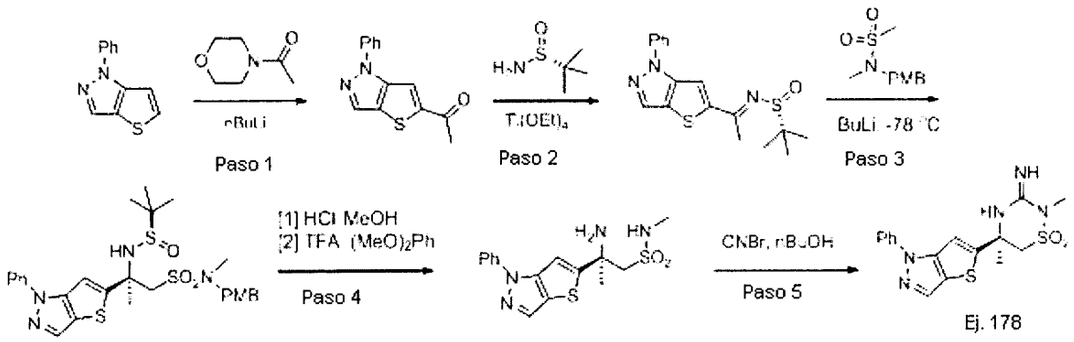
Paso 6: Se agregó hidruro sódico (60% en aceite mineral, 20 mg, 0,5 mmol) a una solución del producto del paso 5 (78 mg, 0,195 mmol) en DMF (2 mL) a TA. Después de 5 min, se agregó 2–fluor–5–bromopiridina (54 mg, 0,306 mmol) y la reacción se agitó durante 19 h a TA, luego se templó con agua y EtOAc. La capa orgánica se lavó con $NaHCO_{3\ (ac.)}$ saturado, acuoso, salmuera, y luego se secó sobre $MgSO_4$, y concentró bajo vacío. A una solución de este residuo en MeOH se le agregó 10% $Pd(OH)_2/C$ (110 mg), y la reacción se agitó bajo una atmósfera de balón de H_2 durante 72 h. El catalizador se extrajo por filtración sobre célite, y el líquido filtrado se concentró bajo presión reducida para proporcionar una mezcla de compuestos intermedios regioisoméricos que se separaron por medio de cromatografía en gel de sílice (elución de gradiente con hexanos:EtOAc). Cada regioisómero fue desprotegido de acuerdo con el procedimiento descrito en el Esquema 11b, Paso 2, luego se sometió a cromatografía en fase inversa (C18: elución de gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar el **Ejemplo 175** y el **Ejemplo 176** como sus sales TFA. LCMS para **Ej. 175**

(condiciones D): t_R = 1,80 min, *m/e* = 377,0 (M+H); LCMS para **Ej. 176** (condiciones D): t_R = 1,78 min, *m/e* = 377,0 (M+H).

Tabla XXIII: Los siguientes ejemplos se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 44 omitiendo la porción de hidrogenación del paso 6.

Ejemplo	
177	 MH$^+$:455,0, 1,92 min, D

Esquema 45:

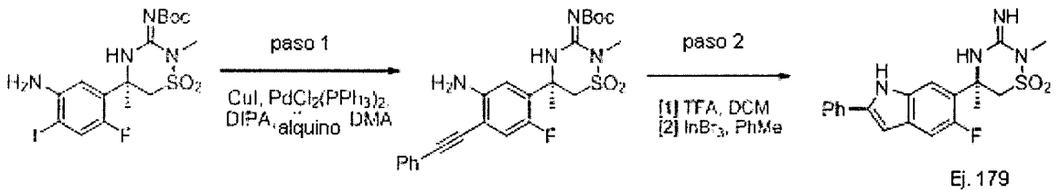


Paso 1: A una solución a –78°C de 1–fenil–1H–tieno[3,2–c]pirazol (1,94 g, 9,68 mmol), obtenida a partir de 3–bromotiofen–2–carbaldehído de acuerdo con el procedimiento de la bibliografía técnica (Lebedev et al., *J. Org. Chem.* **2005**, *70*, 596–602), se le agregó nBuLi (4,25 mL de una solución 2,5 M en hexanos, 10,65 mmol) durante 5 min. Después de 30 min a –78°C, se agregó N–acetilmorfolina (2,3 mL, 20 mmol) y la reacción se agitó durante 60 min a –78°C, luego se agitó durante 6 h calentando lentamente al mismo tiempo hasta TA. La reacción se templó con NH_4Cl acuoso, saturado y se diluyó con EtOAc. La capa orgánica se lavó con $NaHCO_3$ sat., acuoso y salmuera, se secó sobre $MgSO_4$ y concentró bajo presión reducida. El residuo fue sometido a cromatografía en gel de sílice (elución de gradiente 100:0 a 85:15 hexanos:EtOAc) para proporcionar 1–(1–fenil–1H–

tieno[3,2–c]pirazol–5–il)etanona (682 mg, 2,81 mmol, 29%) junto con material de partida recuperado (823 mg, 4,13 mmol, 43%).

Pasos 2–5: Estos pasos se llevaron a cabo utilizando procedimientos similares a la siguiente secuencia: (i) Esquema 1a, pasos 1–4, (ii) Esquema 3b, omitiendo la conversión en el *t*–butil carbamato. El compuesto intermedio final fue sometido a cromatografía en fase inversa (C18: elución del gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar **Ej. 178** como su sal TFA. LCMS para el **Ej. 178** (condiciones D): t_R = 1,82 min, *m/e* = 376,0 (M+H).

Esquema 46:



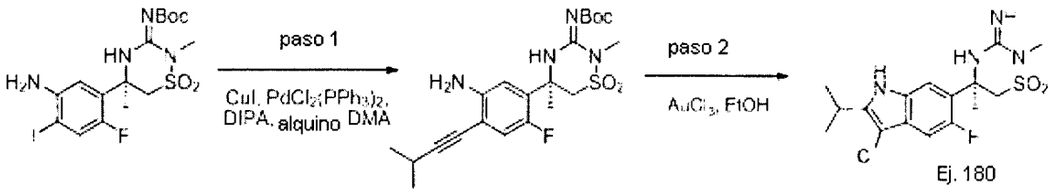
Ej. 179

Paso 1: Se agregó CuI (7,6 mg, 0,04 mmol) a una solución de yodoanilina (200 mg, 0,39 mmol, Esquema 10a), diisopropilamina (0,169 mL, 1,2 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0,04 mmol) y fenil acetileno (0,132 mL, 1,2 mmol) en dimetilacetamida (2 mL), y la reacción se agitó a 40°C durante 6 h. La reacción se diluyó con solución de $NaHCO_3$ ac., saturado, y EtOAc, luego se filtró la reacción sobre célite. Luego de enjuagar el residuo con EtOAc, la capa acuosa se extrajo con EtOAc (3 x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, filtraron y concentraron para proporcionar un residuo el cual fue posteriormente sometido a cromatografía en gel de sílice (10→20 % EtOAc/hexanos) para proporcionar el compuesto intermedio anilino acetileno (181 mg, 95%).

Paso 2: Se agregó ácido trifluoracético (0,2 mL) a una solución del producto del paso 1 (181 mg, 0,37 mmol) en DCM (1 mL) a TA. Después de 2 h, la reacción se concentró bajo vacío. A parte del residuo (50 mg, 0,13 mmol) en tolueno (1 mL) se le agregó $InBr_3$ (46 mg, 0,13 mmol.), y la reacción se calentó hasta 115°C durante 2 h. Después de eliminar los volátiles bajo presión reducida, el residuo se suspendió en MeOH, se filtró a través de un filtro de PTFE y el líquido filtrado se sometió a cromatografía en fase inversa (C18: elución del

gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar el **Ej. 179** como su sal TFA (11,7 mg, 30%). LCMS para el **Ej. 179** (condiciones D): t_R = 1,98 min, *m/e* = 387,2 (M+H).

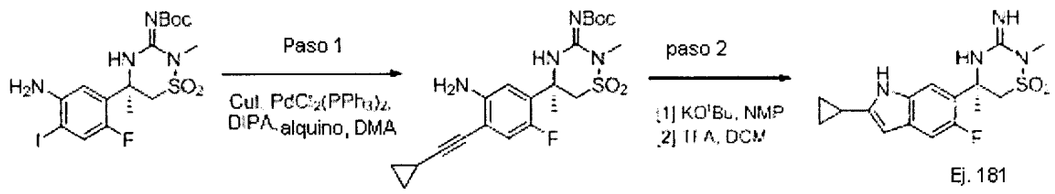
Esquema 47:



Paso 1: el compuesto intermedio anilino acetileno se preparó del mismo modo que en el Esquema 46, Paso 1 excepto que se utilizó isopropilacetileno en lugar de fenilacetileno.

Paso 2: Al compuesto intermedio anilino acetileno del Paso 1 (100 mg, 0,22 mmol) en EtOH (1 mL) se le agregó $AuCl_3$ (133 mg, 0,44 mmol), y la reacción se calentó hasta 70°C durante 3 h. Después de la remoción de los volátiles bajo presión reducida, el residuo se suspendió en MeOH, se filtró a través de un filtro de PTFE y el líquido filtrado se sometió a cromatografía en fase inversa (C18: elución del gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar **Ejemplo 180** como su sal TFA (17,2 mg, 20%). LCMS para **Ejemplo 180** (condiciones D): t_R = 2,04 min, *m/e* = 387,0 (M+H).

Esquema 48:

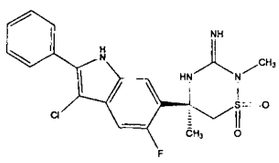
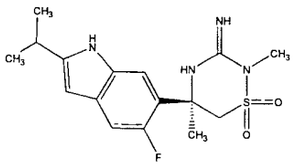
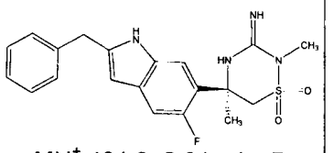
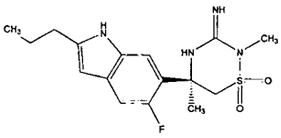
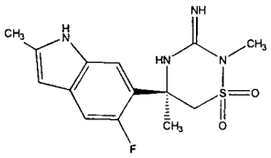
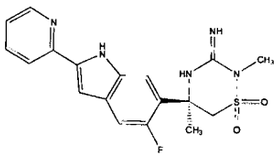
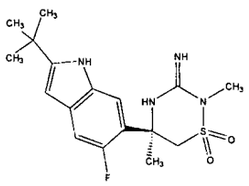
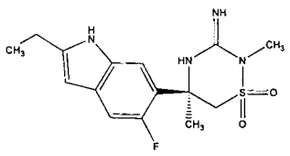


Paso 1: El compuesto intermedio anilino acetileno se preparó del mismo modo que en el Esquema 46, Paso 1 excepto que se empleó ciclopropilacetileno en lugar de fenilacetileno.

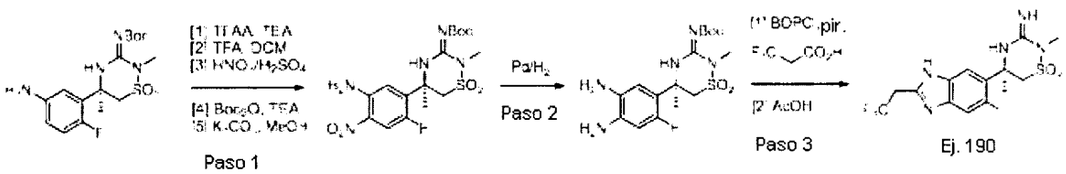
Paso 2: Al compuesto intermedio anilino acetileno del Paso 1 (54 mg, 0,11 mmol) en NMP (1 mL) se le agregó *terc*–butóxido de potasio (37 mg, 0,33 mmol), y

la reacción se agitó durante 18 h a TA. Luego, la mezcla se diluyó con agua y EtOAc, la capa orgánica se secó sobre Na_2SO_4, se filtró y concentró para proporcionar un residuo el cual se sometió posteriormente a cromatografía en gel de sílice (10→25 % EtOAc/hexanos) para proporcionar el compuesto intermedio indol Boc–protegido (35 mg, 70%). Este compuesto intermedio fue desprotegido de acuerdo con el procedimiento descrito en el Esquema 11b, Paso 2, luego se sometió a cromatografía en fase inversa (C_{18}: elución del gradiente, 90:10:0,1 a 0:100:0,1 de agua:MeCN:TFA) para proporcionar el **Ej. 181** como su sal TFA. LCMS para el **Ej. 181** (condiciones D): t_R = 1,91 min, *m/e* = 351,2 (M+H).

abla XXIV: Los siguientes ejemplos se prepararon utilizando un procedimiento similar a aquel descrito en los Esquemas 46, 47 y 48.

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)					
182	 MH^+:421,2, 2,07 min, D	**183**	 MH^+:353,2, 1,96 min, D	**184**	 MH^+:401,2, 2,01 min, D
185	 MH^+:353,0, 1,98 min, D	**186**	 MH^+:325,0, 1,85 min, D	**187**	 MH^+:388,0, 1,74 min, D
188	 MH^+:367,0, 2,02 min, D	**189**	 MH^+:339,0, 1,87 min, D		

Esquema 49:



Paso 1: Se agregó anhídrido trifluoracético (2,34 mL, 16,85 mmol) por goteo a una solución de anilina (5,5 g, 14,24 mmol, Esquema 10) y trietilamina (2,39 mL, 17,1 mmol) en DCM (30 mL) a 0°C. Después de agitación a TA durante 2h, la reacción se templó con $NaHCO_3$ acuoso, saturado, y se diluyó con EtOAc. La capa orgánica se secó sobre Na_2SO_4 y se concentró bajo presión reducida para proporcionar un sólido (6,0 g), el cual se disolvió en DCM (10 mL) y se agitó con TFA (2 mL) durante 1 h a TA. La reacción se concentró bajo presión reducida, y el

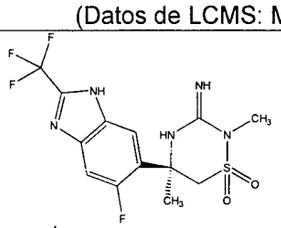
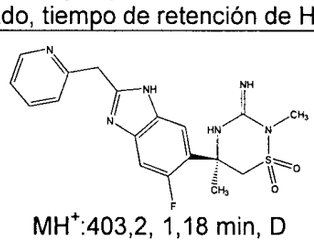
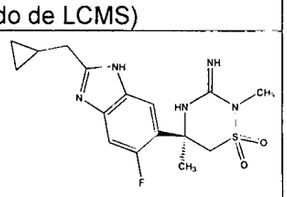
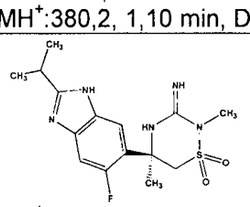
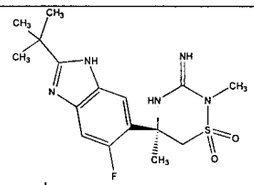
residuo se disolvió en H_2SO_4 concentrado (9 mL). Después de enfriamiento hasta 0°C, se agregó lentamente una mezcla de HNO_3 humeante/H_2SO_4 conc. (1,26 mL / 3 mL) por medio de embudo de adición. Después de 40 min, la reacción se templó cuidadosamente con $NaHCO_3$ saturado acuoso y se diluyó con EtOAc. La capa acuosa se extrajo con EtOAc (3 x), y las capas orgánicas combinadas se secaron sobre Na_2SO_4, y concentraron bajo presión reducida. El residuo resultante se disolvió en DCM (100 mL), y se agregaron trietilamina (7,93 mL, 56,56 mmol) y di–*terc*–butilcarbonato (3,09 g, 28,28 mmol). Después de agitación durante 18 h a TA, la reacción se templó con NH_4Cl saturado, acuoso y se diluyó con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se concentró bajo presión reducida, y el residuo resultante se sometió a cromatografía en gel de sílice (elución del gradiente 80:20 a 75:25 hexanos:EtOAc) para proporcionar una mezcla de material acetilado y desacetilado. A una solución de esta mezcla en MeOH (100 mL) a TA se le agregó una solución de K_2CO_3 (5 g, 36 mmol) en agua (20 mL), y la reacción se agitó durante 2h a TA. La reacción se templó con HCl 1 M (ac) y se diluyó con EtOAc. La capa orgánica se secó sobre Na_2SO_4, y concentró bajo presión reducida para proporcionar el producto (3,3 g, 54%).

Paso 2: A una solución del producto del paso 1 (600 mg, 1,39 mmol) en EtOAc/EtOH (10 mL / 10 mL) se agregó 5% Pd/C (300 mg) y la mezcla resultante se agitó en un Agitador Parr durante 4 h bajo una atmósfera de 306 kPa (45 psi) de H_2. El catalizador se separó por filtración sobre célite, el residuo se enjuagó con EtOAc, y la capa orgánica se concentró bajo presión reducida. El residuo resultante se sometió a cromatografía en gel de sílice (elución del gradiente 95:5 a 90:10 hexanos:EtOAc) para proporcionar el producto (377 mg, 68%).

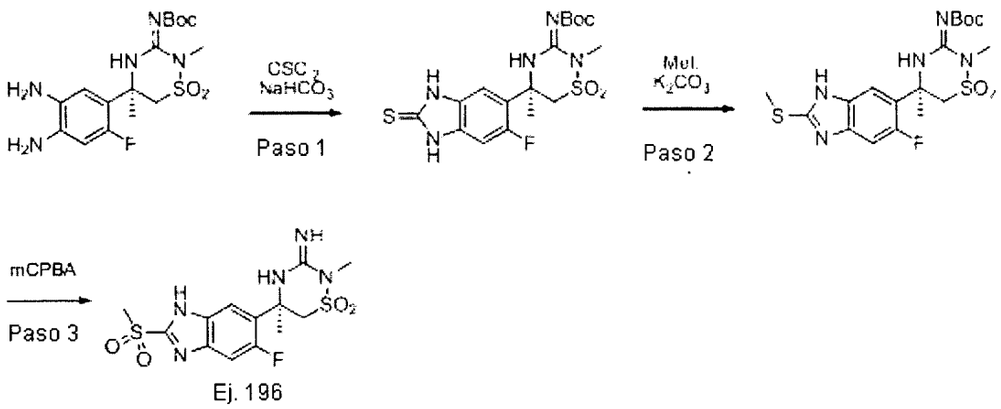
Paso 3: A una solución del producto del paso 2 (150 mg, 0,37 mmol) en piridina (3 mL) se le agregó ácido 3,3,3–trifluorpropiónico (0,032 mL, 0,37 mmol) y cloruro de bis(2–oxo–3–oxazolidinil)fosfínico (188 mg, 0,74 mmol). Después de agitar durante 18 h a TA, se eliminaron los volátiles bajo vacío, y el residuo se sometió a cromatografía en gel de sílice (elución del gradiente 60:40 a 30:70 hexanos:EtOAc) para proporcionar una mezcla de amidas (102 mg, 54%). Esta mezcla se disolvió en AcOH glacial (2 mL) y se calentó hasta 130°C durante 1 h.

Los volátiles se eliminaron bajo presión reducida, y el residuo resultante se purificó mediante cromatografía en fase inversa (C18: elución del gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar el **Ej. 190** como su sal TFA. LCMS para el **Ej. 190** (condiciones D): t_R = 1,29 min, *m/e* = 394,2 (M+H).

Tabla XXV: Los siguientes ejemplos se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 49.

Ejemplos (Datos de LCMS: MH^+ observado, tiempo de retención de HPLC y método de LCMS)					
191	 MH^+:380,2, 1,10 min, D	**192**	 MH^+:403,2, 1,18 min, D	**193**	 MH^+:366,2, 1,18 min, D
194	 MH^+:354,0, 0,97 min, D	**195**	 MH^+:368,0, 1,44 min, D		

Esquema 50:



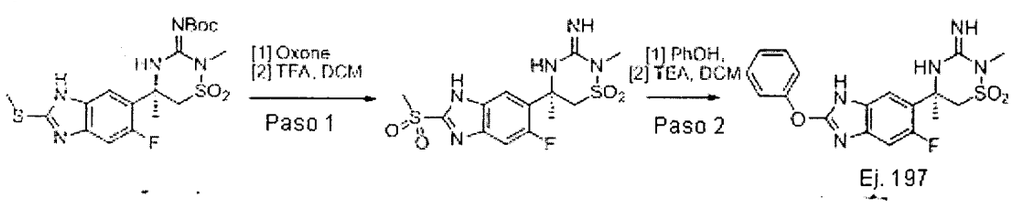
Ej. 196

Paso 1: Se agregó lentamente tiofosgeno (0,320 mL, 4,21 mmol) a una mezcla bifásica de $NaHCO_3$ saturado acuoso y una solución de dianilina (1,566 g, 3,90 mmol, Esquema 49, Paso 2) en DCM (15 mL). Después de 1 h a TA, las fases se separaron y la capa acuosa se extrajo con DCM. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso, saturado, salmuera, luego se secaron sobre Na_2SO_4, se filtraron y concentraron bajo presión reducida para proporcionar la tiourea (1,604 g, 93%).

Paso 2: Se agregó carbonato potásico (750 mg, 5,43 mmol) a una solución de la tiourea del Paso 1 (1,604 g, 3,62 mmol) en DMF (18 mL) a TA. Después de 10 min, se agregó una solución de yoduro de metilo (0,23 mL, 3,68 mmol) en DMF (2 mL) durante 10 min, y la reacción se agitó durante 90 min. La reacción se templó con $NaHCO_3$ saturado, acuoso, y se diluyó con EtOAc, y la capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y concentró bajo presión reducida (1,725 g). El residuo fue sometido a cromatografía en gel de sílice (elución del gradiente 100:0 a 60:40 hexanos:EtOAc) para proporcionar la tiometilurea (846 mg, 51%).

Paso 3: Se agregó a TA ácido meta–cloroperoxibenzoico (72%, 150 mg, 0,63 mmol) a una solución de la tiometilurea del paso 2 (100 mg, 0,21 mmol) en DCM (5 mL). Después de 1 h, la mezcla se diluyó con EtOAc y se lavó con NaHCO3 acuoso saturado (2 x), salmuera, y se secó sobre $MgSO_4$ y se concentró bajo presión reducida para proporcionar un residuo (150 mg) el cual fue sometido adicionalmente a cromatografía de fase inversa (C18: elución del gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar el **Ej. 196** como su sal TFA. LCMS para el **Ej. 196** (condiciones D): t_R = 1,41 min, *m/e* = 390,0 (M+H).

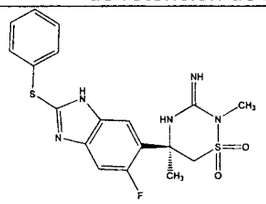
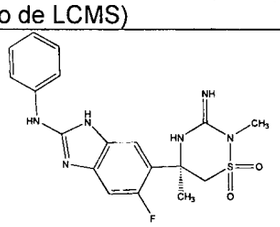
Esquema 51:



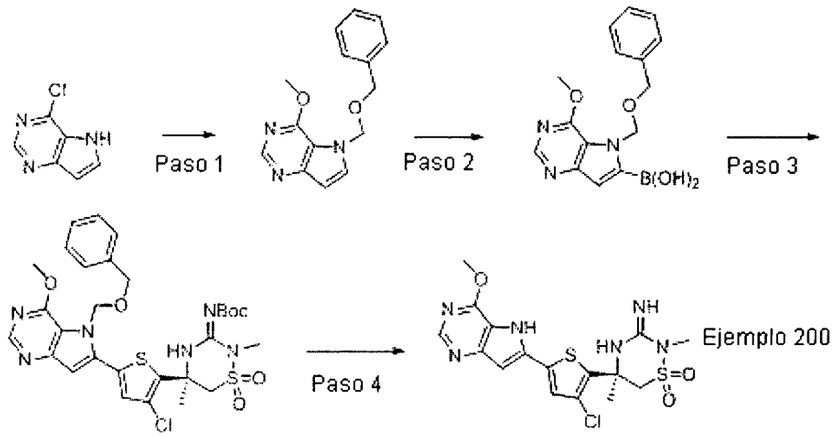
Paso 1: Una solución de oxone (peroximonosulfato de potasio, 3,2 g, 5,20 mmol) en agua (10 mL) se agregó a TA a una solución de la tiometilurea del Esquema 50, paso 2 (755 mg, 1,65 mmol) en MeOH (10 mL). Después de 1 h, la mezcla se filtró sobre célite, la torta del filtro se enjuagó con EtOAc, y el líquido filtrado se diluyó con EtOAc. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado, se secaron sobre $MgSO_4$ y concentraron bajo presión reducida para proporcionar el compuesto intermedio (681 mg) con un rendimiento del 84%.

Paso 2: El producto del Paso 1 (93 mg, 0,19 mmol) fue desprotegido utilizando un método similar a aquel descrito en el Esquema 11b paso 2. Después de la desprotección, el residuo resultante se concentró bajo vacío, y se agregaron trietilamina (0,132 mL, 0,95 mmol) y fenol (90 mg, 0,95 mmol). La mezcla se calentó a 120°C durante 22 h, luego se enfrió hasta TA. El residuo fue sometido a cromatografía en fase inversa (C18: elución del gradiente, 90:10:0,1 a 0:100:0,1 agua:MeCN:TFA) para proporcionar el **Ej. 197** como su sal TFA. LCMS para el **Ej. 197** (condiciones D): t_R = 1,78 min, *m/e* = 404,2 (M+H).

Tabla XXVI: Los siguientes ejemplos se prepararon utilizando un procedimiento similar a aquel descrito en el Esquema 51, reemplazando el fenol en el Paso 2 con tiofenol o anilina, respectivamente.

Ejemplos (Datos de LCMS mostrados con cada compuesto: MH^+ observado, tiempo de retención de HPLC y método de LCMS)			
198	 MH^+:420,0, 1,76 min, D	**199**	 MH^+:403,2, 1,64 min, D

Esquema 52:



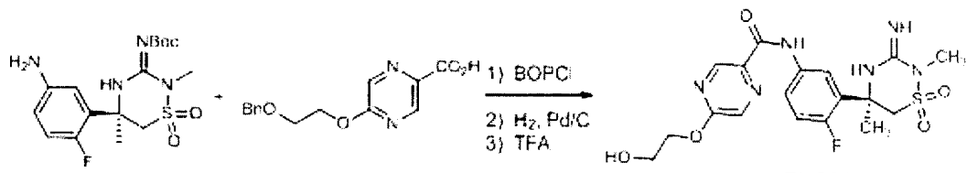
Paso 1: A una suspensión de 4–cloro–5H–pirrolo[3,2–d]pirimidina (1,53 g, 10,0 mmol) en 30 mL de THF se le agregó NaH (560 mg, 14,0 mmol, 60% en aceite mineral) por porción bajo N_2. Después de enfriar la mezcla hasta 0°C, se agregó bencil clorometiléter (1,71 mL, 13,0 mmol). Luego, la mezcla se agitó a TA durante 1 h (monitoreada por TLC 40% EtOAc/Hex). Se agregaron 8 mL de MeOH anhidro en la mezcla de reacción seguido por NaH (400 mg, 10,0 mmol, 60% aceite mineral) por porción. La mezcla resultante se agitó a TA durante la noche. Después de templado con NH_4Cl sat., la mezcla se extrajo con EtOAc (3x). La capa orgánica se lavó con $NaHCO_3$ sat. (ac), salmuera, luego se secó ($MgSO_4$) y concentró. La cromatografía en gel de sílice (elución con 0–30% EtOAc/Hex) proporcionó el producto 5–(benciloximetil)–4–metoxi–5H–pirrolo[3,2–d]pirimidina (2,36 g).

Paso 2 y 3: 5–(Benciloximetil)–4–metoxi–5H–pirrolo[3,2–d]pirimidina se trató de acuerdo con el Esquema 31, Pasos 2 y 3 para proporcionar un producto biarilo.

Paso 4: A una solución del material del paso 3 (26 mg, 0,039 mmol) en 8 mL de DCM se le agregó una suspensión de $AlCl_3$ (52 mg, 0,39 mmol) en 4 mL de DCM. Después de que la mezcla se agitó a TA durante 1,5 h, se agregaron 3 mL de agua. La mezcla de reacción se basificó con $NaHCO_3$ y se extrajo con DCM (3x). La capa orgánica se lavó con salmuera y se secó (Na_2SO_4), y concentró. El residuo en bruto se purificó mediante TLC preparativa (10% 2N NH_3 MeOH en

DCM) para proporcionar el **Ejemplo 200** (10 mg). LCMS (condiciones E): t_R = 0,60 min, *m/e* = 441,0 (M+H).

Esquema 53:



Ej. 201

Paso 1: La anilina del Esquema 10 y el ácido (Entrada 3, Tabla IVb) se acoplaron utilizando un procedimiento similar a aquel descrito en el Esquema 11b paso 1.

Paso 2: A un recipiente de presión que contenía una solución de la amida del paso 1 (181 mg, 0,28 mmol) en EtOH (15 mL) se le agregó Pd/C al 10% (50% agua–Tipo Degussa). El recipiente se cerró herméticamente, se evacuó y retrocargó con N_2 (3x). Luego, el recipiente se evacuó y retrocargó con H_2 (3x). El recipiente se presurizó con H_2 hasta 340 kPa (50 psi) y se agitó a TA durante 6 horas. La mezcla se purgó con N_2, se filtró a través de Célite y se concentró. El producto en bruto se purificó por medio de cromatografía flash (SiO_2: elución del gradiente 100:0 a 1:1 hex.: EtOAc) para proporcionar el compuesto hidroxi (24 mg, 15%).

Paso 3: **Ejemplo 201** se preparó a partir del producto del paso 2 (24 mg) utilizando un procedimiento similar a aquel descrito en el Esquema 11b paso 2. El producto en bruto se purificó mediante cromatografía flash en fase inversa (C_{18}; elución de gradiente 95:5:0,1 a 0:100:0,1 H_2O:MeCN:ácido fórmico) para proporcionar el **Ejemplo 201** (11 mg, 51%) como la sal formiato.

Condiciones de LC/MS

Método A:

Columna: Gemini C–18, 50 x 4,6 mm, 5 micrones, obtenida de Phenomenex.

Fase móvil: A: Ácido trifluoracético al 0,05% en agua

B: Ácido trifluoracético al 0,05% en acetonitrilo

Gradiente: 90:10 a 5:95 (A:B) durante 5 min.

Índice de flujo: 1,0 mL/min

Detección de UV: 254 nm

ESI–MS: Electro Spray Ionization Liquid chromatography–mass spectrometry (ESI–LC/MS) (Ionización por Electropulverización cromatografía líquida – espectrometría de masas) se llevó a cabo en un espectrómetro de masas de cuadrúpolo único PE SCIEX API–150EX.

Método B:

Columna: Waters SunFire C–18 4,6mm x 50 mm

Fase móvil: A: ácido trifluoracético al 0,05% en agua

B: ácido trifluoracético al 0,05% en acetonitrilo

Gradiente: 90:10 (A:B) durante 1 min, 90:10 a 0:100 (A:B) durante 4 min, 0:100 (A:B) durante 2 min.

Índice de flujo: 1,0 mL/min

Detección de UV: 254 nm

Espectrómetro de masas: Finnigan LCQ Duo electropulverización.

Método C:

Columna: Agilent Zorbax SB–C18 (3,0 x 50 mm) 1,8 uM

Fase móvil: A: ácido trifluoracético al 0,05% en agua

B: ácido trifluoracético al 0,05% en acetonitrilo

Gradiente: 90:10 (A:B) durante 0,3 min, 90:10 a 5:95 (A:B) en el transcurso de 5,1 min, 5:95 (A:B) durante 1,2 min.

Índice de flujo: 1,0 mL/min

Detección de UV: 254 y 220 nm

Espectrómetro de masas: Agilent 6140 cuadrúpolo.

Método D:

Columna: Agilent Zorbax SB–C18 (3,0 x 50 mm) 1,8 uM

Fase móvil: A: ácido trifluoracético al 0,05% en agua

B: ácido trifluoracético al 0,05% en acetonitrilo

Gradiente: 90:10 (A:B) durante 0,3 min, 90:10 a 5:95 (A:B) en el transcurso de 1,2 min, 5:95 (A:B) durante 1,2 min.

Índice de flujo: 1,0 mL/min

Detección de UV: 254 y 220 nm

Espectrómetro de masas: Agilent 6140 cuadrúpolo.

Método E:

Columna: Agilent Zorbax SB–C18 (3,0 x 50 mm) 1,8 uM

Fase móvil: A: ácido trifluoracético al 0,05% en agua

B: ácido trifluoracético al 0,05% en acetonitrilo

Gradiente: 90:10 (A:B) durante 0,1 min, 90:10 a 5:95 (A:B) en el transcurso de 1,0 min, 5:95 (A:B) durante 0,36 min.

Índice de flujo: 2,0 mL/min

Detección de UV: 254 y 220 nm

Espectrómetro de masas: Agilent 6140 cuádruplo.

Método F:

Columna: Agilent Zorbax SB–C18 (3,0 x 50 mm) 1,8 uM

Fase móvil: A: ácido fórmico al 0,05% en agua

B: ácido fórmico al 0,05% en acetonitrilo

Gradiente: 90:10 a 5:95 (A:B) durante 1,5 min, 5:95 (A:B) durante 1,2 min.

Índice de flujo: 1,0 mL/min

Detección de UV: 254 y 220 nm

Espectrómetro de masas: Agilent 6140 cuadrúpolo.

ENSAYOS

El protocolo que se utilizó para determinar los valores mencionados es descrito de la siguiente manera.

Ensayo BACE1 HTRF FRET

Reactivos

Na^+–Acetato pH 5.0

1% Brij–35

Glicerol

Sulfóxido de Dimetilo (DMSO)

Dominio catalítico de BACE1 soluble humano recombinante (>95% puro)

sustrato peptídico mutante APP Swedish (QSY7–APP^{swe}–Eu): QSY7–EISEVNLDAEFC–Europio–amida

Se empleó un ensayo FRET de resolución en el tiempo homogéneo para determinar los valores de IC_{50} para los inhibidores del dominio catalítico de BACE1 humano soluble. Este ensayo monitoreó el aumento de 620 nm de fluorescencia que fue resultado de la disociación de BACE1 de un sustrato FRET peptídico mutante APPswedish APP^{swe} (QSY7–EISEVNLDAEFC–Europio–amida). Este

sustrato contenía un resto de terminal N QSY7 que servía como un templador del fluoróforo Europio de terminal C (620 nm Em). En ausencia de actividad enzimática, 620 nm de fluorescencia era baja en el ensayo y aumentó linealmente durante 3 horas en presencia de enzima BACE1 no inhibida. La inhibición de la disociación de BACE1 del sustrato QSY7–APP^{swe}–Eu mediante inhibidores se manifestó como una supresión de la fluorescencia de 620 nm.

Las concentraciones variables de inhibidores a 3x la concentración final deseada en un volumen de 10ul se preincubaron con dominio catalítico de BACE1 humana purificada (3 nM en 10 µl) durante 30 minutos a 30°C en buffer de reacción que contenía 20 mM de Na–Acetato pH 5,0, 10% glicerol, 0,1% Brij–35 y 7,5% DSMO. Las reacciones fueron iniciadas mediante la adición de 10 µl de 600 nM de sustrato QSY7–APP^{swe}–Eu (200 nM final) para proporcionar un volumen de reacción final de 30 µl en una placa Nunc HTRF de 384 pocillos. Las reacciones fueron incubadas a 30°C durante 1,5 horas. Luego, se leyó la fluorescencia 620nm en un lector de placas HTRF Rubystar (BMG Labtechnologies) utilizando un retraso de 50 µs seguido por una ventana de tiempo de adquisición de 400 milisegundos. Los valores de IC_{50} de inhibidor fueron derivados del análisis de regresión no lineal de las curvas de respuesta a la concentración. Luego, los valores de K_i fueron calculados a partir de los valores de IC_{50} utilizando la ecuación Cheng–Prusoff utilizando un valor de µm previamente determinado de 8µM para el sustrato QSY7–APP^{swe}–Eu en BACE1.

Todos los compuestos ejemplares de la invención fueron analizados (excepto por los Ejemplos 8, 9, 10, 14b, 14c, 14d, 14e, y 14f) en este ensayo de BACE–1 y exhibieron valores de K_i de menos de aproximadamente 7,5 µM y superiores a aproximadamente 0,5 nM en este ensayo. Todos los compuestos ejemplares excepto por los ejemplos 19, 40x, 98, 101, y 189 exhibieron valores de K_i de menos de aproximadamente 5 µM en este ensayo. Algunos de los compuestos ejemplares exhibieron valores de K_i de menos de aproximadamente 4 µM en este ensayo; otros menos de aproximadamente 3 µM en este ensayo; otros menos de aproximadamente 2 µM en este ensayo; otros menos de aproximadamente 1 µM en este ensayo; otros menos de aproximadamente

500 nM en este ensayo; otros menos de aproximadamente 300 nM en este ensayo; otros menos de aproximadamente 200 nM en este ensayo; otros menos de aproximadamente 100 nM en este ensayo; otros menos de aproximadamente 50 nM en este ensayo; otros menos de aproximadamente 10 nM en este ensayo; otros menos de aproximadamente 5 nM en este ensayo. El compuesto del Ejemplo 45 exhibió un valor Ki de aproximadamente 26 nM en este ensayo. El compuesto del Ejemplo 47 exhibió un valor de Ki de aproximadamente 6,5 nM en este ensayo.

Ensayo de BACE–2

Las IC_{50s} de inhibidor en autoBACE–2 humana purificada se determinaron en un ensayo de proteólisis de punto de referencia de resolución en el tiempo que mide la hidrólisis del sustrato peptídico QSY7–EISEVNLDAEFC–Eu–amida FRET (ensayo BACE–HTRF). La hidrólisis mediada por BACE de este péptido da como resultado un aumento en la fluorescencia relativa (RFU, correspondiente a "relative fluorescence") a 620 nm después de excitación con 320 nm de luz. Los compuestos inhibidores, preparados a 3x la concentración final deseada en buffer de ensayo 1x BACE (acetato de sodio 20 mM pH 5,0, 10% de glicerol, 0,1% Brij–35) suplementado con 7,5% de DMSO se preincubaron con un volumen igual de enzima autoBACE–2 diluida en buffer de ensayo de 1x BACE (concentración enzimática final 1 nM) en placas NUNC de 384 pocillos negras durante 30 minutos a 30ºC. El ensayo fue iniciado mediante la adición de un volumen igual del sustrato QSY7–EISEVNLDAEFC–Eu–amida (200 nM de concentración final, K_m=8 µM para 4 µM para autoBACE–2) preparado en buffer de ensayo de 1x BACE suplementado con 7,5% de DMSO y se incubó durante 90 minutos a 30ºC. DMSO estaba presente a una concentración final al 5% en el ensayo. Después de la excitación por láser de los pocillos de muestra a 320 nm, se recolectó la señal de fluorescencia a 620 nm durante 400 ms después de un retardo de 50 µs en un lector de placas HTRF RUBYstar (BMG Labtechnologies). Los datos de RFU sin elaborar fueron normalizados a valores RFU máximos (1,0 nM BACE/DMSO) y mínimos (sin enzima /DMSO). Se determinaron IC_{50s} mediante análisis de regresión no lineal (respuesta a la dosis sigmoidal, inclinación variable) de datos

de porcentaje de inhibición con valores mínimos y máximos fijados a 0 y 100 por ciento respectivamente. Se obtuvieron IC_{50s} similares cuando se utilizaron datos de RFU sin elaborar. Los valores de K_i fueron calculados de la IC_{50} usando la ecuación Cheng–Prusoff.

Todos los compuestos ejemplares de la invención fueron analizados en este ensayo de BACE–2 excepto por los siguientes ejemplos: 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14b, 14c, 14d, 14e, 14f, 15, 16, 17, 19, 40a, 40b, 40ea, 40h, 40o, 40p, 40q, 40u, 40w, 40x, 40y, 40aa, 40au, 40cc, 40co, 40cp, 40cy, 40dj, 40gy, 40gz, 40ha, 40hb, 40hc, 40ih, 41, 43, 45, 49, 60, 61, 67, 68, 69, 70, 71, 73, 74, 75, 77, 85, 86, 88, 89, 90, 91, 96, 97, 98, 99, 100, 101, 102, 103, 105, 108, 109, 109, 115, 116, 117, 122, 123, 125, 130b, 137, 138, 143, 145, 161b, 176, 179, 182, 189, 192, 194, 195, 199. De los compuestos ejemplares de la invención que fueron ensayados en este ensayo de BACE–2, todos exhibieron valores de K_i de menos de aproximadamente 900 nM y superiores a aproximadamente 0.04 nM en este ensayo. Todos los compuestos ejemplares que fueron ensayados en este ensayo, excepto por los ejemplos 40ex, 40do, 160, 161a, 164, y 197 exhibieron valores de K_i de menos de aproximadamente 500 nM en este ensayo. Algunos de los compuestos ejemplares exhibieron valores de K_i de menos de aproximadamente 200 nM en este ensayo; otros menos de aproximadamente 100 nM en este ensayo; otros menos de aproximadamente 50 nM en este ensayo; otros menos de aproximadamente 25 nM en este ensayo; otros menos de aproximadamente 10 nM en este ensayo; otros menos de aproximadamente 5 nM en este ensayo; otros menos de aproximadamente 1 nM en este ensayo; otros menos de aproximadamente 0.5 nM en este ensayo. El compuesto del Ejemplo 47 exhibió un valor de Ki de aproximadamente 1 nM en este ensayo.

Se ha descubierto, sorprendentemente, que los compuestos novedosos de dióxido de iminotiadiazina de la invención exhiben propiedades las cuales los tornan ventajosos como inhibidores de BACE y/o para los diversos métodos de uso en esta invención.

$A\beta_{40}$ Cortical

Se ha descubierto, sorprendentemente y ventajosamente, que los compuestos de dióxido de iminotiadiazina de la invención exhiben eficacia mejorada en la reducción de la producción de $A\beta_{40}$ en la corteza cerebral que sus análisis de iminopirimidona. Se emplearon los siguientes procedimientos. Los resultados son mostrados en la tabla que aparece más adelante.

Recolección de Tejido de Rata

ratas machos CD (~100 g; Crl:CD(SD); Charles River Laboratories, Kingston, NY) fueron alojadas en grupos y aclimatadas al vivario durante 5–7 días antes del uso en un estudio. Los compuestos fueron formulados en 20% hidroxipropil–β–ciclodextrina y administrados por vía oral con un volumen de dosificación de 5 ml/kg para las ratas. Tres horas después de la administración de la droga, las ratas fueron sacrificadas con exceso de CO_2. Se extrajo el cerebro del cráneo e inmediatamente se congeló sobre hielo seco. Todos los tejidos fueron almacenados a –70°C hasta la cuantificación de Aβ.

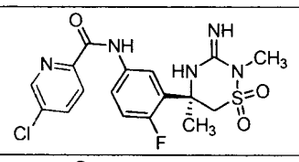
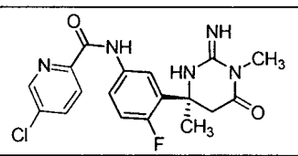
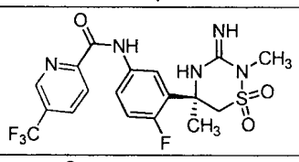
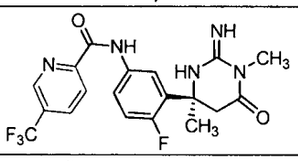
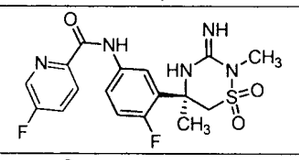
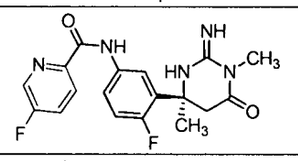
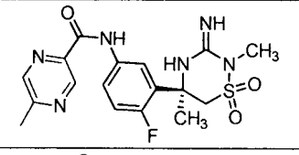
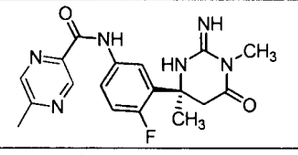
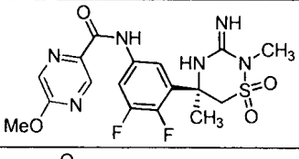
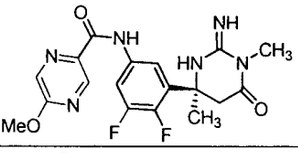
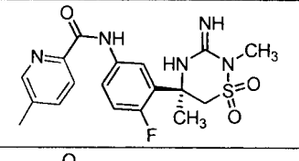
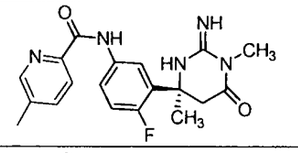
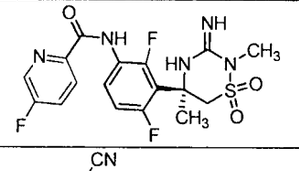
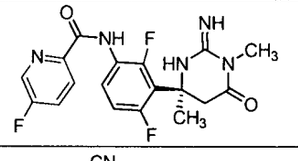
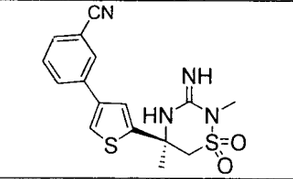
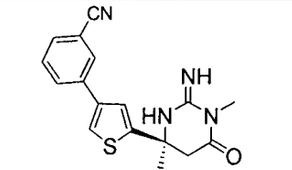
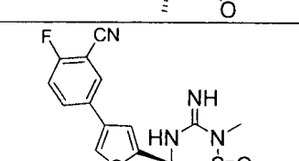
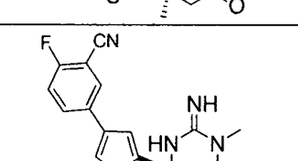
Determinación de Niveles de $A\beta_{40}$ en Corteza de Rata por ELISA

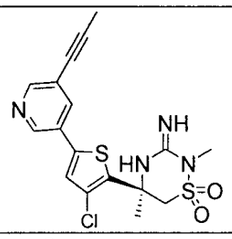
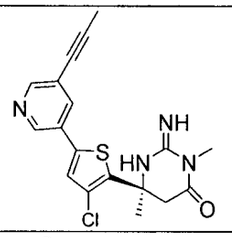
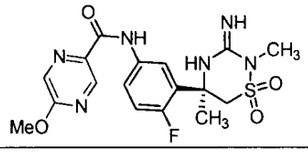
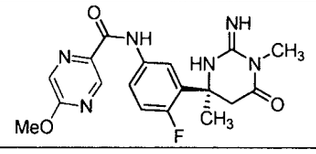
La medición de Aβ1–40 (Aβ40) de rata endógeno en corteza se basó en el anticuerpo 585 (Ab585, BioSource), catálogo no. NONO585), el cual reconoce específicamente la secuencia de terminal N de Aβ40 de roedor, y el anticuerpo monoclonal, G2–10, el cual reconoce específicamente el término C libre de Aβ40. Ab585 fue etiquetado con biotina (b–Ab585) primero dializando la muestra de anticuerpo extensamente contra PBS (pH 7,8) para eliminar impurezas, seguido por dilución hasta entre 1 y 2 mg/mL de concentración de proteína. EZ–Link Sulfo–NHS–LC–Biotina (Pierce) se disolvió en PBS (pH 7,8) a una concentración de 1 mg/mL inmediatamente antes del uso. Ab585 fue etiquetado con EZ–Link Sulfo–NHS–LC–biotina utilizando una relación de 10:1 biotina: anticuerpo mediante incubación a temperatura ambiente durante 1 hora. La reacción de etiquetado se apagó mediante adición de glicina 1,0 M a una concentración final de 0.1 M seguido por incubación de 10 minutos a temperatura ambiente. Se extrajo la glicina mediante diálisis extensiva versus PBS.

El uso del inmunoensayo basado en Luminex para la medición de Aβ40 cortical de rata requirió que el anticuerpo G2–10 sea etiquetado con Bio–Plex COOH Bead 25 (Bio–Rad laboratories catálogo no. 171506025). El anticuerpo fue acoplado a las perlas (beads) empleando el Kit de Acoplamiento de Amina Bio–Plex Amine Coupling Kit (Bio–Rad) de acuerdo con las recomendaciones del fabricante.

Se midieron los niveles de Aβ40 de corteza de rata de extractos de HCl de guanidina de cortezas de rata individuales empleando un ensayo de inmunodetección basado en Luminex. Los cerebros de rata fueron descongelados brevemente a 37°C y se extrajeron regiones de mesencéfalo y romboencéfalo. El material remanente, que consiste principalmente de corteza (~800 mg) se llevó a través del procedimiento de extracción de guanidina. Se agregaron las cortezas a un tubo BioPur (Eppendorf) de 2 ml junto con una bola de acero recubierta con cromo de 6,35 mm y 1,0 ml de buffer de homogenización de sacarosa (HEPES 20 mM [pH 7,5], KCl 50 mM, sacarosa 50 mM, EDTA 2 mM, EGTA 2 mM suplementado con inhibidores de proteasa completa [Roche, libre de EDTA]). Luego, las muestras se homogenizaron mediante agitación durante 1,5 min a 30 ciclos/seg. en una mezcladora de tejidos MM300 (Retsch®). El homogenado cortical resultante se extrajo con guanidina–HCl mezclando 67 µl de homogenado con 133 µl de Guanidina HCl 5 M, Tris HCl 50 mM (pH 8.0). Para maximizar la eficacia de la extracción de Aβ, las muestras se sometieron a vórtice y luego se sonicaron durante 2 minutos en un baño de hielo empleando un sonicador de cuernos de copa Ultrasonics XL a una potencia fijada en 8 (Heat Systems, Inc.). El material insoluble fue extraído mediante ultracentrifugación empleando un rotor TLA–55 en una centrífuga de mesa (benchtop) TL–100 (Beckman) a 100.000xg durante 30 minutos. Luego, el sobrenadante resultante se diluyó 1:10 en guanidina HCl 5 M, Tris HCl 0.05 M (pH 8.0) para análisis de proteína (ensayo de proteína BCA, Pierce Biochemicals) o se ensayó en forma pura para determinar los niveles de Aβ40. El ensayo de Aβ40 de roedor Luminex se llevó a cabo de la siguiente manera. En primer lugar, se humedecieron placas de unión de filtro de 96 pocillos (Millipore, catálogo # MSBVN12) con 100 µl de buffer LAβ40 1x (HEPES 0.05 M

[pH 7,5], 0,2% BSA, 0,2% Tween–20, NaCl 0,15 M) mediante filtración de vacío en un manifold de 96 pocillos Millipore. El fondo de la placa se selló y se agregaron 100 µl de buffer 1x LAβ40 a cada pocillo seguido por la adición de 50 µl cada uno de perlas G2–10:COOH (1000 perlas/ pocillo) y 50 µl de b–Ab585 a 0,5 µg/ml en buffer LAβ40 1 x. Se agregó guanidina HCl a estándares de Aβ40 de roedor sintéticos a fin de controlar el efecto de guanidina en extractos de cerebro sobre el rendimiento del ensayo. Se agregaron a cada pocillo diez microlitros de extracto cortical, estándares de Aβ40 de roedor o extracto cortical de ratones "knockout" o con desactivación de proteína precursora amiloide (para definir la inmunoreactividad de fondo). Las placas se cubrieron y se incubaron durante la noche a 4ºC. Luego de la incubación, los pocillos se evacuaron mediante vacío y se lavaron dos veces con 100 µl de buffer LAβ40 1x en un manifold de Millipore. Se diluyó estreptavidina conjugada a ficoeritrina (PE–estreptavidina, BioRad) para la detección de b–Ab585 unido 100 veces en buffer LAβ40 1x y se agregaron 50 µl a cada pocillo y se incubaron durante 1 hora a temperatura ambiente con agitación. Se eliminó la PE-estreptavidina no unida mediante tres lavados de 100 µl con buffer de ensayo de citoquina (BioRad). Las perlas lavadas fueron resuspendidas en 125 µl de buffer de ensayo de citoquina mediante agitación en un agitador de microplacas. Las placas fueron leídas en un sistema de arreglos de suspensión de BioPlex (BioRad) con perlas de regiones objetivo fijadas en 40 perlas/ región y el extremo superior de la entrada DD fijado en 10.000. Se analizaron los datos de fluorescencia sin elaborar empleando análisis de regresión no lineal y los niveles de Aβ40 absolutos fueron extrapolados a partir de la curva estándar utilizando GraphPad Prism 4.0.2. Las cantidades absolutas de $A\beta_{1-40}$ son expresadas como picogramos por microgramos de proteína. Los valores porcentuales de cambio para cada compuesto se calcularon mediante normalización del nivel de Aβ1–40 cortical absoluto promedio en cada cohorte tratado con compuesto a los niveles de Aβ1–40 cortical absolutos promedio en el cohorte tratado con vehículo. Los resultados comparativos son mostrados en la tabla que aparece a continuación. "NE" significa no ensayado.

Cambio en $A\beta_{40}$ Cortical en Ratas 3 h Después de una Dosis Oral de 10 mg/kg de Compuesto					
Dióxido de Iminotiadiazina				Iminopirimidinona	
Ej. #	Estructura	BACE–1 Ki (nM) / BACE–2 Ki (nM)	Cambio en $A\beta_{40}$ de corteza de rata	Estructura	Cambio en $A\beta_{40}$ de corteza de rata
34		0,949 / 0,22	–51%		–19%
26		1,261 / 2,46	–33%		0%
25		1,753 / 0,37	–49%		–11%
36		10 / 4,85	–25%		NE
40di		1,05 / 2,15	–38%		+5%
35		3,0 / 0,45	NE		NE
173		4,88 / 0,47	–27%		–3%
45		25,6 / NE	NE		–5%
46		46 / 8,23	NE		NE

Cambio en $A\beta_{40}$ Cortical en Ratas 3 h Después de una Dosis Oral de 10 mg/kg de Compuesto					
Dióxido de Iminotiadiazina				Iminopirimidinona	
Ej. #	**Estructura**	**BACE–1 Ki (nM) / BACE–2 Ki (nM)**	**Cambio en $A\beta_{40}$ de corteza de rata**	**Estructura**	**Cambio en $A\beta_{40}$ de corteza de rata**
52		2,387 / 0,37	–53%		–54%
40ai		1,64 / 1,99	–51%		

Permeabilidad Bidireccional de Caco–2

Se ha descubierto que los compuestos de la invención exhiben susceptibilidad inesperadamente reducida al flujo saliente por P–glicoproteína (P–gp) versus compuestos que tienen un resto iminopirimidinona que son de otro modo estructuralmente idénticos. P–gp se encuentra, entre otros sitios, en la barrera hemato-encefálica, y la susceptibilidad reducida al flujo por esta proteína es una característica deseable de compuestos de acción central (A. Schinkel *Advanced Drug Delivery Reviews* **1999**, *36*, 179–194). Se emplearon los siguientes procedimientos. Los resultados son mostrados en la tabla que aparece a continuación.

Permeabilidad Bidireccional de Caco–2

La permeabilidad bidireccional con potencial de flujo saliente de compuestos seleccionados de la invención contra iminopirimidinonas de algún otro modo estructuralmente idénticas (denominadas colectivamente compuestos de ensayo, mostrados en la tabla que aparece a continuación) se evaluaron empleando la línea celular Caco–2. Las células Caco–2 se mantuvieron en DMEM (Dulbecco's Modified Eagle Medium, Medio Eagle Modificado de Dulbecco) que contenía suero bovino fetal 10%, aminoácidos no esenciales 1%, L–glutamina

2 mM, y 1% penicilina–estreptomicina en una incubadora a ~37°C en una atmósfera de 5% CO_2 y aproximadamente 90% de humedad relativa. El medio de cultivo celular fue cambiado tres veces por semana. Las monocapas de células Caco–2 se cultivaron en filtros de tereftalato de polietileno empleando Placas de Inserto de Cultivos Celulares BD Falcon™ de 24 pocillos (área de inserto 0,33 cm^2, tamaño de poro 1 µm; BD BioSciences, Bedford, MA). El medio de cultivo de la placa fue cambiado día por medio hasta utilizarse para el experimento de transporte (21–28 días luego del sembrado).

El buffer de transporte (TM) fue solución salina equilibrada de Hank (HBSS, Hank's balanced salt solution) con HEPES 10 mM y glucosa 25 mM (pH 7,4) para dosificación y TM con 4% de seroalbúmina bovina para receptor (pH 7,4). Se analizó la permeabilidad bidireccional de los compuestos de ensayo en concentraciones de 1, 10 y 100 µM medidas por triplicado con 2 horas de incubación. Se controló la integridad de las monocapas celulares con resistencia eléctrica trans-epitelial pre- y post-experimental y permeabilidad de Amarillo Lucifer (LY, según el inglés) post-experimental con 1 hora de incubación. Se analizaron muestras de artículos de ensayo empleando LC–MS/MS y se midió la concentración de LY empleando un Lector Perkin Elmer HTS 7000 Plus Bio Assay Reader (Waltham, MA) con una longitud de onda de excitación y emisión de 485 nm y 538 nm, respectivamente.

Se calcularon los valores aparentes de permeabilidad, recuperación y relación de flujo saliente empleando las siguientes ecuaciones:

$$P_{ap.}\ (nm/s) = \frac{dM/dt}{S * C_0} = \frac{dC_R/dt * V_R}{S * C_0} * 10^7$$

$$\text{Rel. de Flujo} = \frac{P_{ap.}\ \_BL\ a\ AP}{P_{ap.}\ \_AP\ a\ BL}$$

$$\text{Recuperación Total}(\%) = \frac{C_{D,final}}{C_0} \times 100 + \frac{\text{Cantidad Acumulada en Receptor}}{C_0 * V_D} \times 100$$

donde,

dC_R/dt: La inclinación de la concentración acumulada en el compartimento receptor contra incubación en el tiempo ($\mu M \cdot s^{-1}$)

C_{0hr}: Concentración en donante (μM) inmediatamente después de dosificación

$C_{D, final}$: concentración en donante (μM) al final de incubación

S: Área superficial de membrana (cm^2)

V_D: Volumen de compartimento donante (mL)

V_R: Volumen de compartimento receptor (mL)

P_{app_BLtoAP}: Permeabilidad de transporte basolateral (BL) a apical (AP)

P_{app_APtoBL}: Permeabilidad de transporte AP a BL

Evaluación de inhibición del flujo de P–gp empleando ensayo de permeabilidad bidireccional de Caco–2

Se llevó a cabo un estudio preliminar para evaluar los compuestos en la tabla que aparece más adelante como potenciales sustratos de P-gp empleando el ensayo de transporte bidireccional de Caco–2. Se empleó digoxina como un sustrato P-gp sonda. La solución de dosificación de ^{3}H–digoxina se preparó diluyendo un material base de digoxina DMSO con TM y/o las soluciones de inhibidor y titulación con ^{3}H–digoxina (la concentración final de digoxina fue 5 μM con 0,5 μCi/mL de radioactividad). Se prepararon dos concentraciones de compuestos de ensayo (5 y 50 μM) diluyendo una solución base de DMSO con TM (pH 7,4). La permeabilidad bidireccional de Caco–2 de ^{3}H–digoxina con o sin compuesto de ensayo como inhibidor se midió según lo descrito en la sección de permeabilidad bidireccional de Caco–2. Se contó la radioactividad total para cada muestra empleando un Analizador de Centelleo Líquido Packard 2250CA Tri–Carb Liquid Scintillation Analyzer.

Se calculó el porcentaje de inhibición de flujo de digoxina empleando la siguiente ecuación:

$$\%\_\text{Inhibición} = \left(1 - \frac{P_{app\_BLtoAP}^{inhibidor} - P_{app\_APtoBL}^{inhibidor}}{P_{app\_BLtoAP} - P_{app\_APtoBL}}\right) * 100$$

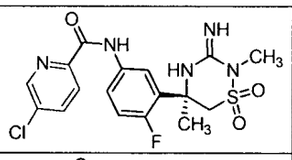
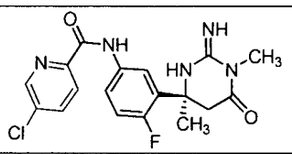
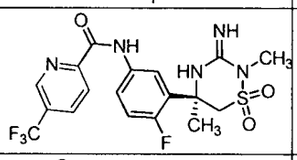
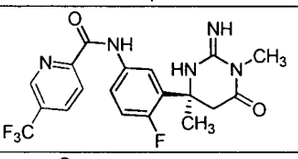
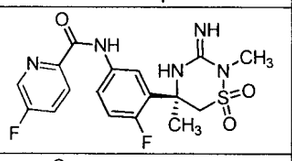
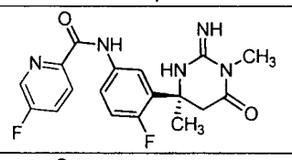
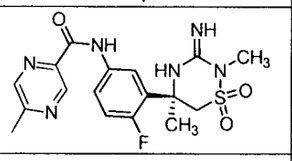
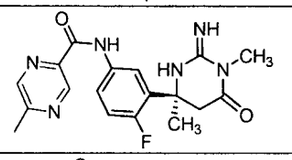
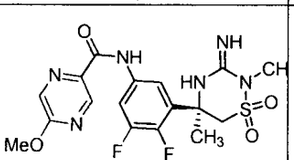
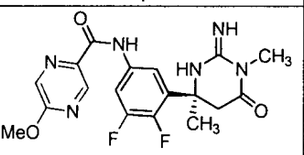
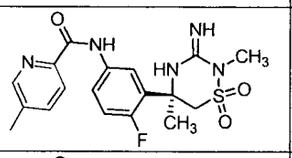
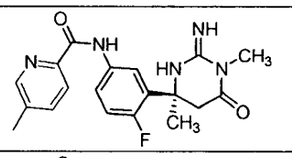
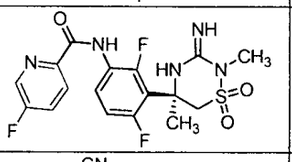
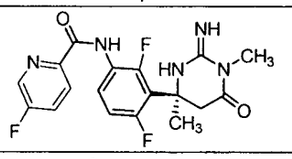
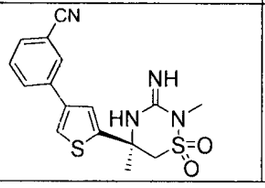
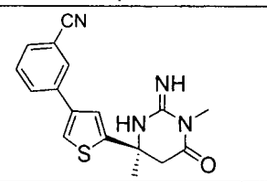
donde,

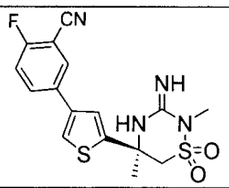
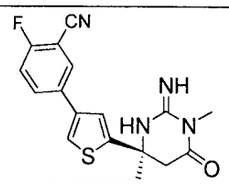
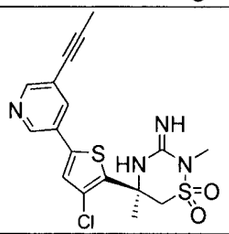
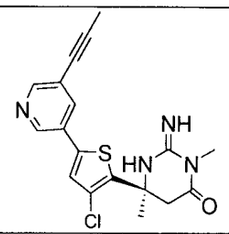
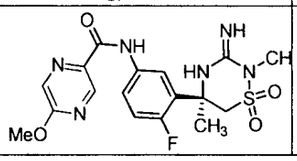
P_{app_BLtoAP}: Permeabilidad a digoxina del transporte de BL a AP

P_{app_APtoBL}: Permeabilidad a digoxina del transporte de AP a BL

$P_{app\_BLtoAP}^{inhibidor}$: Permeabilidad a digoxina con inhibidor del transporte de BL a AP :

Permeabilidad a digoxina con inhibidor del transporte de AP a BL

Permeabilidad (AP→BL) y relación de flujo en células Caco–2 *(AP = apical, BL = basolateral)*						
Dióxido de Iminotiadiazina				**Iminopirimidinona**		
Ej. #	**Estructura**	**Caco–2 AP→BL (nm/s)**	**relación de flujo de Caco–2**	**Comp. #**	**Caco–2 AP → BL (nm/s)**	**relación de flujo de Caco–2**
34		118	3,1		0	NE
26		89	2,9		17	11,3
25		128	2,4		22	10,6
36		54	3,3		11	12,9
40di		136	2,0		65	3,2
35		151	2,1		0	NE
173		126	2,2		25	6,1
45		226	1,4		174	2,6

46		189	1,9		136	2,6
52		278	1,6		153	2,4
40ai		133	1,8	NE		

Estabilidad en Solución

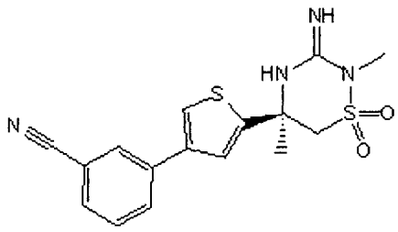
Se ha descubierto, sorprendente y ventajosamente, que los compuestos de dióxido de iminotiadiazina de la invención exhiben estabilidad en solución mejorada (por ej., mediante resistencia a hidrólisis) en comparación con iminopirimidinonas estructuralmente similares. Se emplearon los siguientes procedimientos comparativos. Los resultados son informados como Ejemplos A y B a continuación.

Se preparó una solución inicial de 1,05 mg/mL (5 mL) del **Ej. 45** en MeOH. De la solución inicial se sacaron 1,25 mL y se diluyó hasta 25 mL con la adición de 23,75 mL de buffer de fosfato 10 mM (pH 7,4)/MeOH (70/30 v/v). Esta nueva solución se dividió en tres. Una solución se incubó a 4°C, otra se incubó a 25°C y la tercera se incubó a 40°C. Cada solución se analizó por LC/MS después del dia 1, día 2 y día 6 y se comparó con una curva de calibración estándar para el **Ej. 45.**

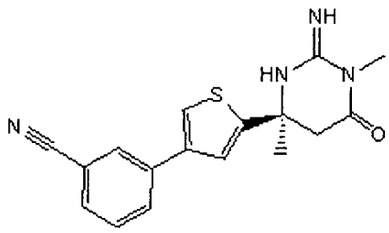
Ejemplo A: Estudios de Estabilidad Que Comparan el Ejemplo 45 con el Compuesto Z:

En el siguiente estudio, se midió la estabilidad en solución del compuesto del Ejemplo 45 y se comparó con la del Compuesto Z. El compuesto del Ejemplo 45 es un compuesto de dióxido de iminotiadiazina de la invención. El compuesto Z es el compuesto de iminopirimidinona correspondiente. Las estructuras del compuesto del Ejemplo 45 y del Compuesto Z son mostradas a continuación. Se llevaron a cabo estudios en buffer acuoso de pH 7,4 que contenía metanol a 4 °C,

25°C y 40°C. A 4°C, el compuesto del Ejemplo 45 mostró 0,93% de degradación después de 6 días mientras que el compuesto Z mostró 18,3% de degradación después de 1 día. A 25°C, el compuesto del Ejemplo 45 mostró 7,4 % de degradación después de 6 días mientras que el Compuesto Z mostró 53,87% de degradación. A 40°C, el compuesto del Ejemplo 45 mostró 30,71% de degradación después de 6 días mientras que el Compuesto Z mostró 79,93% de degradación después del 1 día.



Ejemplo 45



Compuesto Z
(US20060111370)

Estabilidad en Solución para el Ej. 45 en pH 7,4					
Condición	**4°C**				
Número de Lote	**7**				
Tiempo, días	**Inicial**	**1**	**2**	**6**	
Ensayo (Área %)	99,82	99,69	99,04	98,89	
Condición	**25°C**				
Ensayo (% Área)	99,82	98,45	96,07	92,43	
Condición	**40°C**				
Ensayo (% Área)	99,82	96,32	89,70	69,11	–
a: Resultados por normalización de área ND = No Detectado. (–) representa > 20 % de degradación					

Estabilidad en Solución para Compuesto Z en pH 7,4	
Condición	**4°C**
Número de Lote	**7**

Tiempo, días	Inicial	1	2	6	
Ensayo (% Área)	88,15	69,84	–	–	–
Condición	**25°C**				
Ensayo (% Área)	88,15	34,28	–	–	–
Condición	**40°C**				
Ensayo (% Área)	88,15	8,22	–	–	–
a: RRT aproximado para compuestos relacionados. Resultados por normalización de área ND = No Detectado. (–) representa > 20 % de degradación					

Se prepararon soluciones iniciales de los compuestos ensayados disolviendo aproximadamente 3 mg de cada compuesto en 3 mL de acetonitrilo. Se prepararon los patrones para los compuestos de ensayo diluyendo 1 mL de la solución inicial con 4 mL adicionales de acetonitrilo. Estos patrones se almacenaron a 4°C. Las muestras se prepararon diluyendo 1 mL de la solución inicial con 4 mL de buffer de fosfato pH 7,4 50 mM. Estas muestras se almacenaron a 25°C en ausencia de luz. Los patrones y muestras se analizaron por LC/MS inicialmente y en el día 1, día 4 y día 6.

Condiciones de HPLC:

Fase móvil A: buffer de acetato de amonio pH 5 10 mM : metanol (90 : 10)

Fase móvil B: buffer de acetato de amonio pH 5 10 mM : metanol (10 : 90)

Columna: Zorbax SB–Fenilo 4,6 x 50 mm, 1,8 µm
Temperatura de Columna: 40°C
Flujo: 0,8 mL/min.
Gradiente:

Tiempo (min.)	% B
0	40
9	100
11	100

Detectores: UV a 220 nm y 236 nm

MS, ES ionización, modo positivo, para identificación solamente en punto en el tiempo final.

Los términos reportados en las tablas que aparecen a continuación tienen los siguientes significados:

% de área es la integración de pico de la HPLC según lo informado por el programa informático Waters Empower II.

RRT es el tiempo de retención relativa de nuevo producto en comparación con el patrón del compuesto de ensayo.

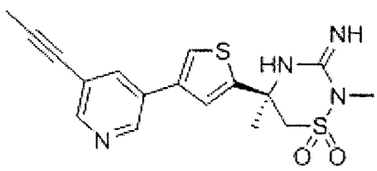
Fórmula para RRT es:

$$\frac{\text{Tiempo de retención de producto nuevo}}{\text{Tiempo de retención de patrón}}$$

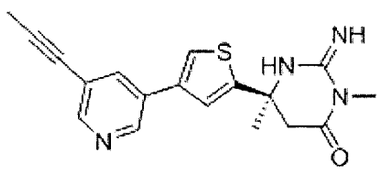
M + 1 es la masa observada incluyendo protonación (+ 1 unidad de masa).
ND representa ningún pico detectado por el detector de UV.
* representa ningún ión detectado por el espectrómetro de masas.

Ejemplo B: Estudios de Estabilidad que Comparan el Ejemplo 47 Con el Compuesto Y:

En el siguiente estudio, la estabilidad en solución del compuesto del Ejemplo 47 se midió y comparó con la del Compuesto Y. El compuesto del Ejemplo 47 es un compuesto de dióxido de iminotiadiazina de la invención. El Compuesto Y es el compuesto de iminopirimidinona correspondiente. Las estructuras del compuesto del Ejemplo 47 y del Compuesto Y se muestran a continuación. Los estudios se llevaron a cabo en buffer pH 7,4 a 25°C. Bajo estas condiciones, el compuesto del Ejemplo 47 mostró *0*% de producto de hidrólisis después de 6 días mientras que el Compuesto Z mostró 12,45% de producto de hidrólisis.



Ejemplo 47



Compuesto Y
(US 20070287692)

Ejemplo 20: base libre PM = 374,09

	Descripción de Pico	RRT	M + 1	% de área, Inicial	% de área, Día 1	% de área, Día 4	% de área, Día 6
Patrón	Ejemplo 47	1,00	375,10	98,53	98,55	98,52	98,52
	Desconocido	1,49	*	1,47	1,45	1,48	1,48
Muestra a pH 7,4	Ejemplo 47	1,00	375,10	98,55	98,56	98,53	98,53
	Desconocido	1,49	*	1,45	1,44	1,47	1,47

Compuesto Y: Base Libre PM = 338,12

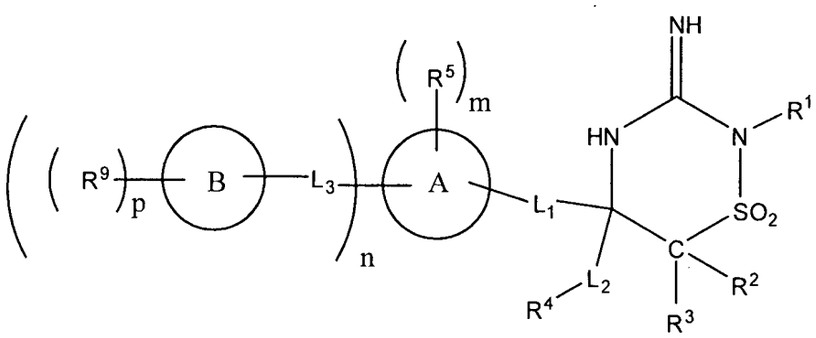
	Descripción de Pico	RRT	M + 1	% de área, Inicial	% de área, Día 1	% de área, Día 4	% de área, Día 6
Patrón	Compuesto Y	1,00	339,15	100,0	100,0	100,0	100,0
Muestra a pH 7,4	Compuesto Y	1,00	339,10	99,36	96,89	93,02	87,55
	Producto de hidrólisis	0,76	357,10	0,64	3,11	6,98	12,45

Si bien la presente invención ha sido descrita en vista de las realizaciones específicas expuestas anteriormente, muchas alternativas, modificaciones y otras variaciones de las mismas serán evidentes para los expertos en la técnica. Todas esas alternativas, modificaciones y variaciones tienen el propósito de caer dentro del espíritu y alcance de la presente invención.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma cómo la misma ha de ser llevada a la práctica se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, teniendo dicho compuesto la Fórmula estructural (I):



(I)

donde:

-L_1–representa un enlace o un resto divalente seleccionado del grupo formado por -alquil-, -haloalquil-, -heteroalquil-, -alquenil-, y -alquinil-;

-L_2– representa un enlace o un resto divalente seleccionado del grupo formado por -alquil-, -haloalquil-, -heteroalquil-, -alquenil-, y -alquinil-;

cada -L_3– representa independientemente un enlace o un resto divalente seleccionado independientemente del grupo formado por -alquil-, -haloalquil-, -heteroalquil-, -alquenil-, -alquinil-, -N(R^7)-, –NHC(O)-, -C(O)NH-, -NHS$(O)_2$-, -S$(O)_2$NH-, -O-alquil-, -alquil-O-, -N(R^7)-alquil-, -alquil-N(R^7)-, -haloalquil-NH-, y –NH-haloalquil-;

m, n, y p son cada uno números enteros independientemente seleccionados, donde:

m es 0 o más;

n es 0 o más; y

p es 0 o más,

donde el valor máximo de la suma de m y n es el número máximo de átomos de hidrógeno sustituibles disponibles en el anillo A, y donde el valor

máximo de p es el número máximo de átomos de hidrógeno sustituibles disponibles en el anillo B;

R^1 se selecciona del grupo formado por: H, alquilo, heteroalquilo, heterohaloalquilo, cicloalquilo, cicloalquilalquil-, heterocicloalquilo, heterocicloalquilalquil-, arilo, arilalquil-, heteroarilo, y heteroarilalquil-,

donde cada uno de dicho alquilo, heteroalquilo, heterohaloalquilo, cicloalquilo, cicloalquilalquil-, heterocicloalquilo, heterocicloalquilalquil-, arilo, arilalquil-, heteroarilo, y heteroarilalquil– de R^1 está sin sustituir o sustituido con uno o más grupos R^{10} independientemente seleccionados;

R^2 se selecciona del grupo formado por H, halo, alquilo, haloalquilo, y heteroalquilo,

donde cada uno de dicho alquilo y dicho haloalquilo de R^2 está sin sustituir o sustituido con uno o más grupos R^{10} independientemente seleccionados;

R^3 se selecciona del grupo formado por H, halo, alquilo, haloalquilo, y heteroalquilo,

donde cada uno de dicho alquilo y dicho haloalquilo de R^2 está sin sustituir o sustituido con uno o más grupos R^{10} independientemente seleccionados;

R^4 se selecciona del grupo formado por alquilo, arilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, y heterocicloalquenilo,

donde cada uno de dicho alquilo, arilo, heteroarilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, y heterocicloalquenilo de R^4 está sin sustituir o sustituido con uno o más grupos R^{10} independientemente seleccionados;

el anillo A se selecciona del grupo formado por arilo monocíclico, heteroarilo monocíclico, cicloalquilo monocíclico, cicloalquenilo monocíclico, heterocicloalquilo monocíclico, heterocicloalquenilo monocíclico, y un grupo multicíclico;

cada anillo B (cuando está presente) se selecciona independientemente del grupo formado por arilo monocíclico, heteroarilo monocíclico, cicloalquilo monocíclico, cicloalquenilo monocíclico, heterocicloalquilo monocíclico, heterocicloalquenilo monocíclico, y un grupo multicíclico;

cada R^5 (cuando está presente) se selecciona independientemente del grupo formado por halo, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$,

$-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo,

donde cada uno de dichos alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, cicloalquilo, heterocicloalquilo, arilo, y heteroarilo de R^5 (cuando está presente) está opcional e independientemente sin sustituir o sustituido adicionalmente con uno o más grupos independientemente seleccionados, seleccionados del grupo formado por alquilo inferior, alquenilo inferior, alquinilo inferior, heteroalquilo inferior, halo, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-N(R^8)_2$, $-OR^7$, $-C(O)N(R^8)_2$, y cicloalquilo;

cada R^6 (cuando está presente) se selecciona independientemente del grupo formado por alquilo, arilo, arilalquil-, haloalquilo, cicloalquilo, cicloalquilalquil-, heteroarilo, y heteroarilalquil-;

cada R^7 (cuando está presente) se selecciona independientemente del grupo formado por H, alquilo, alquenilo, heteroalquilo, haloalquilo, arilo, arilalquil-, heteroarilo, heteroarilalquil-, cicloalquilo, cicloalquilalquil-, heterocicloalquilo, y heterocicloalquilalquil-;

cada R^8 (cuando está presente) se selecciona independientemente del grupo formado por H, alquilo, alquenilo, heteroalquilo, haloalquilo, haloalquenilo, arilo, arilalquil-, heteroarilo, heteroarilalquil-, cicloalquilo, cicloalquilalquil-, heterocicloalquilo, y heterocicloalquilalquil-;

cada R^9 (cuando está presente) se selecciona independientemente del grupo formado por: halógeno, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alquilo, haloalquilo, heteroalquilo, alquenilo, alquinilo, arilo, arilalquil-, cicloalquilo, heteroarilo, heteroarilalquil-, y heterocicloalquilo;

cada R^{10} (cuando está presente) se selecciona independientemente del grupo formado por halo, -CN, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$,

$-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, y cicloalquilo,

donde cada uno de dichos alquilo, haloalquilo, haloalcoxi, heteroalquilo, alquenilo, alquinilo, y cicloalquilo de R^{10} (cuando está presente) está opcional e independientemente sin sustituir o adicionalmente sustituido con uno o más grupos independientemente seleccionados seleccionados del grupo formado por alquilo inferior, alquenilo inferior, alquinilo inferior, heteroalquilo inferior, halo, -CN, $-NO_2$, $-N(R^8)_2$, $-OR^7$, y $-C(O)N(R^8)_2$.

2. Un compuesto de acuerdo con la reivindicación 1, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, donde:

R^1 se selecciona del grupo formado por H, alquilo inferior, y ciclopropilo.

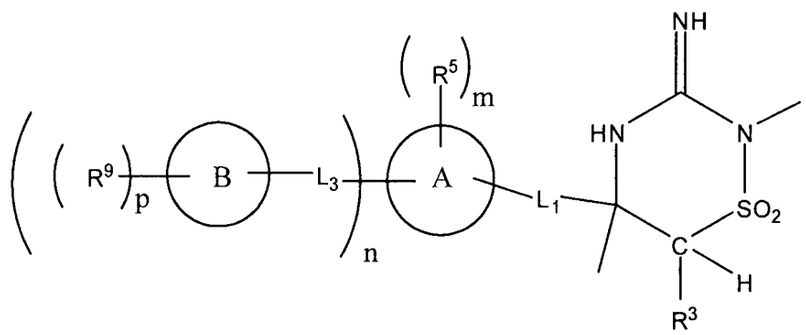
3. Un compuesto de acuerdo con la reivindicación 1, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, donde:

R^2 es H.

4. Un compuesto de acuerdo con la reivindicación 1, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, donde:

R^3 se selecciona del grupo formado por H, alquilo, haloalquilo, y heteroalquilo.

5. Un compuesto de acuerdo con la reivindicación 1, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, teniendo dicho compuesto una Fórmula estructural (II):



(II).

6. Un compuesto de acuerdo con la reivindicación 5, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, donde:

el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, benzotienilo, bencimidazolilo, indazolilo, indolilo, y tienopirazolilo;

m es 0 o más;

cada grupo R^5 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y cicloalquilo;

n es 1;

$-L_3-$representa un enlace o un resto divalente seleccionado del grupo formado por –NHC(O)– y –C(O)NH-;

el anillo B se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, isoxazolilo, isotiazolilo, indolilo, pirrolopiridilo, y pirrolopirimidinilo;

p es 0 o más; y

cada grupo R^9 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, alquilo inferior,

haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, fenilo, bencilo, y cicloalquilo.

7. Un compuesto de acuerdo con la reivindicación 5, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, donde:

n es 0;

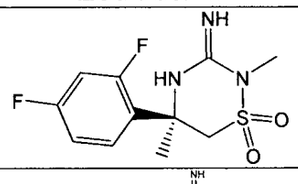
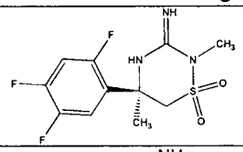
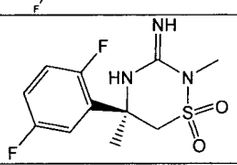
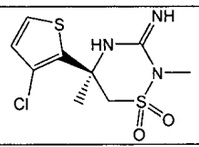
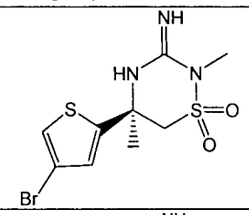
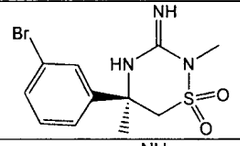
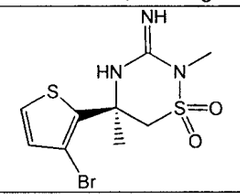
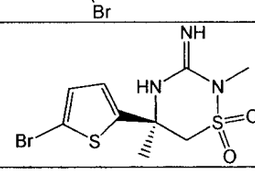
m es 1 o más;

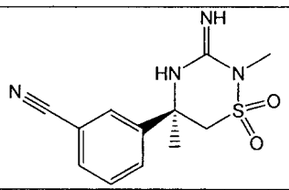
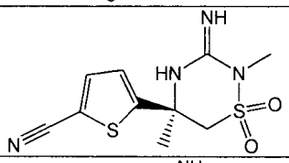
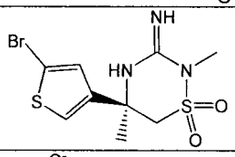
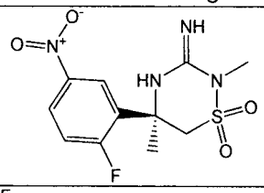
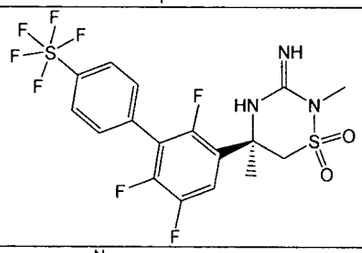
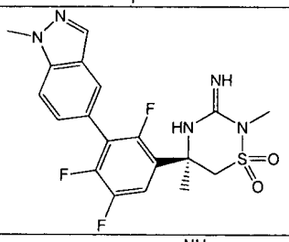
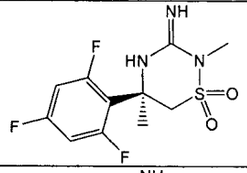
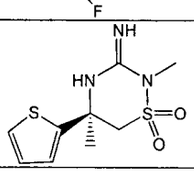
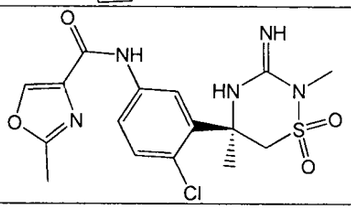
$-L_1-$ representa un enlace, $-CH_2-$, o $-CH_2CH_2-$;

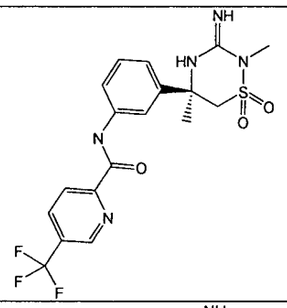
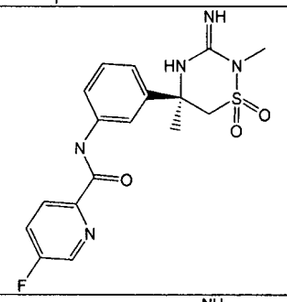
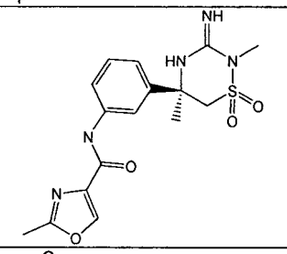
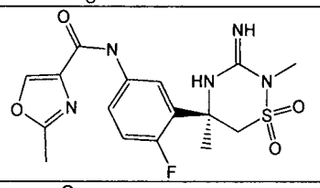
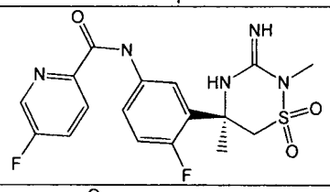
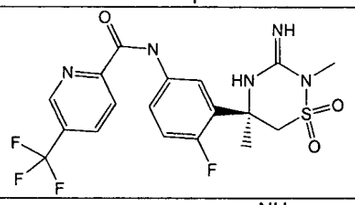
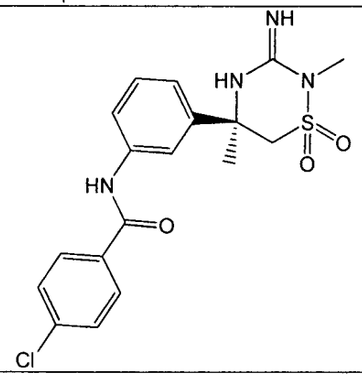
el anillo A se selecciona del grupo formado por fenilo, piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, imidazolilo, pirazolilo, quinazolinilo, benzofuranilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, benzotienilo, naftilo, quinolilo, isoquinolilo, indazolilo, indolilo, y tienopirazolilo; y

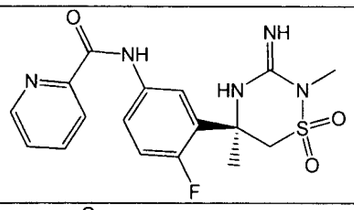
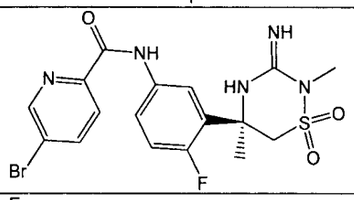
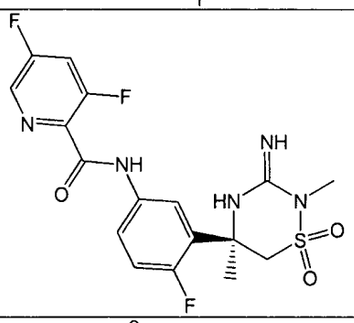
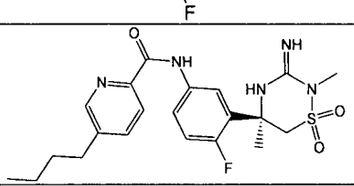
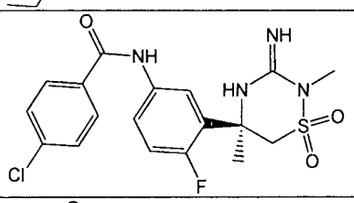
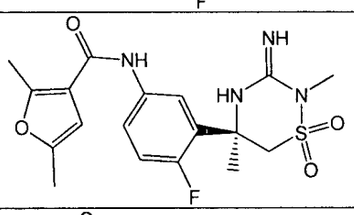
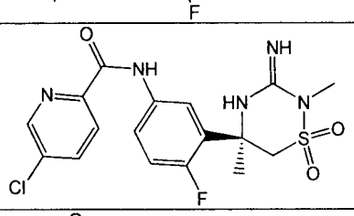
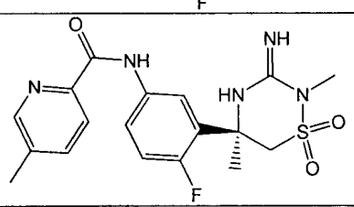
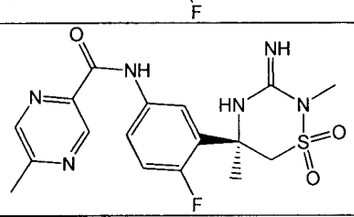
cada grupo R^5 (cuando está presente) se selecciona independientemente del grupo formado por halógeno, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, alquilo inferior, haloalquilo inferior, heteroalquilo inferior, alquinilo inferior, y cicloalquilo.

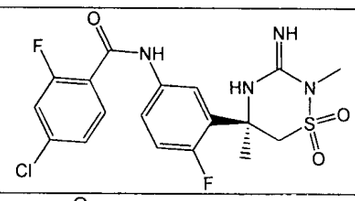
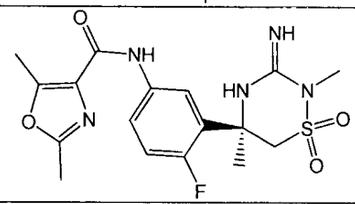
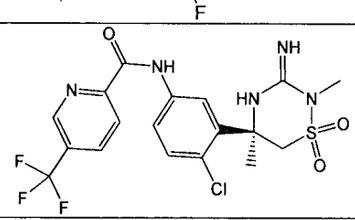
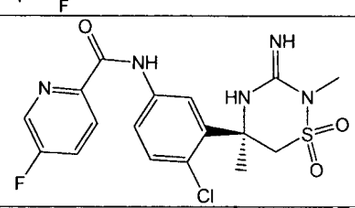
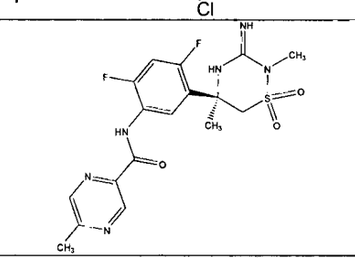
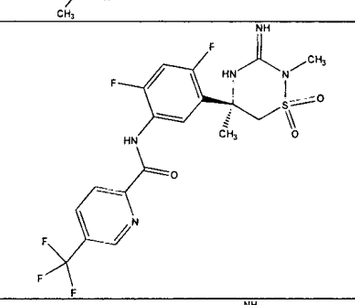
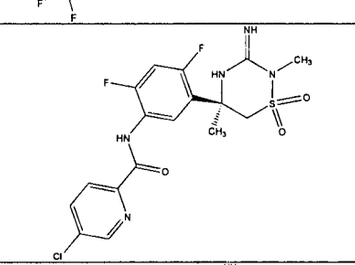
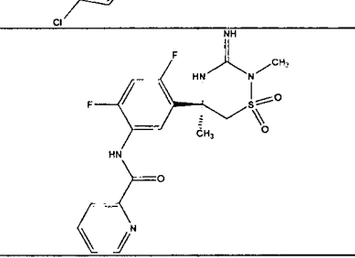
8. Un compuesto, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, seleccionándose dicho compuesto del grupo formado por:

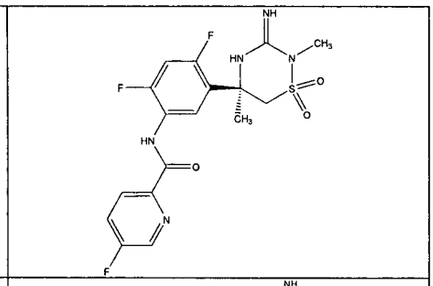
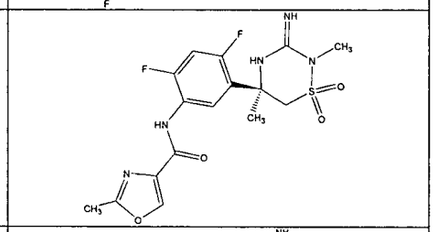
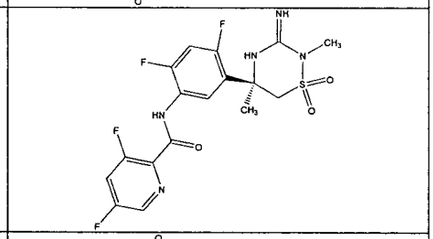
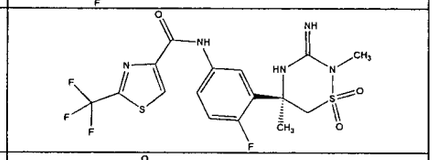
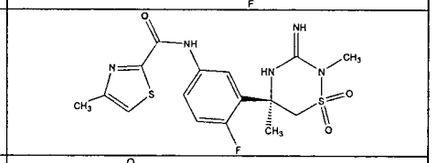
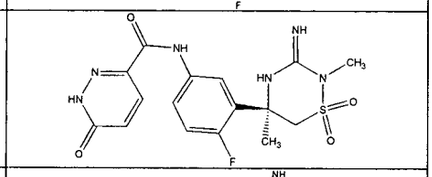
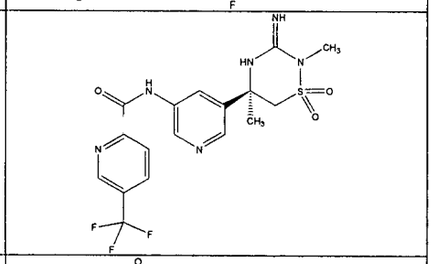
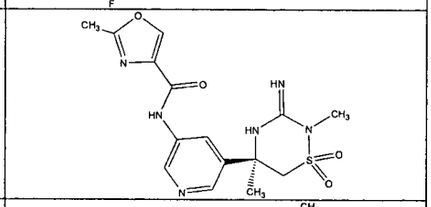
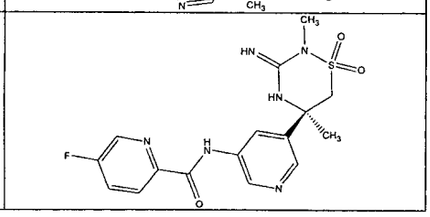
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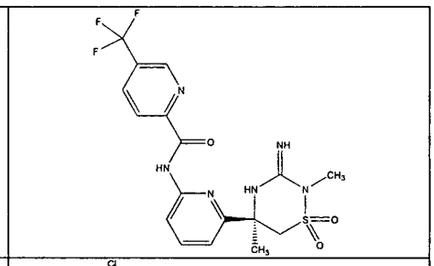
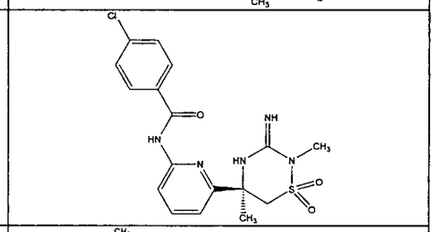
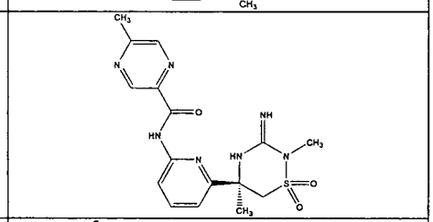
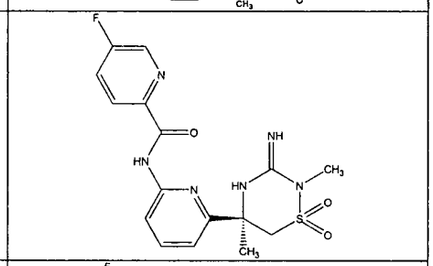
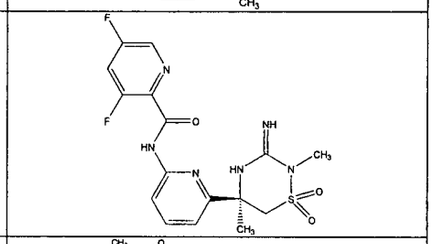
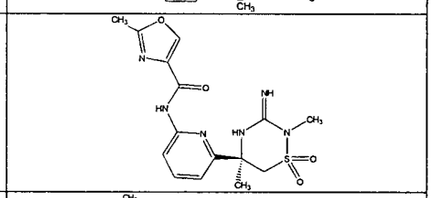
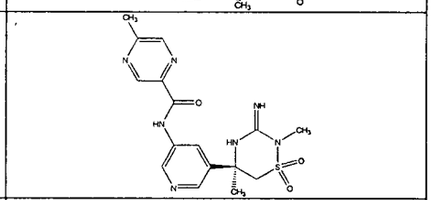
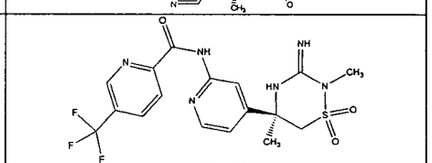
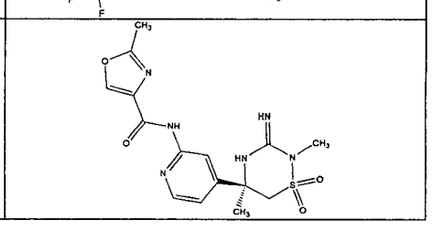
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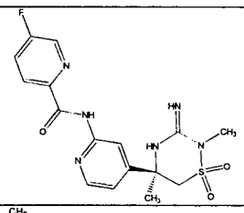
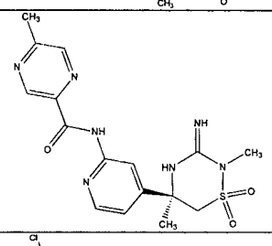
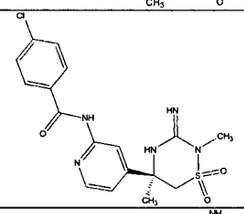
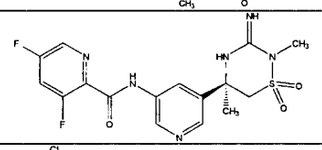
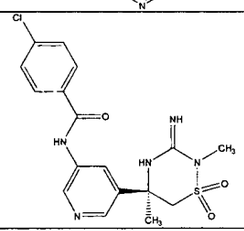
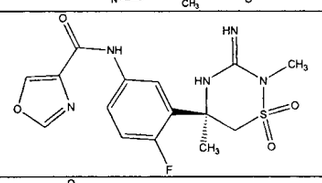
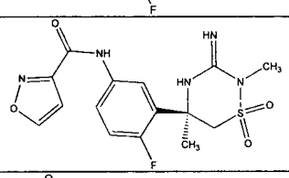
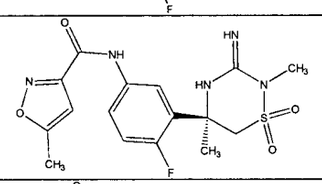
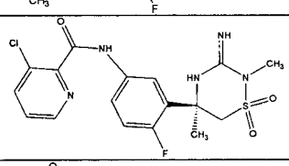
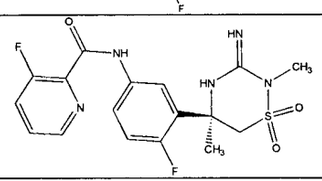
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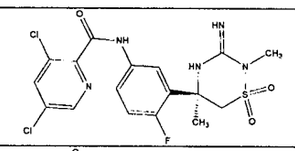
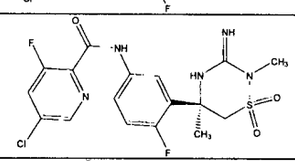
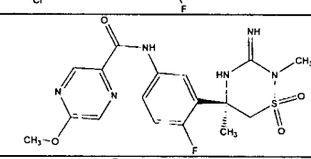
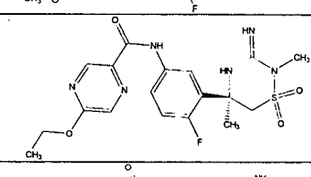
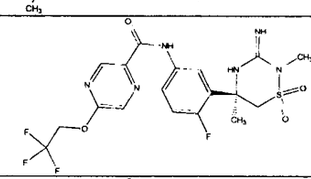
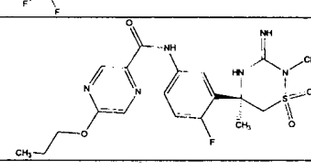
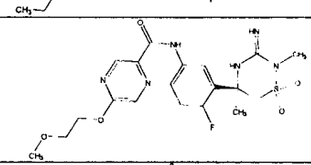
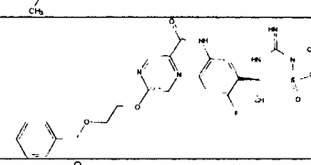
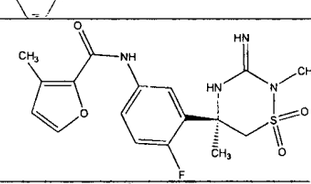
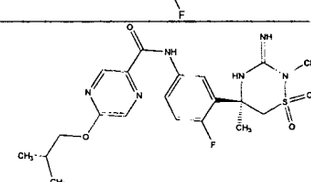
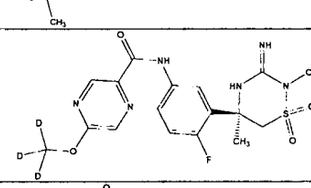
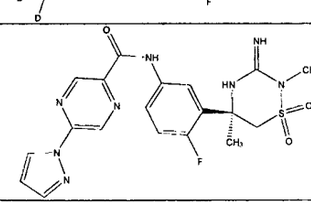
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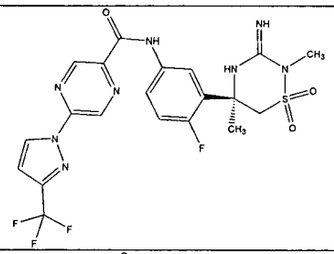
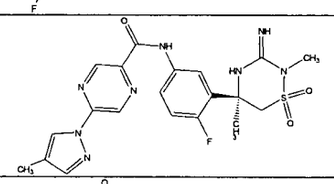
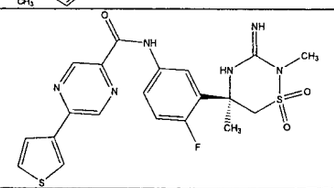
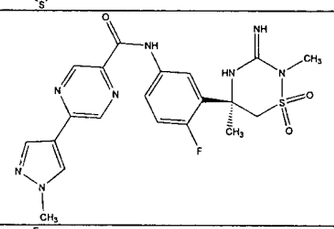
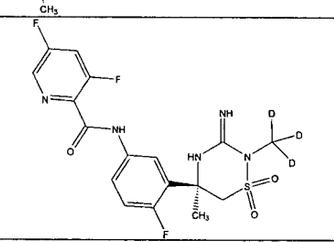
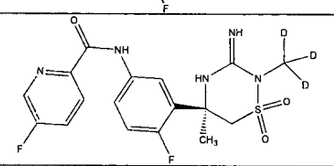
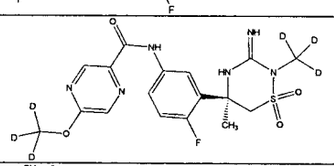
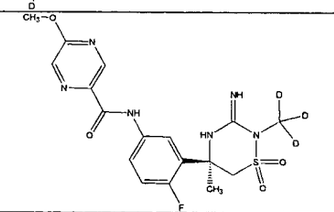
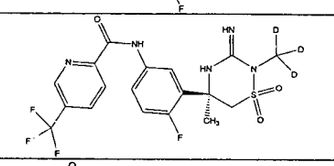
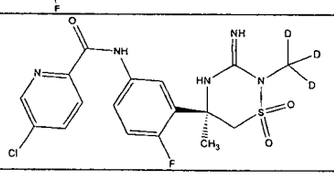
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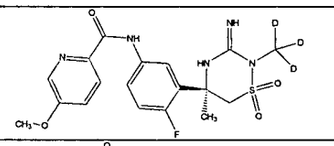
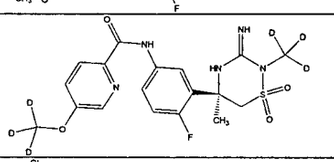
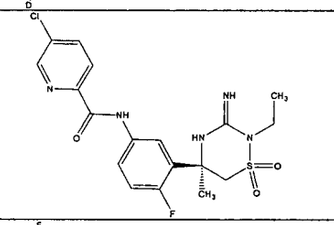
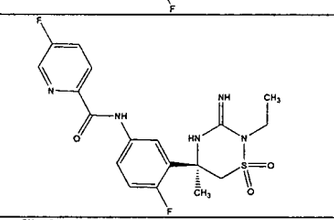
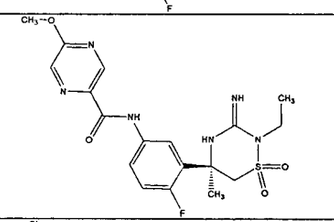
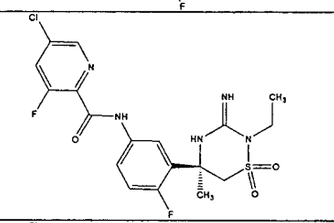
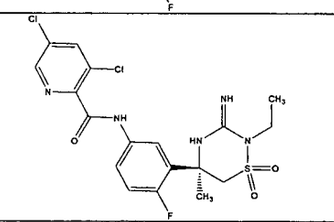
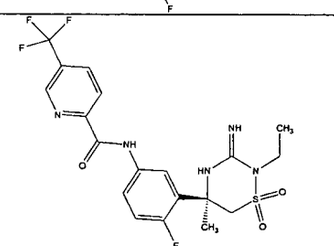
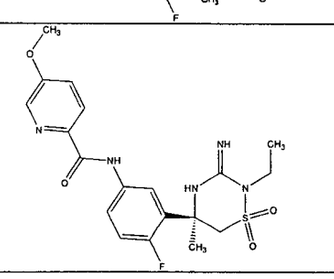
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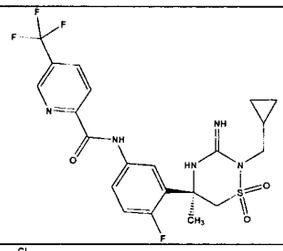
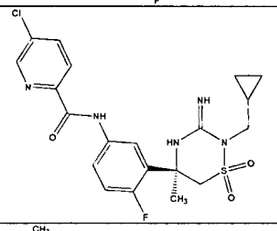
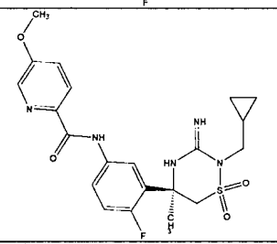
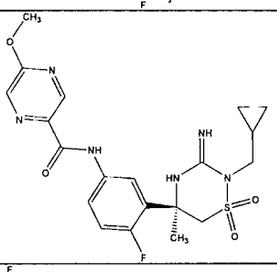
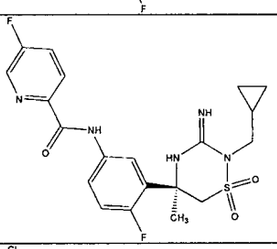
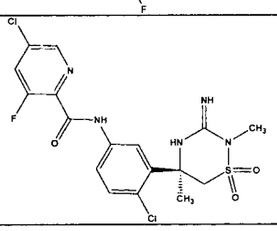
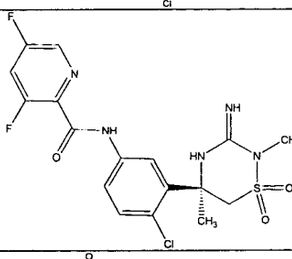
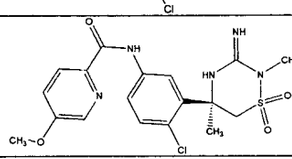
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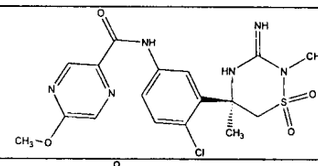
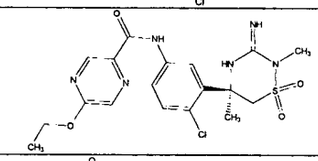
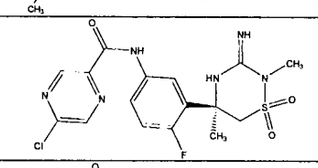
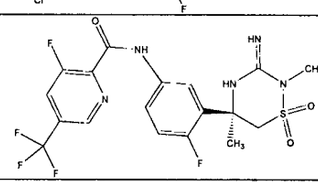
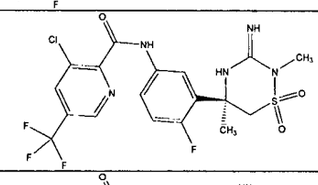
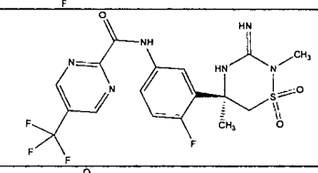
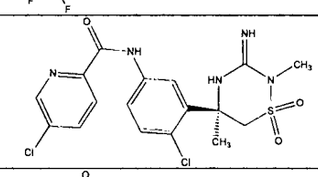
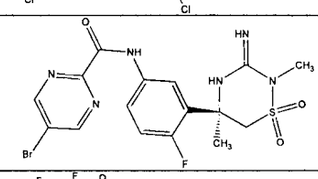
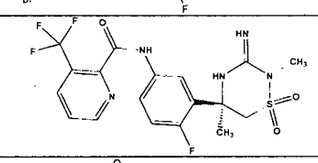
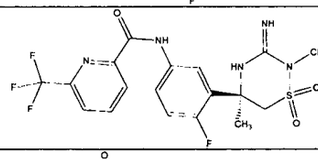
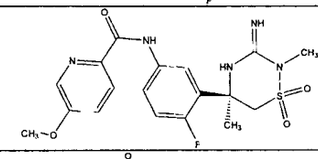
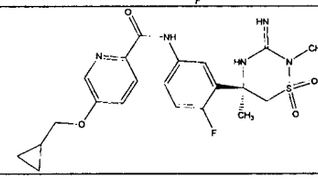
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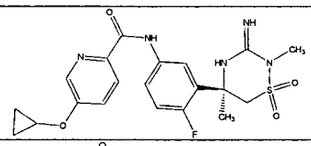
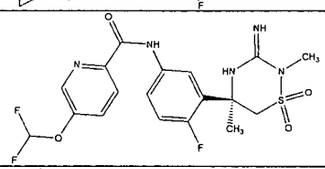
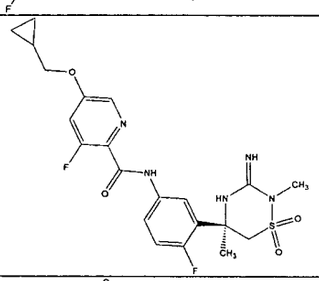
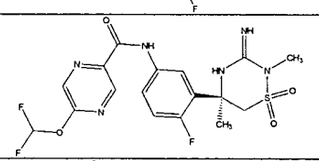
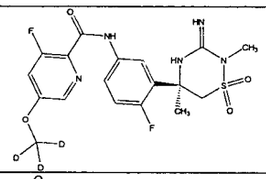
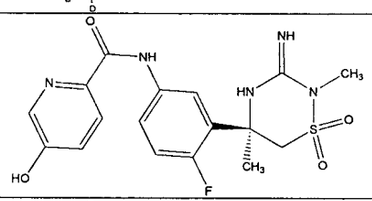
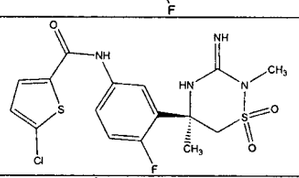
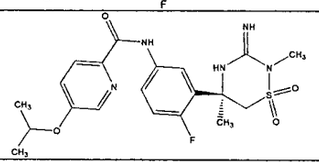
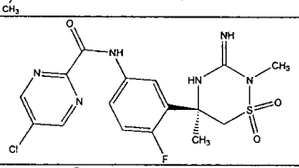
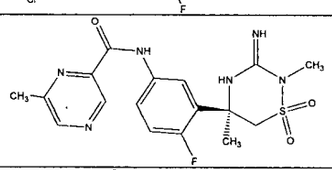
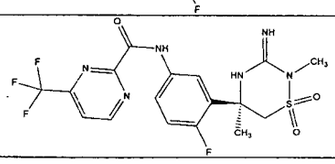
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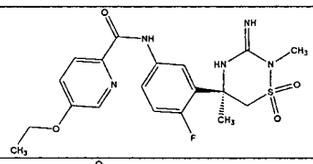
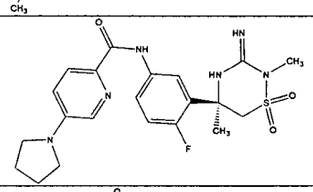
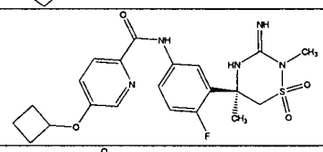
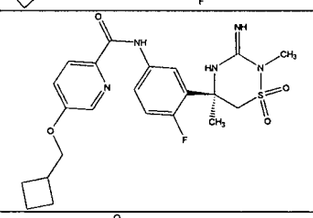
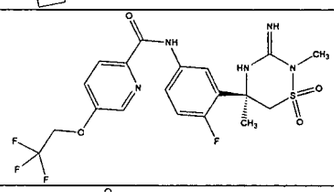
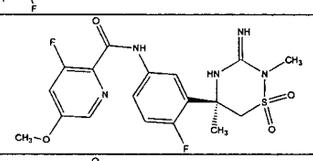
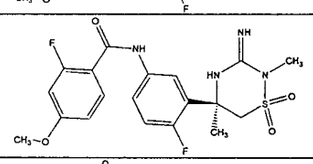
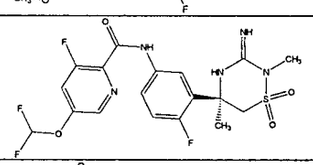
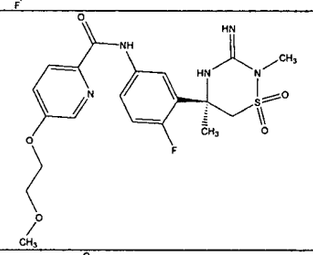
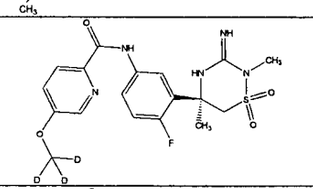
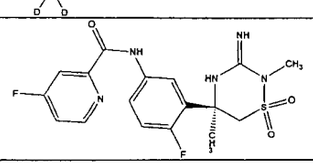
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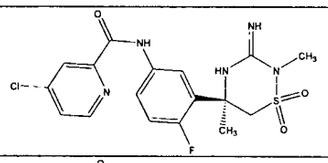
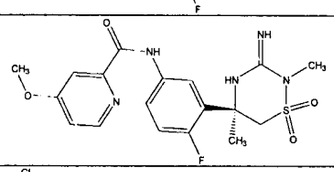
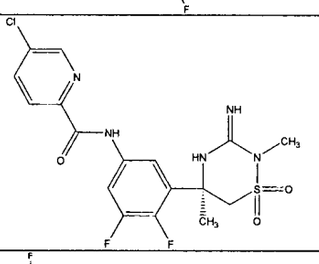
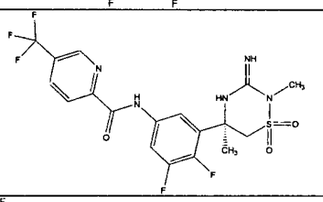
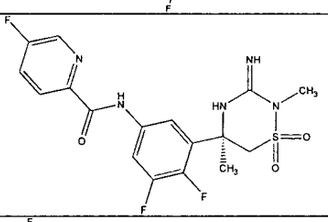
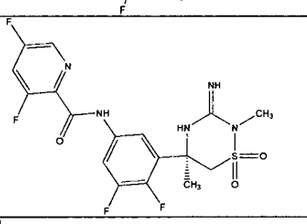
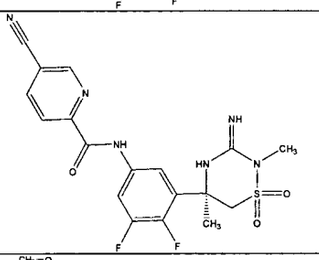
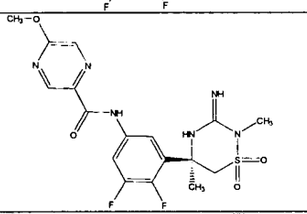
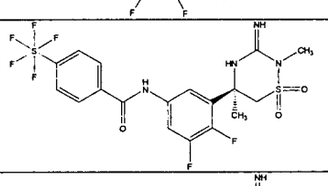
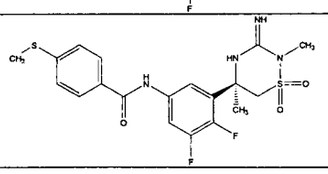
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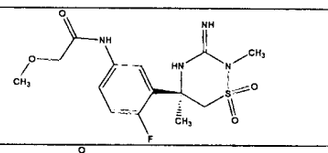
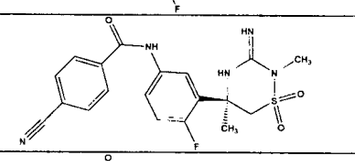
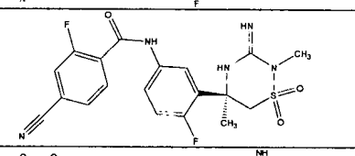
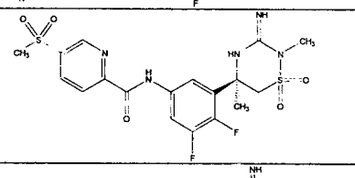
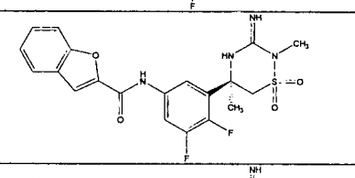
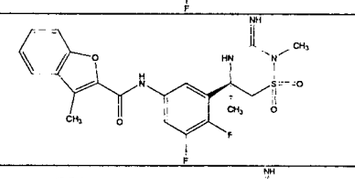
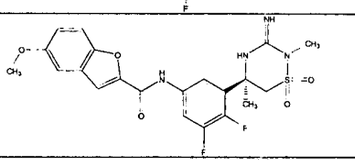
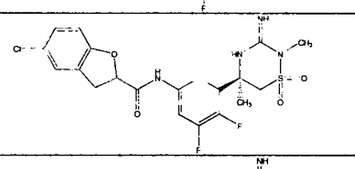
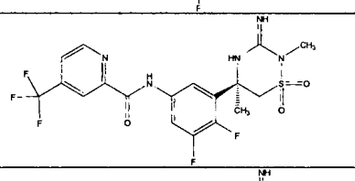
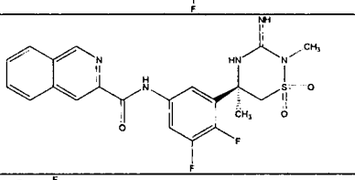
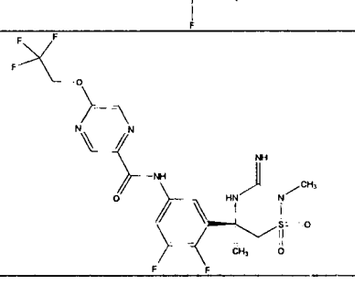
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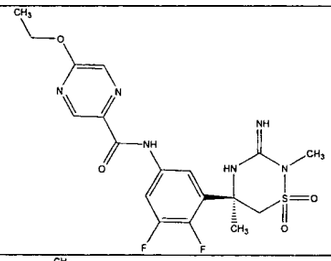
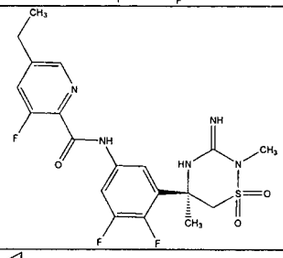
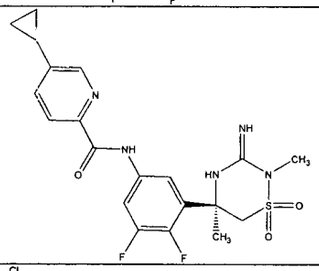
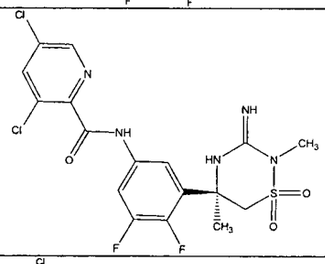
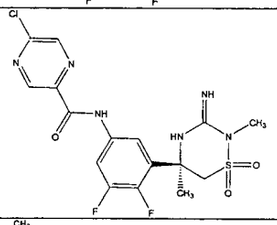
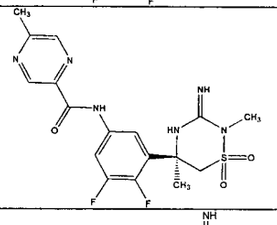
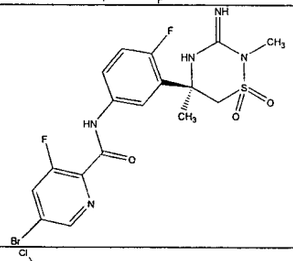
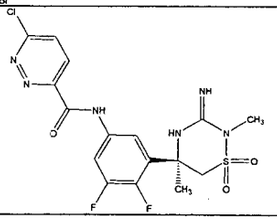
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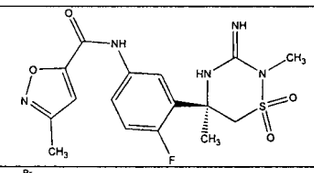
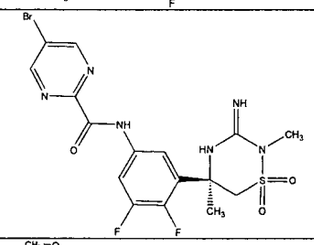
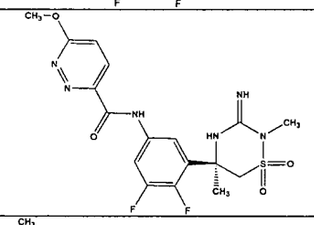
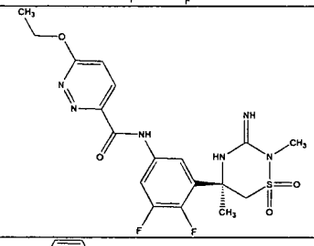
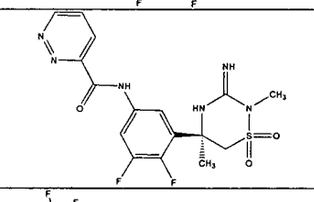
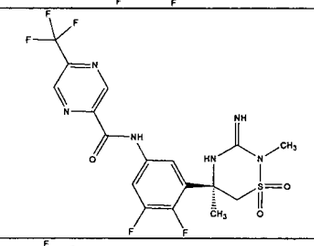
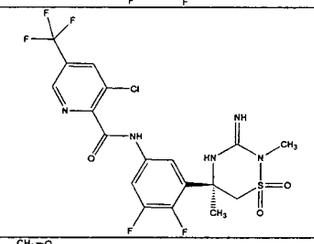
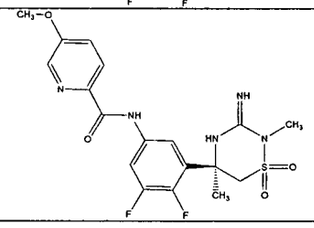
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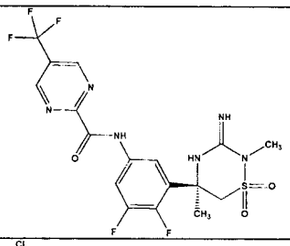
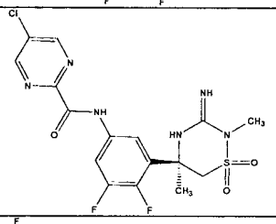
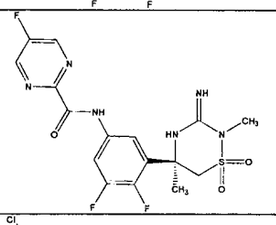
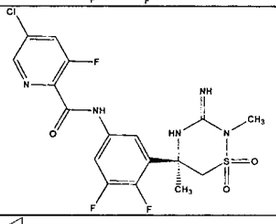
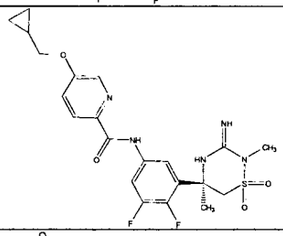
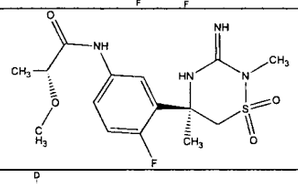
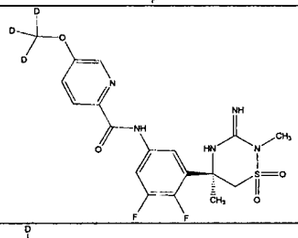
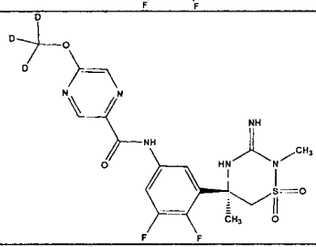
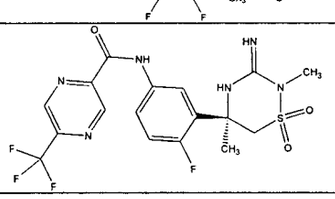
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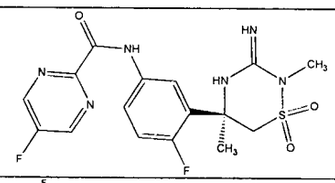
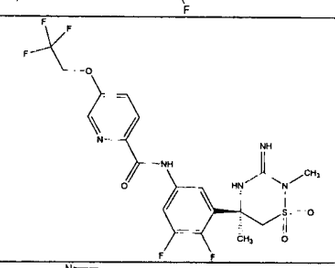
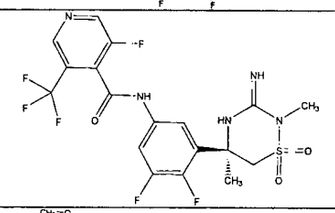
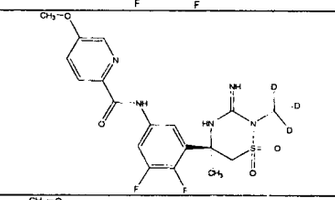
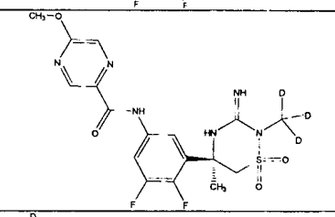
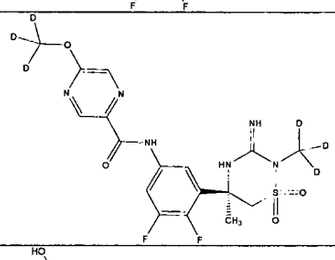
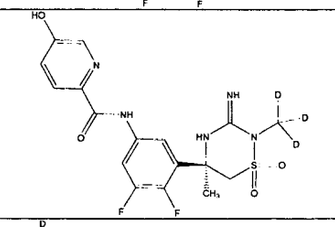
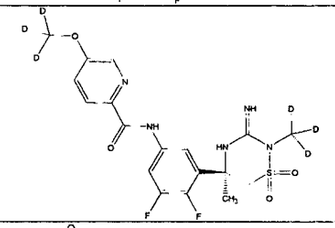
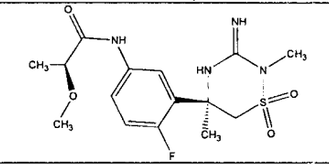
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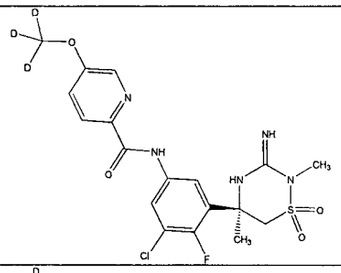
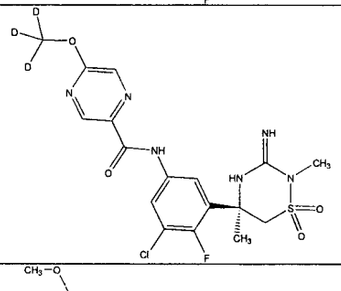
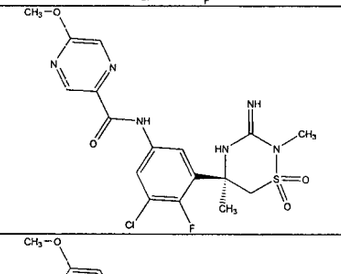
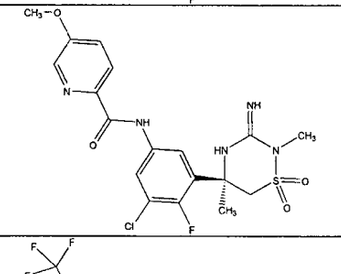
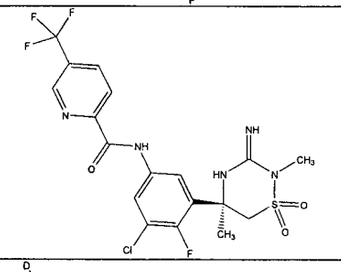
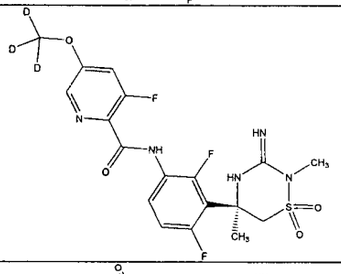
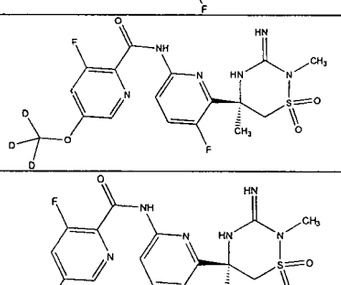
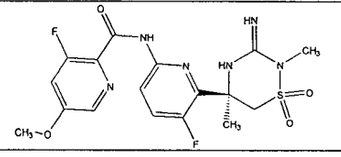
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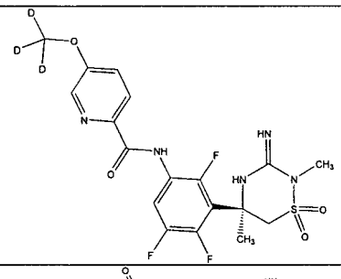
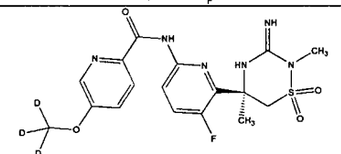
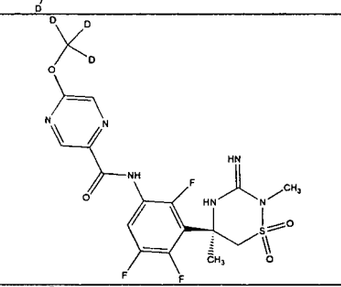
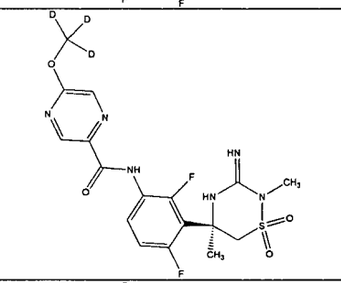
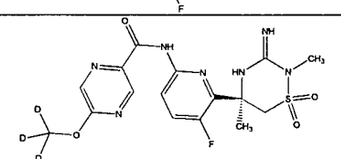
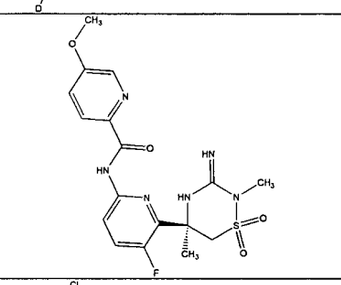
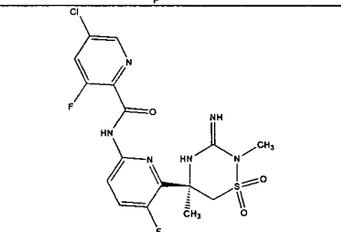
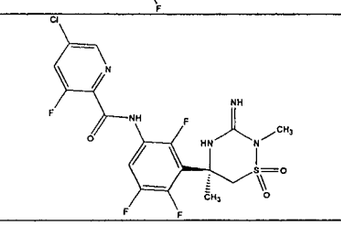
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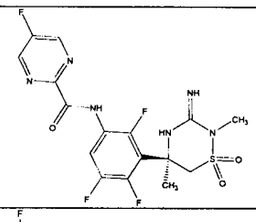
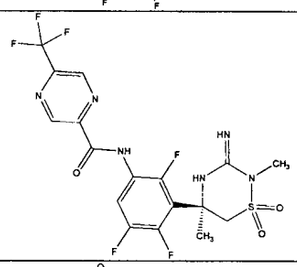
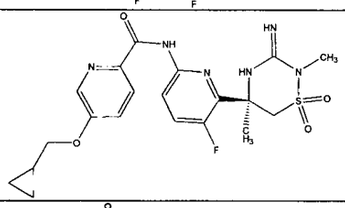
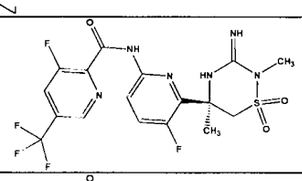
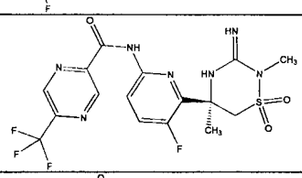
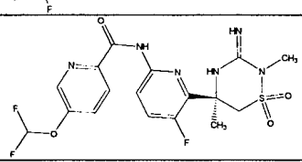
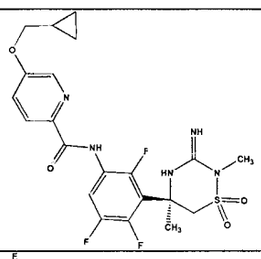
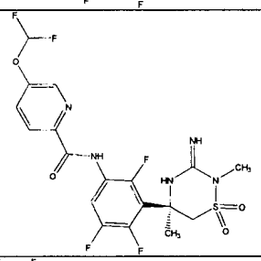
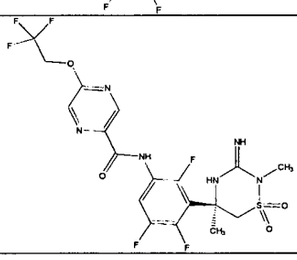
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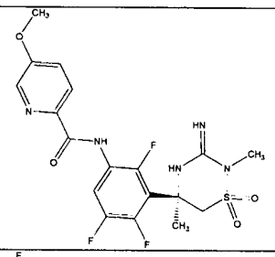
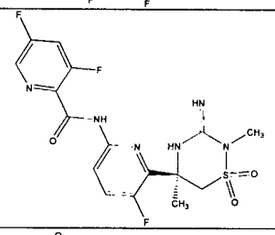
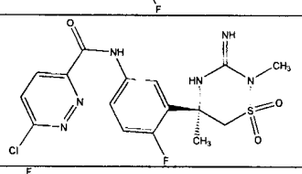
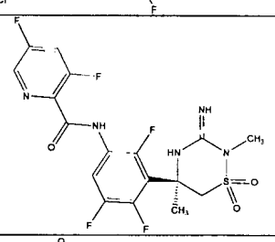
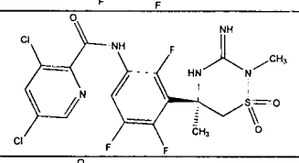
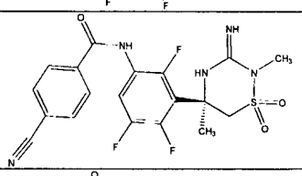
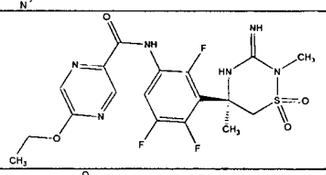
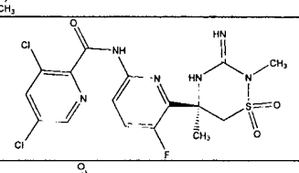
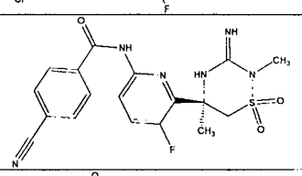
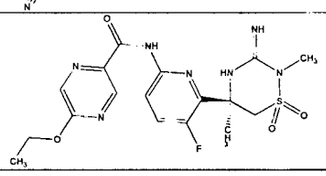
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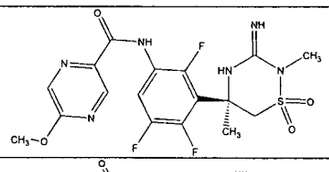
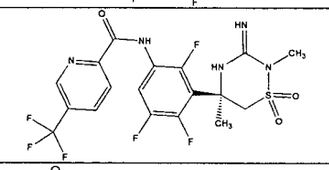
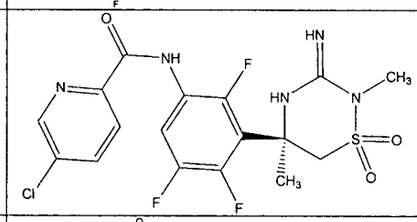
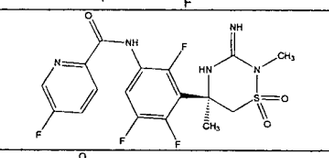
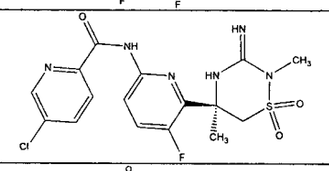
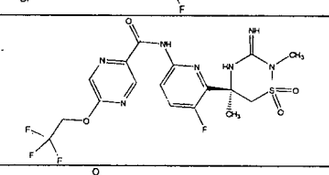
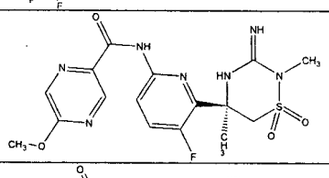
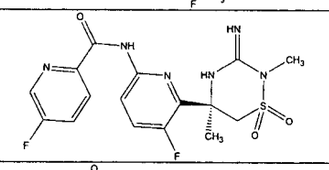
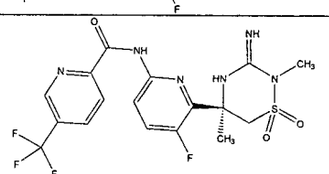
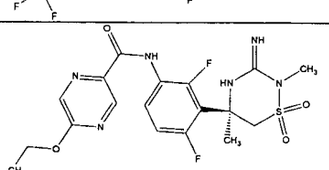
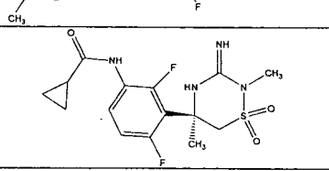
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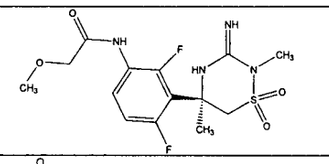
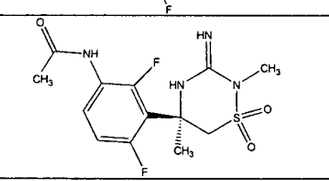
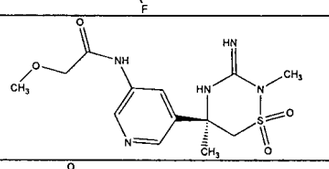
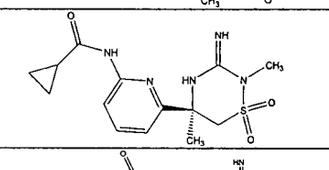
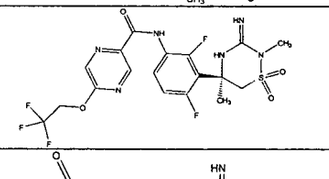
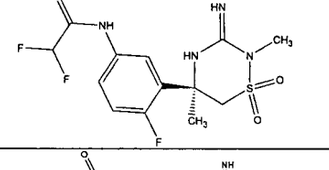
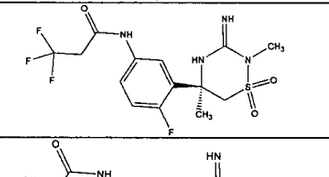
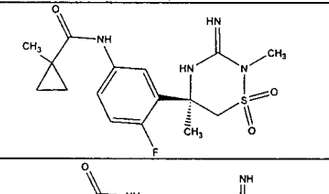
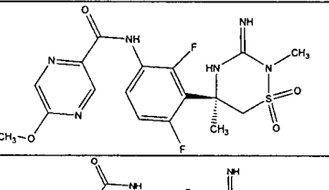
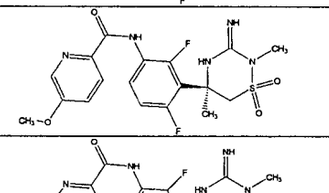
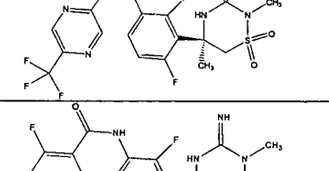
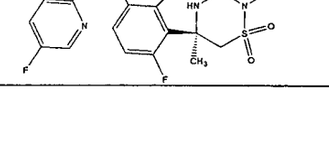
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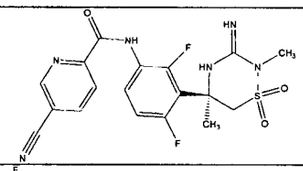
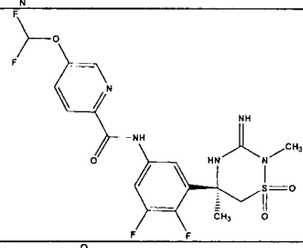
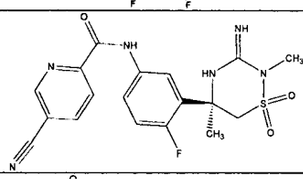
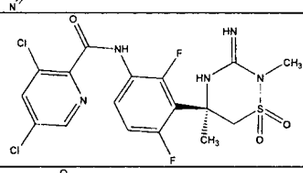
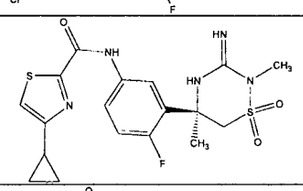
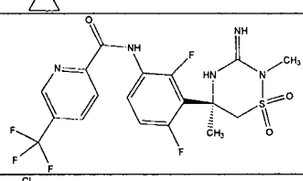
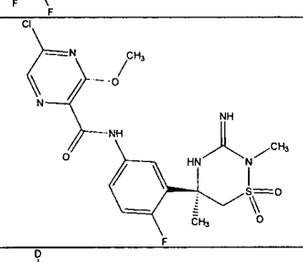
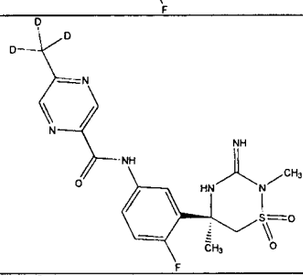
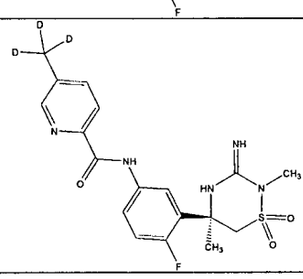
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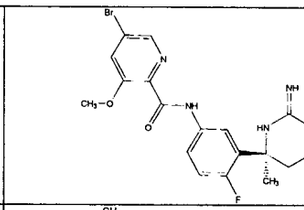
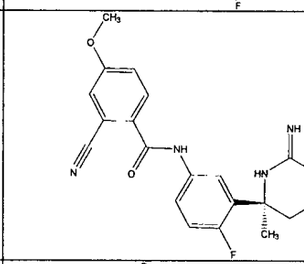
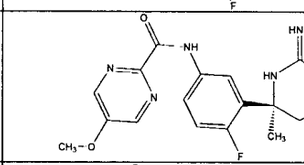
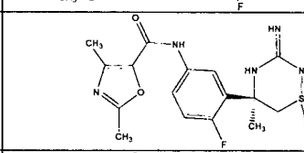
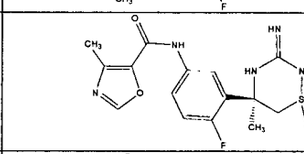
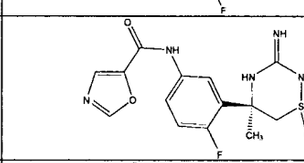
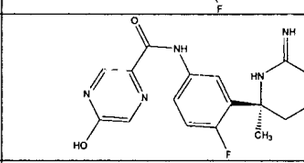
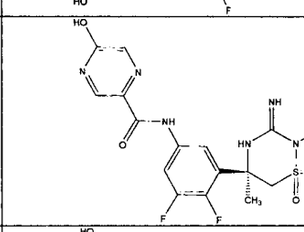
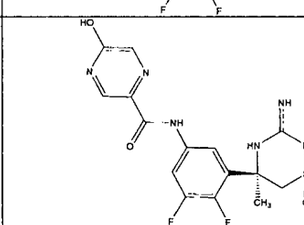
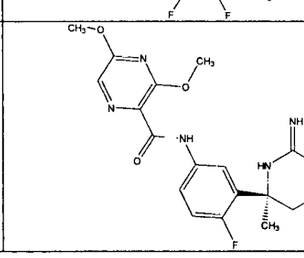
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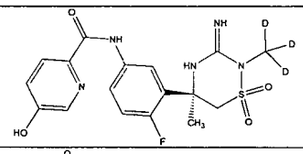
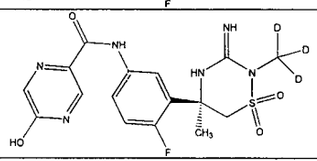
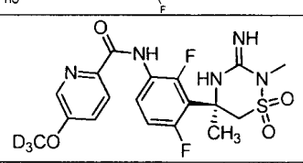
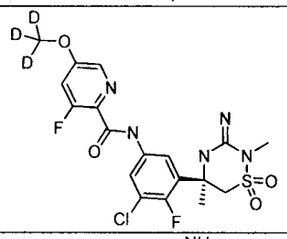
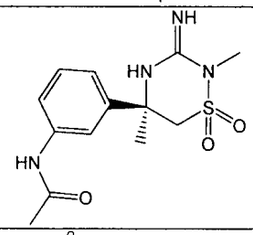
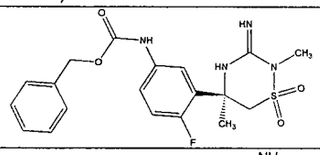
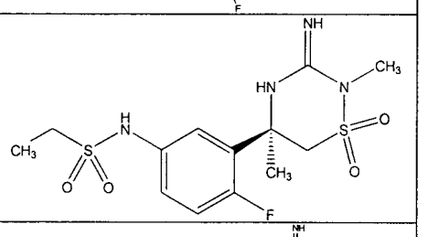
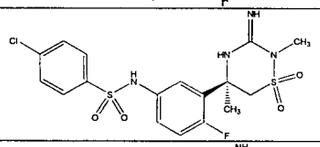
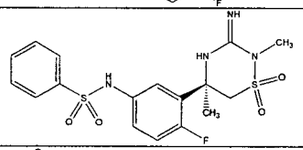
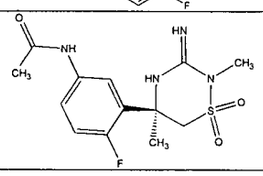
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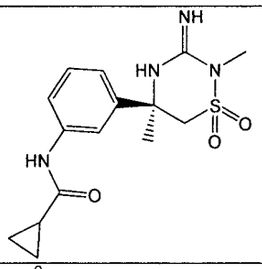
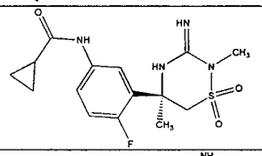
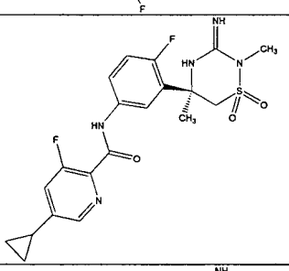
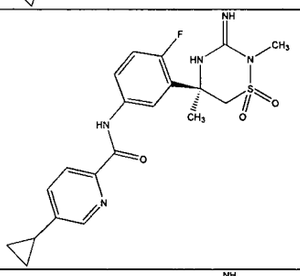
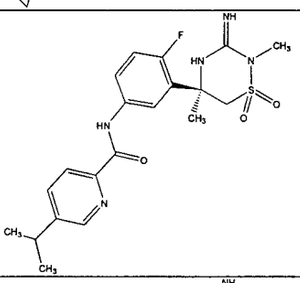
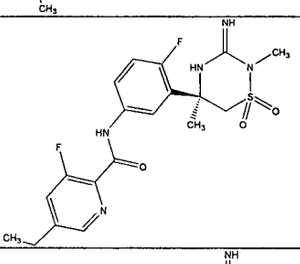
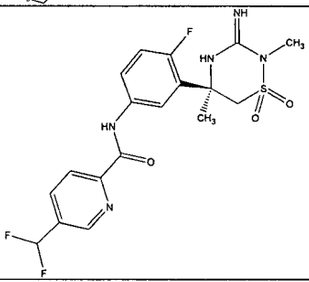
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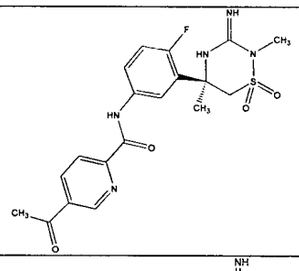
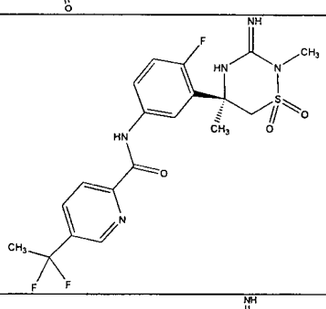
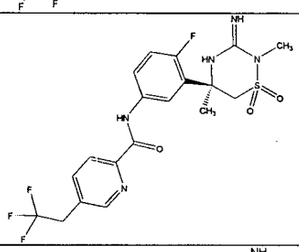
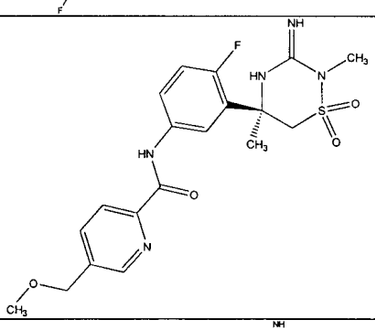
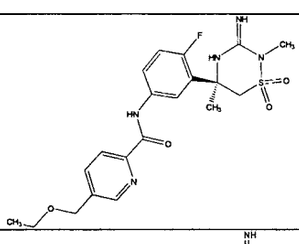
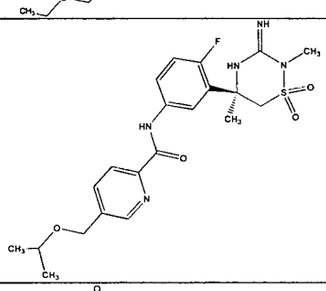
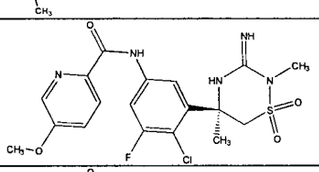
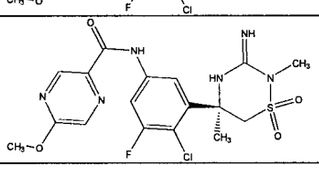
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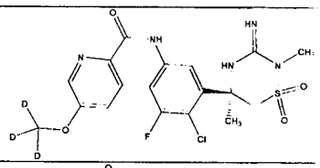
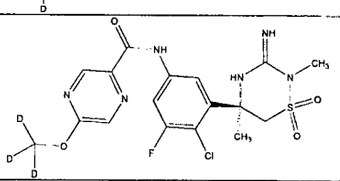
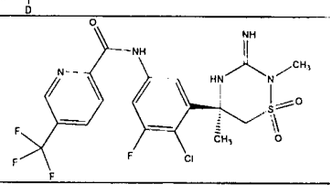
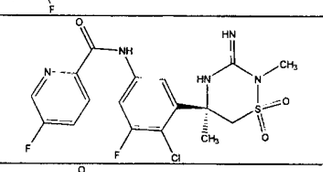
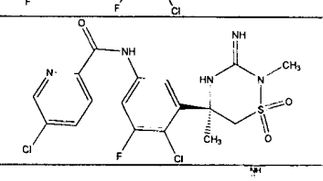
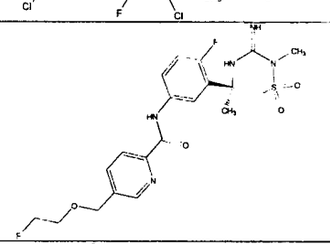
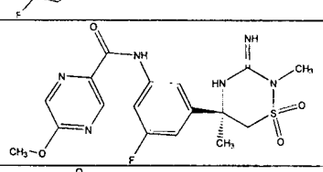
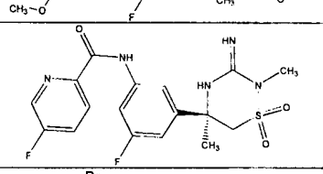
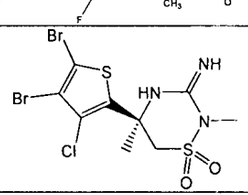
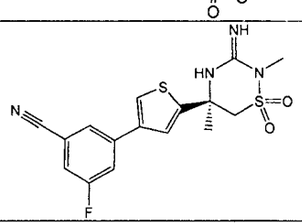
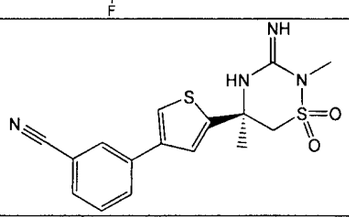
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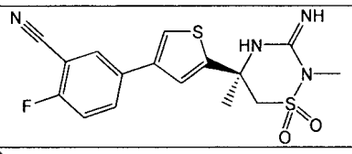
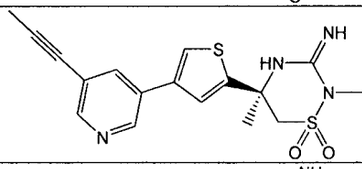
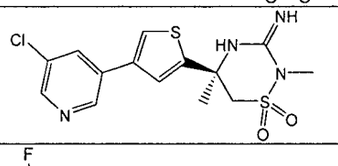
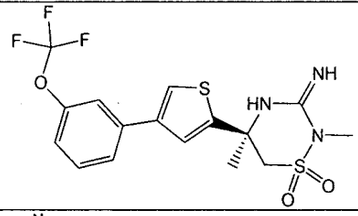
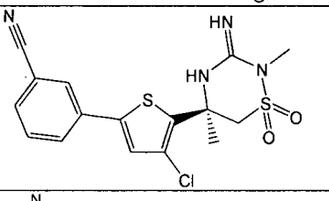
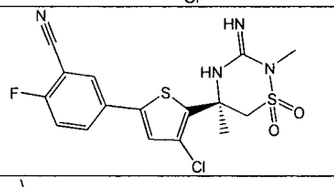
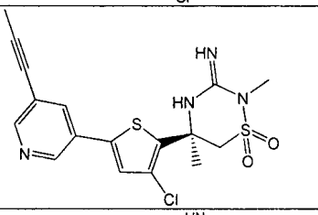
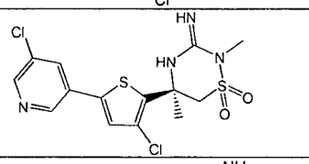
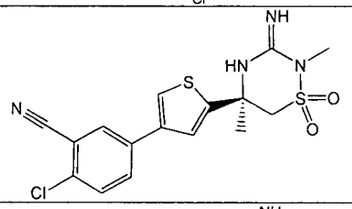
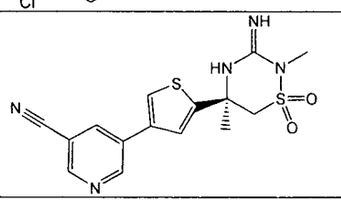
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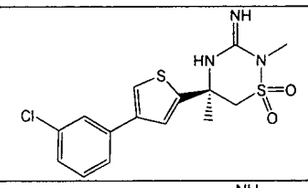
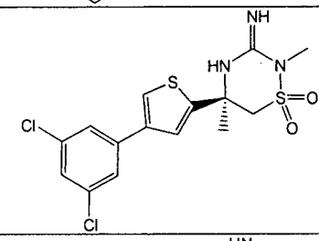
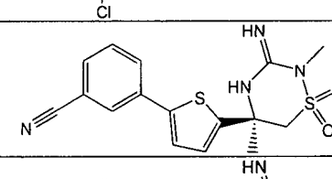
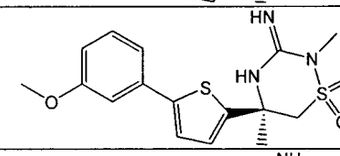
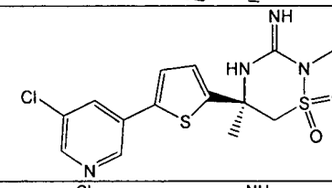
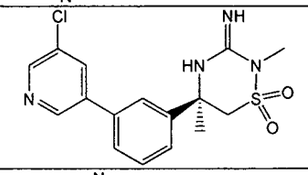
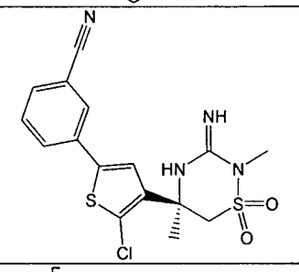
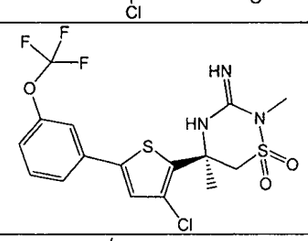
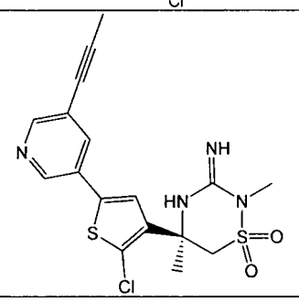
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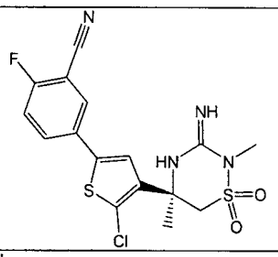
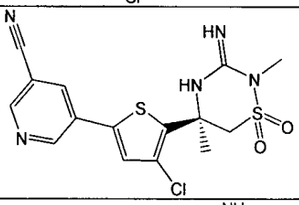
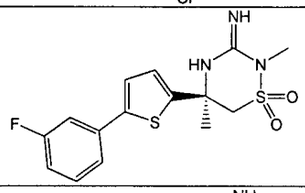
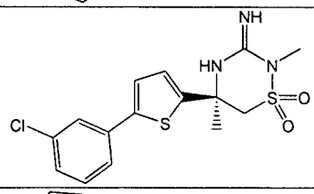
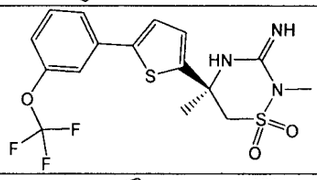
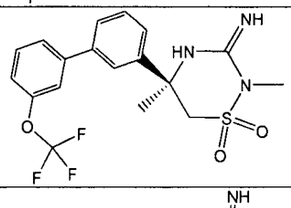
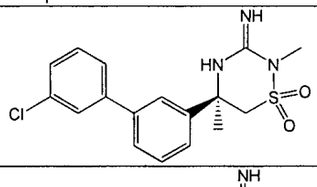
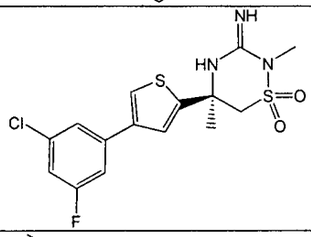
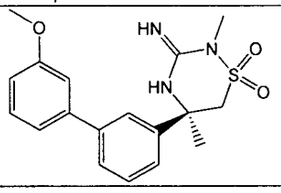
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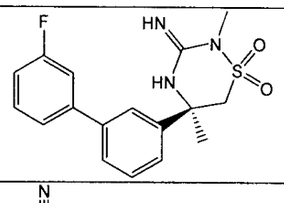
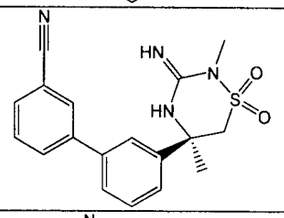
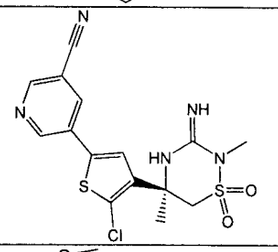
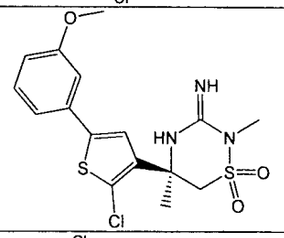
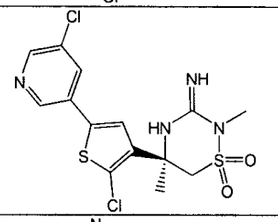
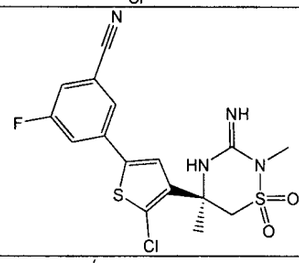
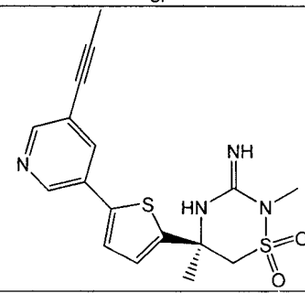
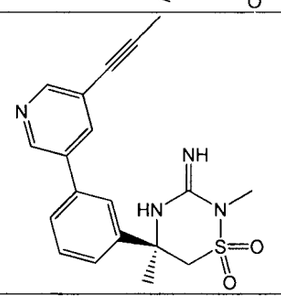
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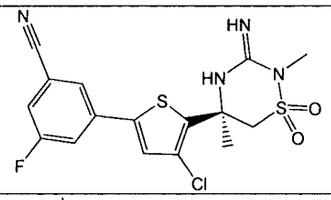
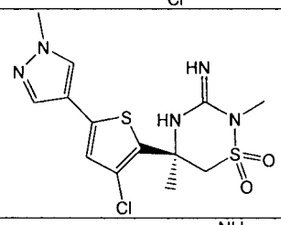
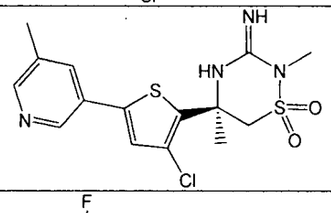
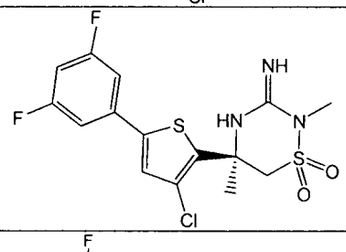
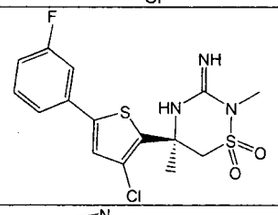
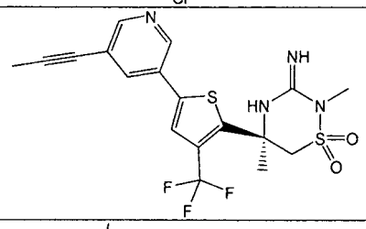
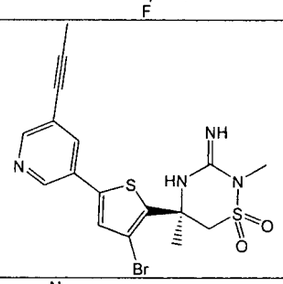
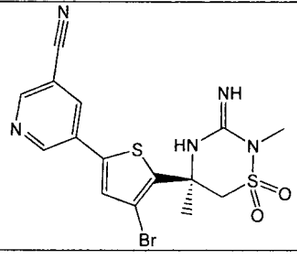
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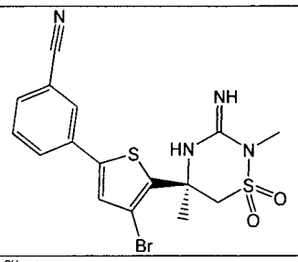
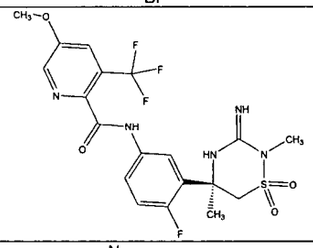
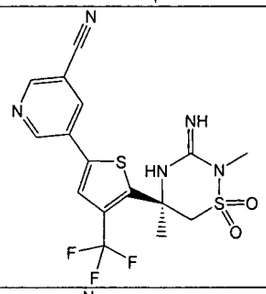
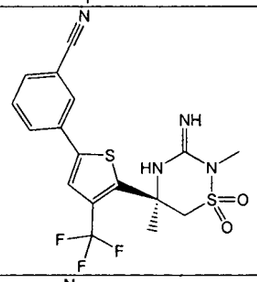
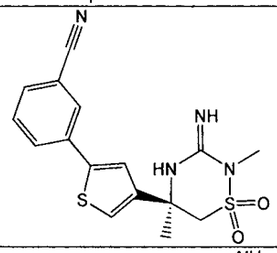
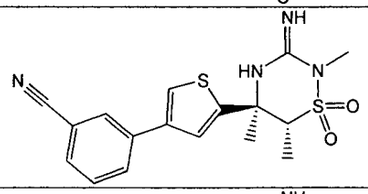
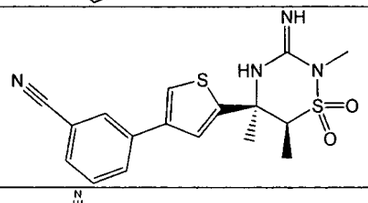
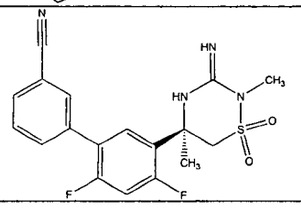
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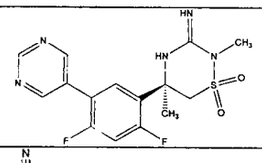
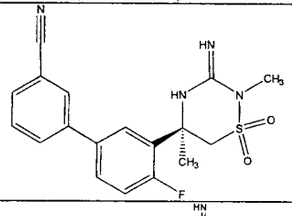
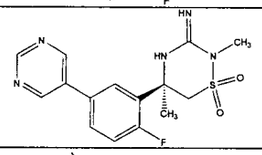
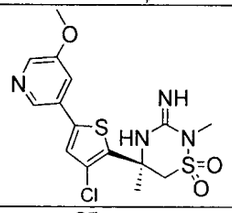
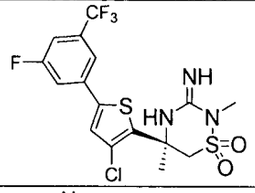
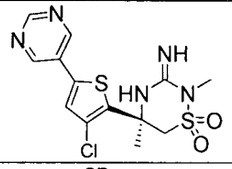
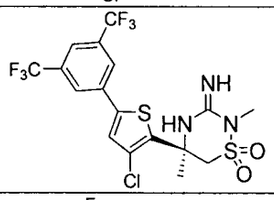
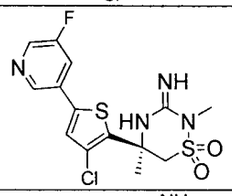
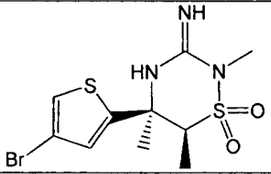
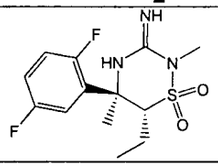
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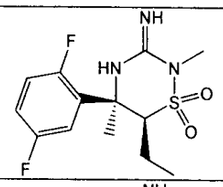
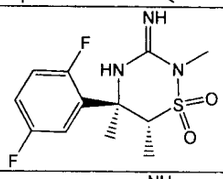
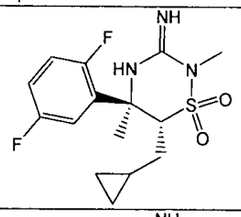
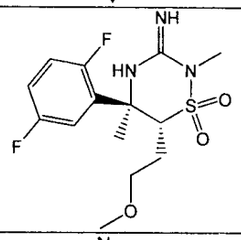
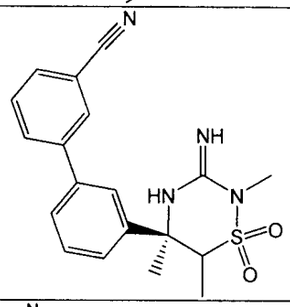
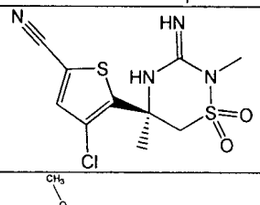
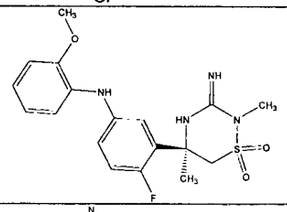
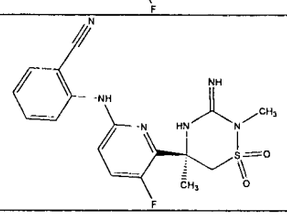
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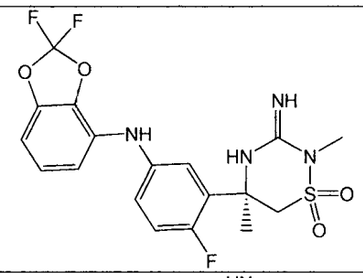
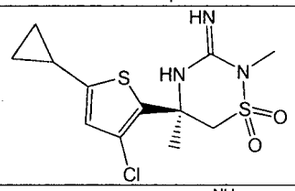
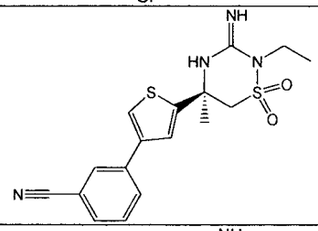
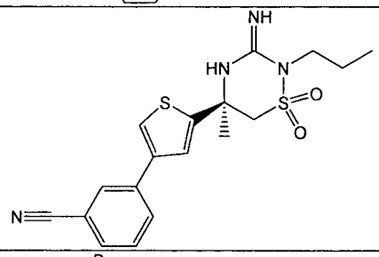
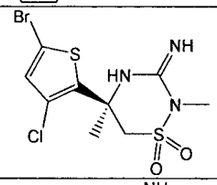
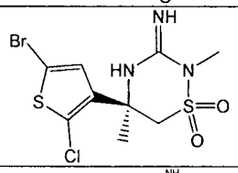
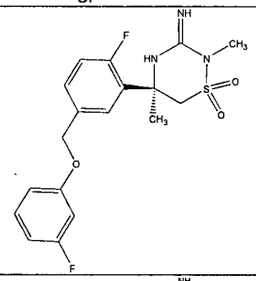
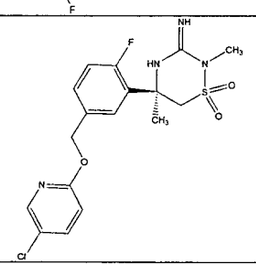
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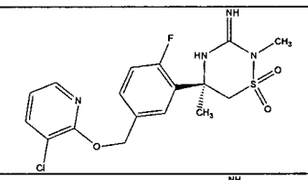
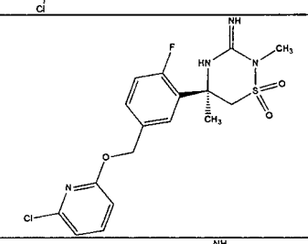
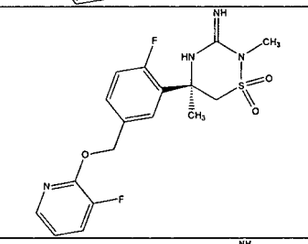
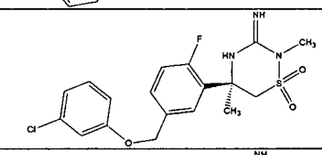
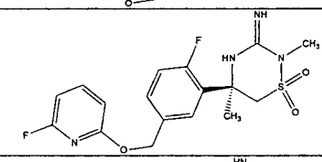
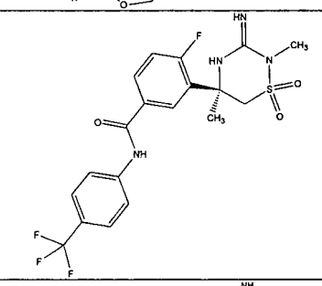
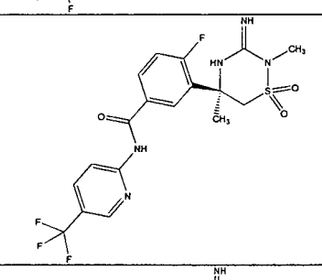
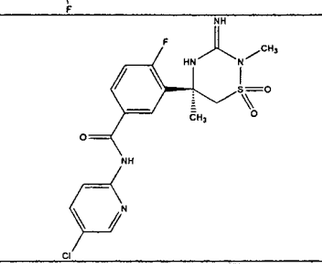
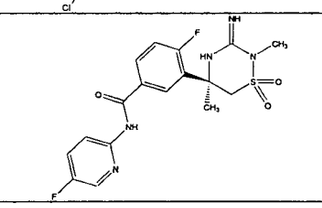
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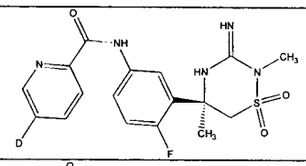
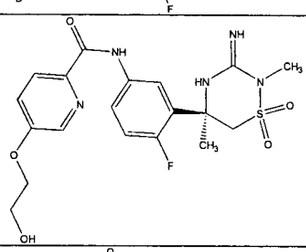
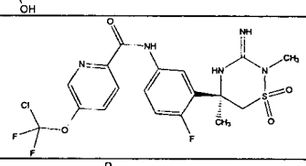
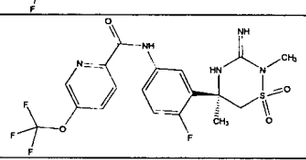
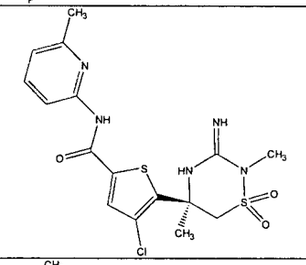
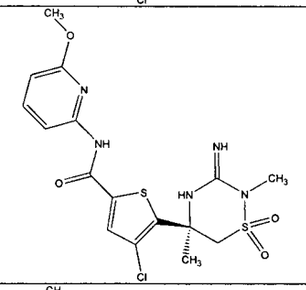
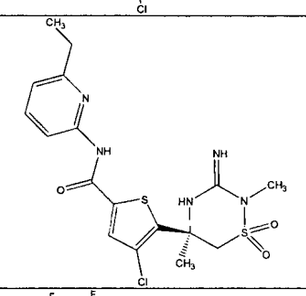
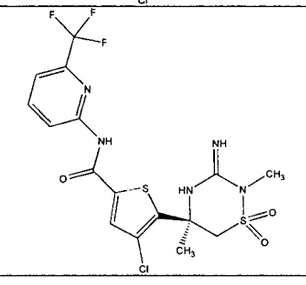
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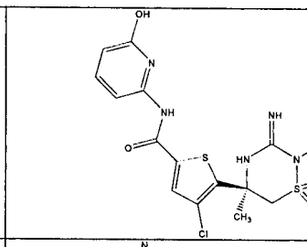
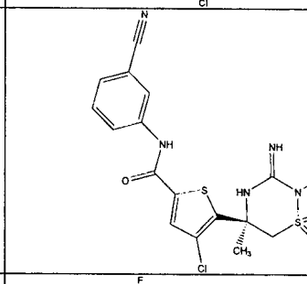
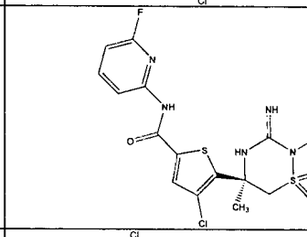
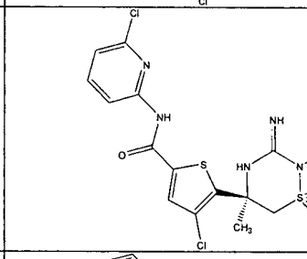
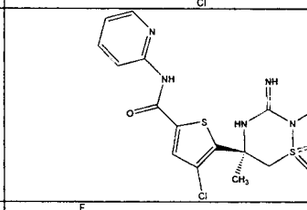
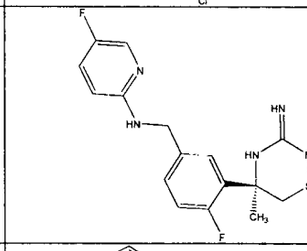
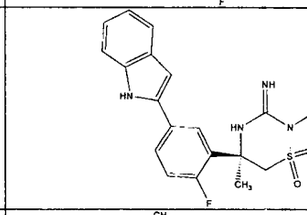
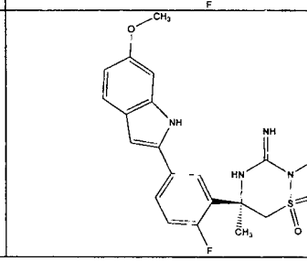
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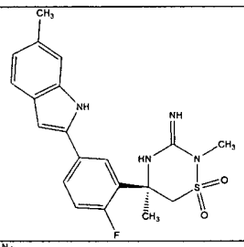
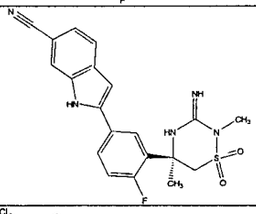
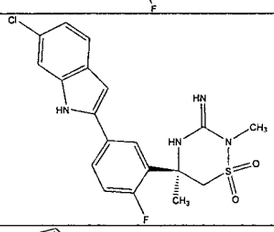
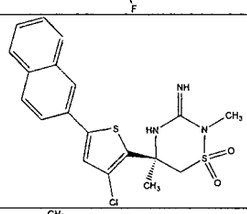
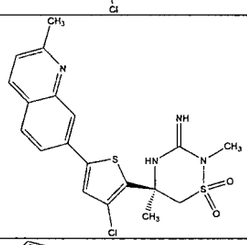
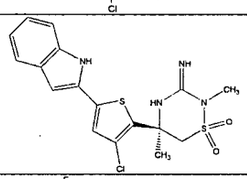
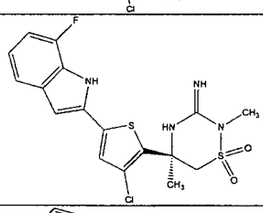
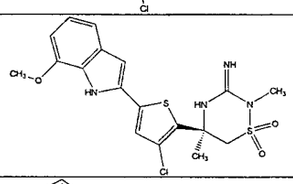
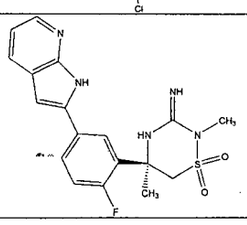
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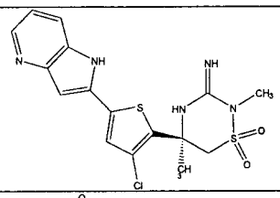
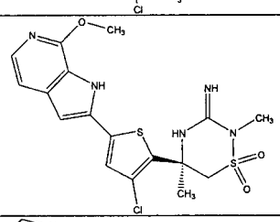
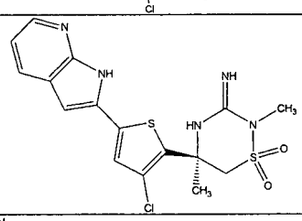
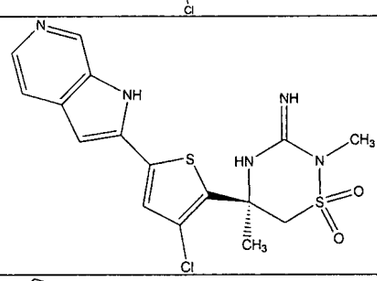
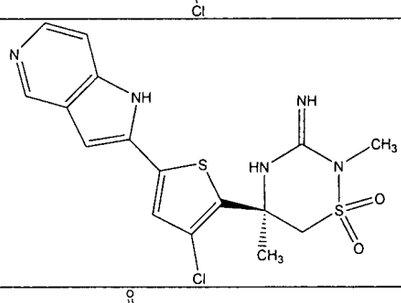
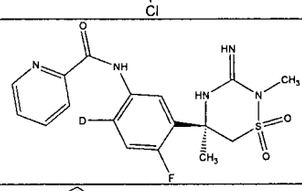
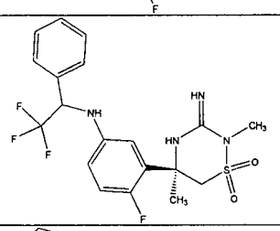
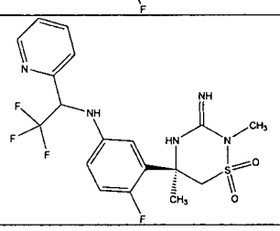
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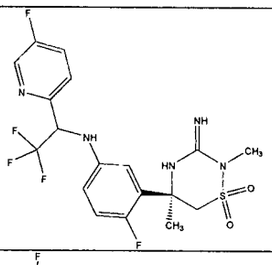
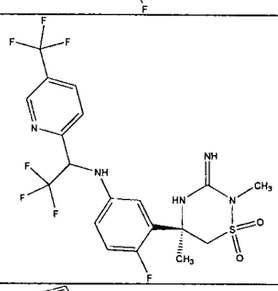
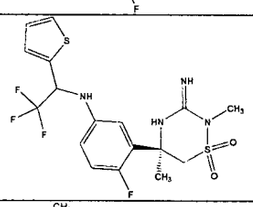
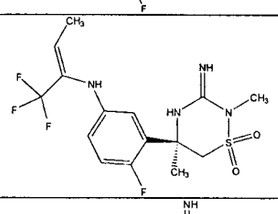
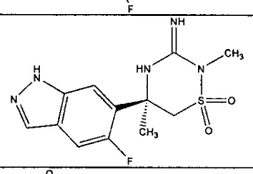
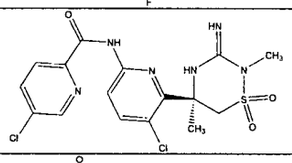
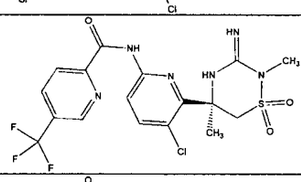
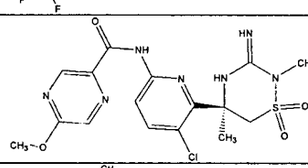
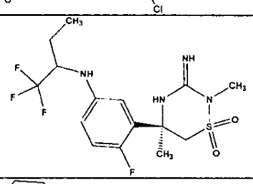
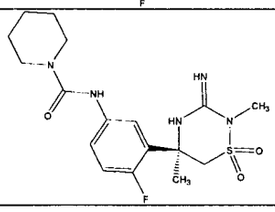
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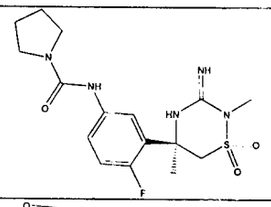
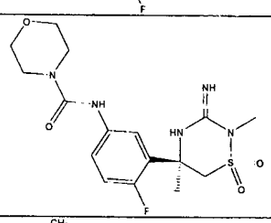
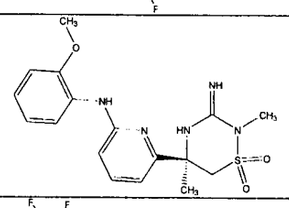
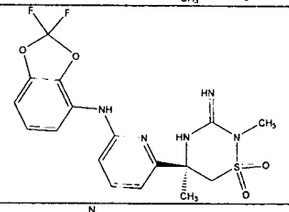
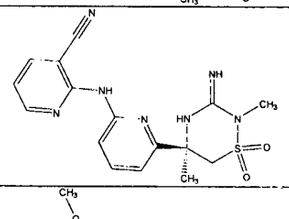
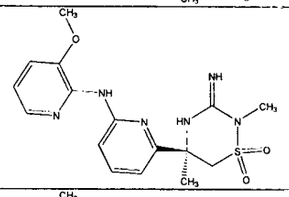
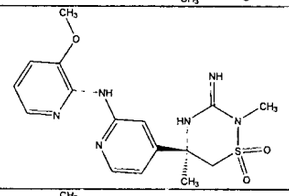
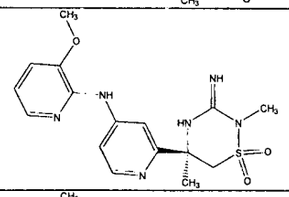
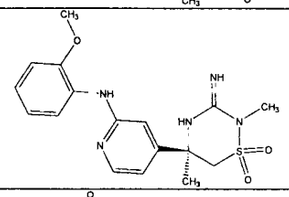
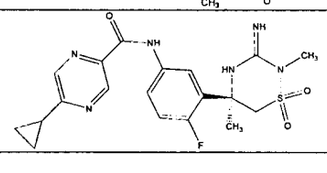
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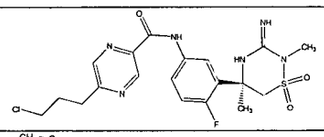
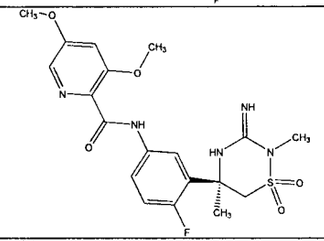
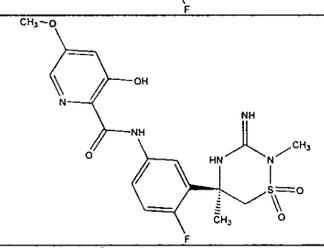
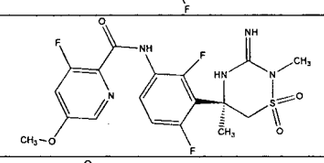
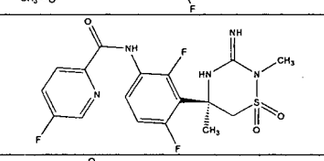
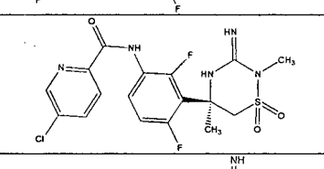
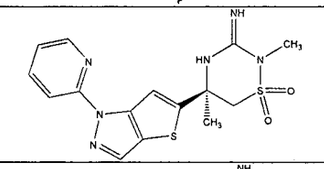
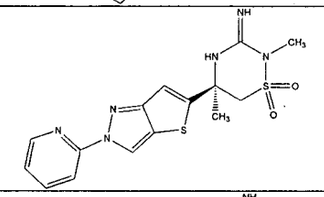
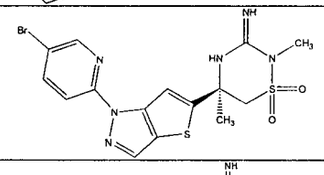
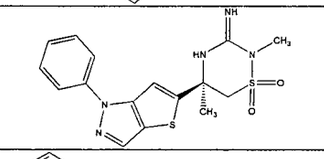
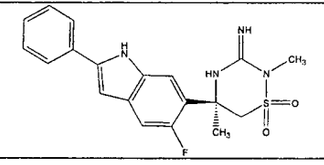
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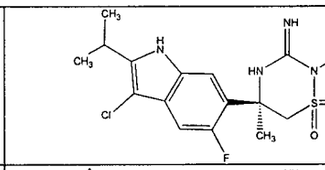
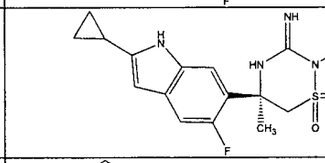
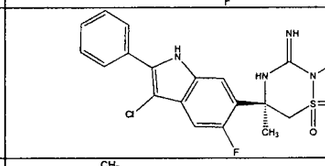
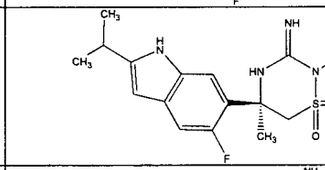
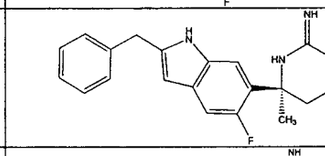
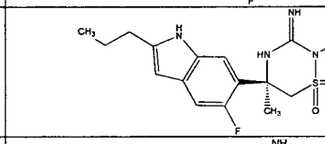
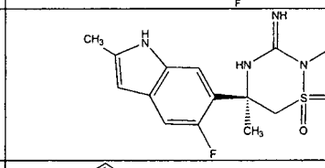
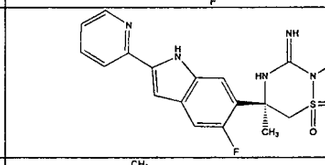
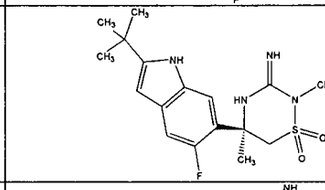
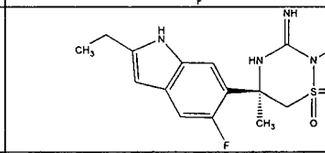
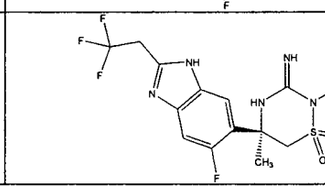
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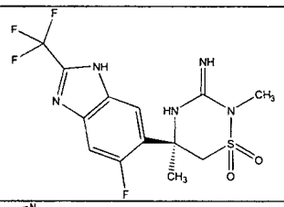
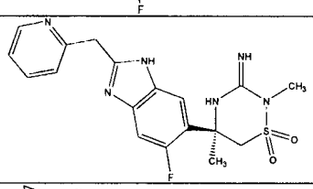
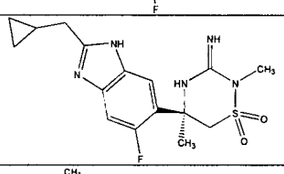
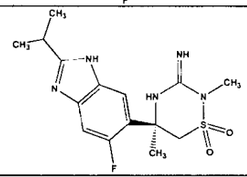
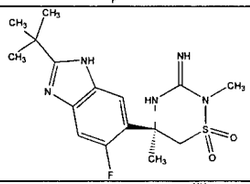
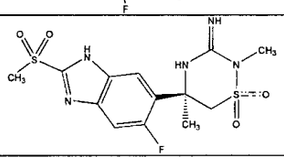
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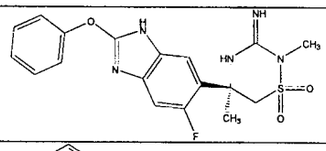
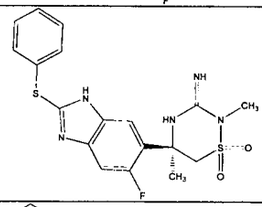
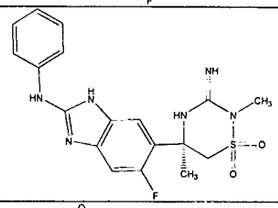
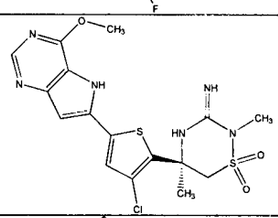
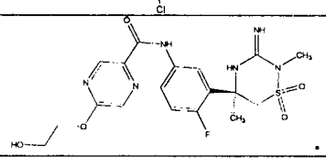
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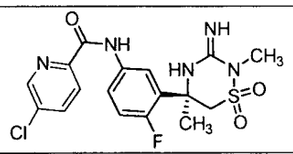
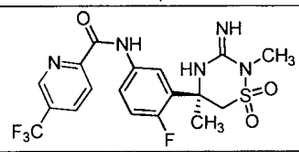
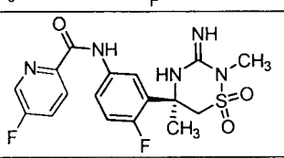
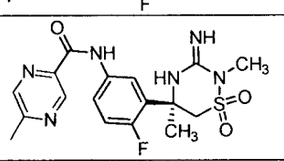
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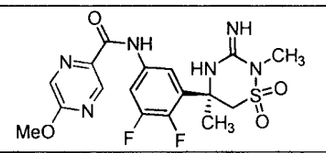
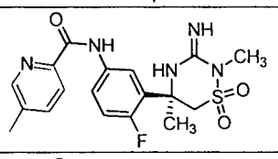
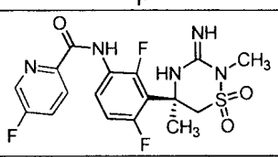
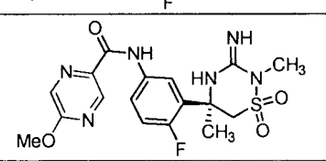
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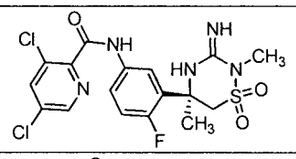
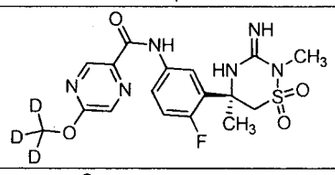
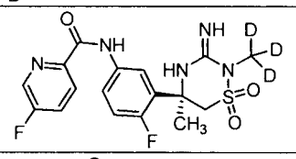
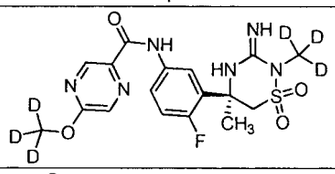
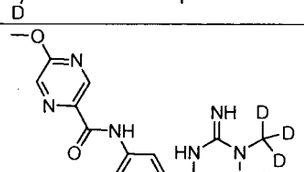
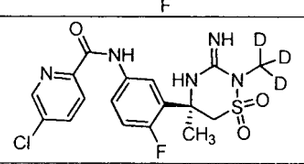
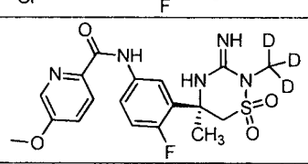
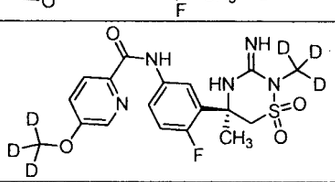
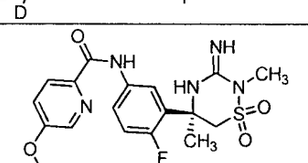
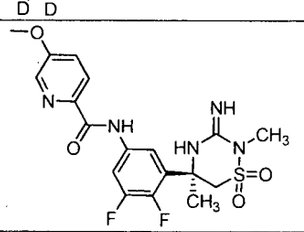
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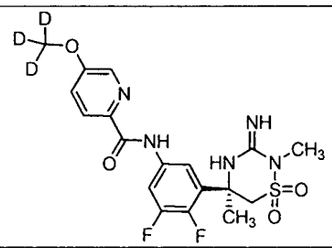
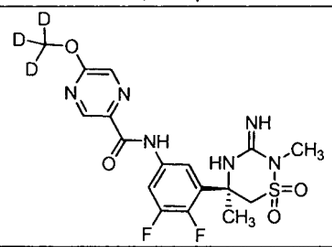
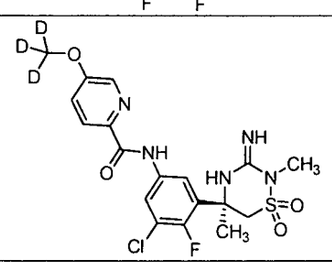
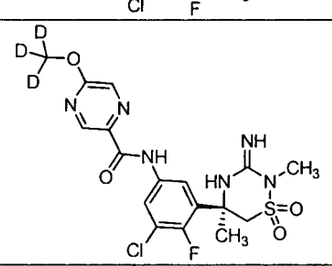
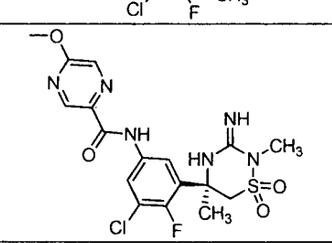
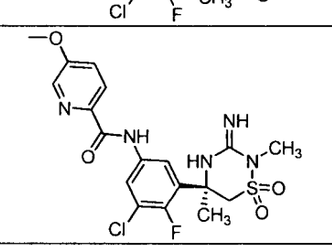
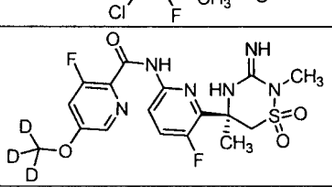
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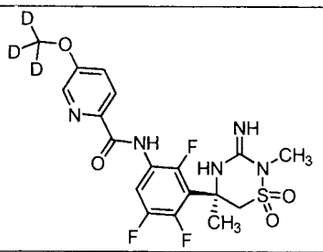
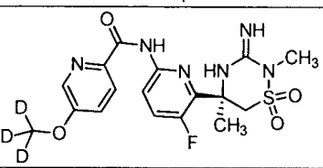
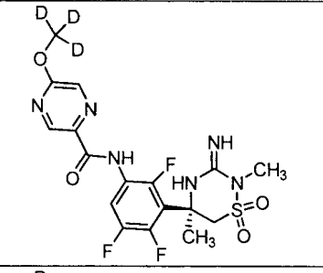
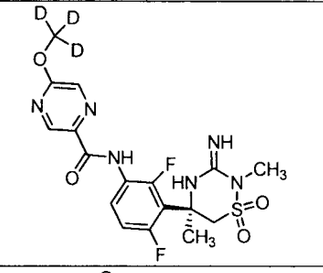
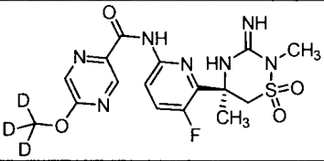
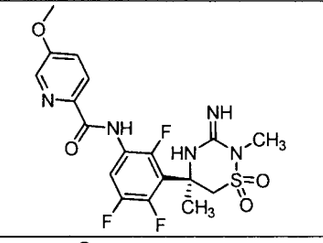
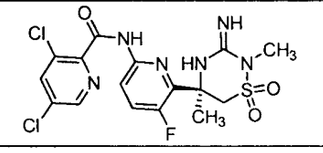
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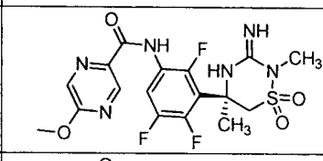
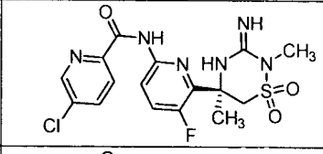
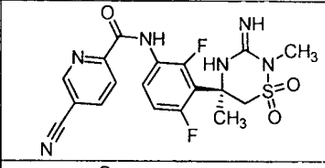
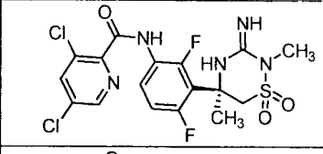
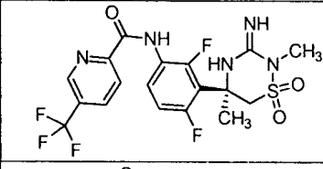
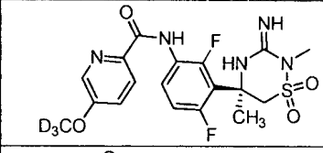
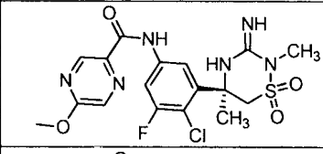
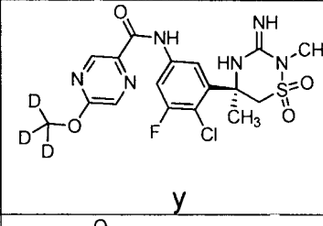
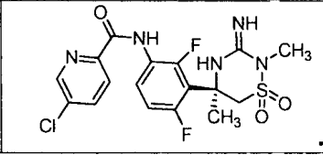
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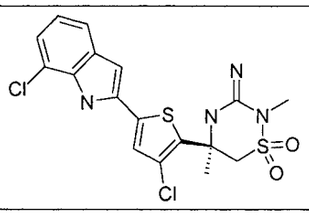
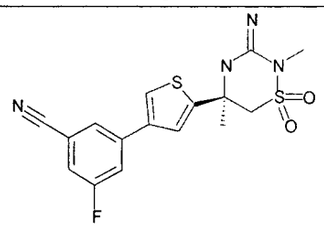
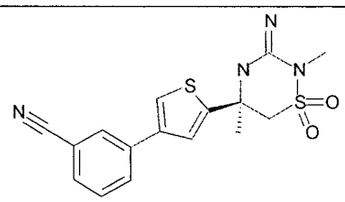
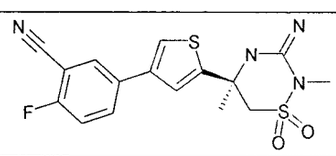
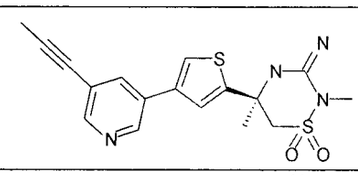
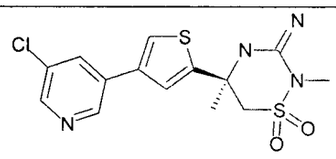
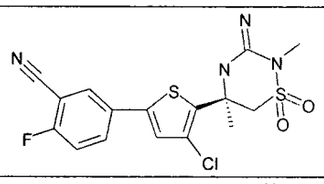
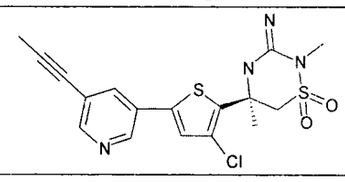
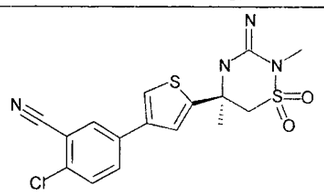
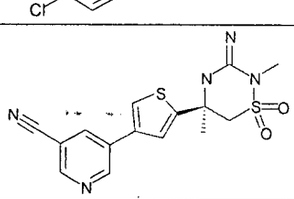
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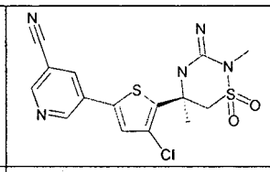
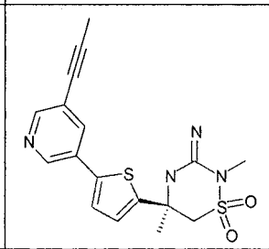
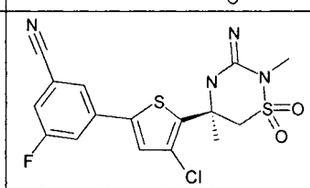
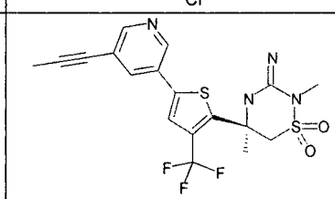
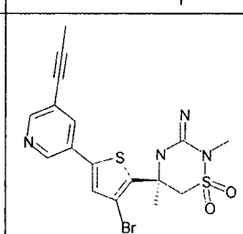
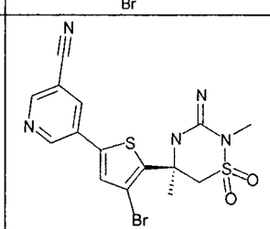
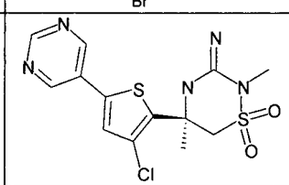
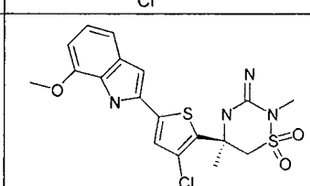
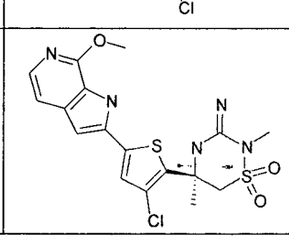
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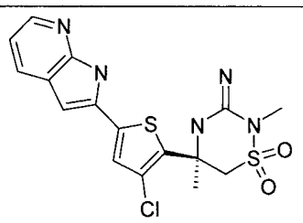
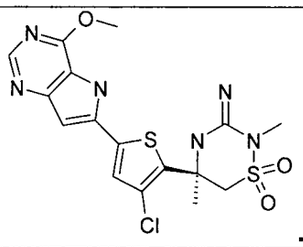
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10. Un compuesto, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, seleccionándose dicho compuesto del grupo formado por

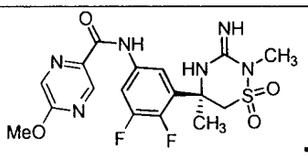
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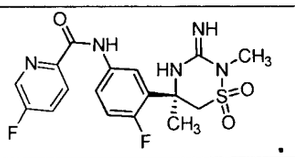
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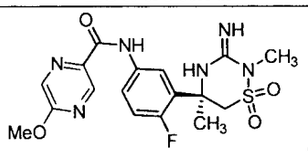
11. Un compuesto, o su tautómero, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho tautómero, teniendo dicho compuesto una estructura:

Ej. #	Estructura
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12. Un compuesto, o su tautómero, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho tautómero, teniendo dicho compuesto una estructura:

Ej. #	Estructura
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13. Un compuesto, o su tautómero, o una sal farmacéuticamente aceptable de dicho compuesto o de dicho tautómero, teniendo dicho compuesto una estructura:

Ej. #	Estructura
40ai	

14. Una composición farmacéutica que comprende por lo menos un compuesto de acuerdo con cualquiera de las reivindicaciones 1-13, o un

tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, y un portador o diluyente farmacéuticamente aceptable.

15. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1-13, o un tautómero del mismo, o un estereoisómero de dicho compuesto o dicho tautómero, o una sal farmacéuticamente aceptable del mismo, junto con por lo menos un agente terapéutico adicional, y un portador o diluyente farmacéuticamente aceptable.

16. Una composición farmacéutica de acuerdo con la reivindicación 15, donde dicho por lo menos un agente terapéutico adicional es por lo menos un agente seleccionado entre:

agonistas m_1; antagonistas m_2; inhibidores de colinesterasa; galantamina; rivastigmina; antagonistas del receptor de N-metil-D-aspartato; combinaciones de inhibidores de colinesterasa y antagonistas del receptor de N-metil-D-aspartato; moduladores de gamma secretasa; inhibidores de gamma secretasa; agentes antiinflamatorios no esteroideos; agentes antiinflamatorios que pueden reducir la neuroinflamación; anticuerpos antiamiloides; vitamina E; agonistas del receptor de acetilcolina nicotínicos; agonistas inversos del receptor CB1; antagonistas del receptor CB1; antibióticos; secretagogos de la hormona de crecimiento; antagonistas de histamina H3; agonistas de AMPA; inhibidores de PDE4; agonistas inversos de $GABA_A$; inhibidores de la agregación amiloide; inhibidores de glicógeno sintasa quinasa beta; promotores de la actividad de alfa secretasa; inhibidores de PDE-10; inhibidores de la quinasa Tau; inhibidores de la agregación de Tau; inhibidores de RAGE; vacuna anti-Abeta; ligandos de APP; agentes que regulan ascendentemente la insulina, agentes reductores de colesterol; inhibidores de la absorción de colesterol; combinaciones de inhibidores de HMG-CoA reductasa e inhibidores de la absorción de colesterol; fibratos; combinaciones de fibratos y agentes reductores de colesterol y/o inhibidores de la absorción de colesterol; agonistas de receptores nicotínicos; niacina; combinaciones de niacina e inhibidores de la absorción de colesterol y/o agentes reductores de colesterol; agonistas de LXR; mímicos de LRP; antagonistas de receptores H3; inhibidores de

histona desacetilasa; inhibidores de hsp90; agonistas de 5-HT4; antagonistas de receptores 5-HT6; moduladores o antagonistas de receptores mGluR1; moduladores o antagonistas de receptores mGluR5; antagonistas de mGluR2/3; antagonistas de receptor EP2 de prostaglandina; inhibidores de PAI-1; agentes que pueden inducir el flujo de Abeta; compuesto atenuador de proteína de metal; moduladores de GPR3; y antihistaminas.

17. Un método para tratar, prevenir y/o retardar el inicio de una patología amiloide β ("patología Aβ") y/o uno o más síntomas de dicha patología que comprende administrar por lo menos un compuesto de acuerdo con cualquiera de las reivindicaciones 1-13, o una sal farmacéuticamente aceptable del mismo, a un paciente que lo necesita e una cantidad eficaz para tratar dicha patología.

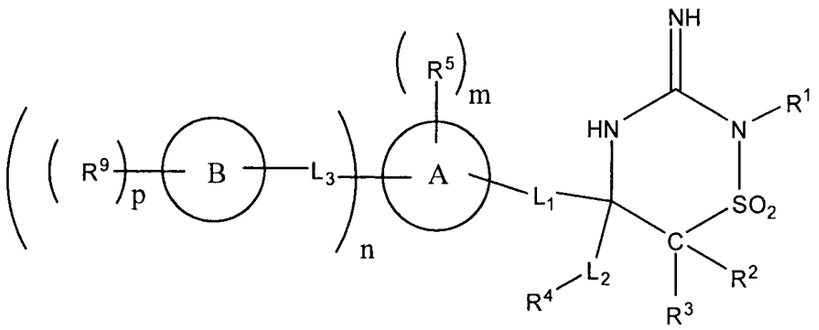
18. Un método de acuerdo con la reivindicación 17, donde dicha patología Aβ se selecciona entre la enfermedad de Alzheimer, síndrome de Down, enfermedad de Parkinson, pérdida de memoria, pérdida de memoria asociada con la enfermedad de Alzheimer, pérdida de memoria asociada con la enfermedad de Parkinson, síntomas de déficit de atención, síntomas de déficit de atención asociados con la enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, demencia, accidente cerebrovascular, microgliosis e inflamación cerebral, demencia presenil, demencia senil, demencia asociada con la enfermedad de Alzheimer, enfermedad de Parkinson, y/o síndrome de Down, parálisis supranuclear progresiva, degeneración córtico-basal, neurodegeneración, deterioro olfativo, deterioro olfativo asociado con la enfermedad de Alzheimer, enfermedad de Parkinson y/o síndrome de Down, angiopatía β-amiloide, angiopatía amiloide cerebral, hemorragia cerebral hereditaria, deterioro cognitivo leve ("MCI" (según siglas en inglés)), glaucoma, amiloidosis, diabetes tipo II, amiloidogénesis asociada con diabetes, complicaciones de hemodiálisis (de microglobulinas β_2 y complicaciones que surgen de las mismas en pacientes con hemodiálisis), scrapie, encefalitis espongiforme bovina, lesión cerebral traumática ("TBI" (según siglas en inglés)), enfermedad de Creutzfeld-Jakob, y lesión cerebral traumática.

19. Un método de acuerdo con la reivindicación 18, donde dicha patología Aβ es la enfermedad de Alzheimer.

p.de: SCHERING CORPORATION

RESUMEN

En sus muchas realizaciones, la presente invención proporciona ciertos compuestos de dióxido de iminotiadiazina, incluyendo los compuestos de la Fórmula (I):



(I)

e incluyen sus estereoisómeros, y las sales farmacéuticamente aceptables de dichos compuestos, estereoisómeros, donde cada uno de R^1, R^2, R^3, R^4, R^5, R^9, el anillo A, el anillo B, m, n, p, $-L_1-$,$-L_2-$, y $-L_3-$ se selecciona independientemente y según lo definido en esta invención. Se ha descubierto, sorprendentemente, que los compuestos de dióxido de iminotiadiazina novedosos de la invención exhiben propiedades las cuales se espera que los convierta en ventajosos como inhibidores de BACE y/o para el tratamiento y prevención de diversas patologías relacionadas con la producción de β-amiloides ("Aβ"). También se describen composiciones farmacéuticas que comprenden uno o más de dichos compuestos (solos y en combinación con uno o más otros agentes activos), y métodos para su preparación y uso en el tratamiento de patologías asociadas con la proteína amiloide beta (Aβ), incluyendo la enfermedad de Alzheimer.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CN20097055	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/51553	International filing date *(day/month/year)* 06 October 2010 (06.10.2010)	(Earliest) Priority Date *(day/month/year)* 08 October 2009 (08.10.2009)
Applicant SCHERING CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

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

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

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/51553

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/54 (2010.01)
USPC - 514/222.5
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)
USPC: 514/222.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 222.8, 223.2, 223.8, 224.2, 226.8, 227.2, 227.8, 228.2; 544/8, 10, 13 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Patentscope
1,2,4-thiadiazine, thiadiazin$, $thiadiazine, iminothiadiazine, aspartyl protease, beta-secretase, BACE$, inhibit$, modulat$, Alzheimer's, treat$, ameliorat$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/065277 A2 (ZHU et al.) 22 June 2006 (22.06.2006) pg 1, ln 14-19; pg 2, ln 16 to pg 3, ln 7; pg 3, ln 32 to pg 4, ln 20; pg 7, ln 11-23; pg 11, ln 10-12; pg 12, ln 6-19; pg 17, ln 11-12; ln 21-28; pg 19, ln 31-32; pg 24, ln 6-9 This document can be viewed by entering the doc number at the following url: http://ep.espacenet.com/numberSearch?locale=en_EP	1-19
Y	US 2008/0200445 A1 (ZHU et al.) 21 August 2008 (21.08.2008) para [0057], [0156], [0660]	1-19

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
15 November 2010 (15.11.2010)	03 DEC 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-056873- -00000-0000

Fecha: 2012-04-04 15:16:50 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 254

Act: 411 PRESENTACION ~~Folios: 255~~

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 presenta la 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 ☐